Cover Page for Protocol

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16.1.1 Protocol and protocol amendments

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Redacted protocol
Includes redaction of personal identifiable information only.

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Protocol

Trial ID: NN9535-4114

SUSTAIN™ CHINA

Efficacy and safety of semaglutide once-weekly versus sitagliptin once-daily as add-on to metformin in subjects with type 2 diabetes

A 30-week randomised, double-blind, double-dummy, active-controlled, parallel-group, multi-centre and multi-national trial

Trial phase: 3a

Protocol originator

[redacted]

ClinOps, Obesity, Liraglutide & Obesity

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Table 5–1 Treatment of subjects 30

List of abbreviations

AACE	American Association of Clinical Endocrinologists
ADA	American Diabetes Association
AE	adverse event
BG	blood glucose
BMI	Body mass index
CMC	calcitonin monitoring committee
CRF	case report form
CRO	contract research organisation
CTR	clinical trial report
CVD	cardiovascular disease
DPP-4	dipeptidyl peptidase 4
DMC	data monitoring committee
DUN	dispensing unit number
DTSQs	Diabetes Treatment Satisfaction Questionnaire status
EAC	event adjudication committee
ECG	electrocardiogram
eCRF	electronic case report form
EE	ethinylestradiol
EFD	embryo-foetal development
eGFR	estimated glomerular filtration rate
FAS	full analysis set
FDAAA	Food and Drug Administration Amendment Act
FPFV	first patient first visit
FPG	fasting plasma glucose
FSFV	first subject first visit
GCP	Good Clinical Practice
GI	gastrointestinal
GIP	gastric inhibitory polypeptide

GLP-1	glucagon-like peptide-1
HbA_{1c}	glycosylated haemoglobin
hCG	human chorionic gonadotrophin
HDL	high density lipoprotein
hsCRP	highly sensitive C-reactive protein
IB	Investigator's Brochure
ICMJE	International Committee of Medical Journal Editors
IEC	independent ethics committee
IMP	investigational medicinal product
IRB	Institutional Review Board
IUD	intrauterine device
IV/WRS	interactive voice/web response system
LDL	low density lipoprotein
LN	levonorgestrel
LPFV	last patient first visit
LPLV	last patient last visit
LSFV	last subject first visit
LSLV	last subject last visit
MACE	major adverse cardiovascular events
MAR	missing at random
MCAR	missing completely at random
MDRD	modification of diet in renal disease
MEN2	multiple endocrine neoplasia syndrome type 2
MESI	medical event of special interest
MMRM	mixed model for repeated measurements
MTC	medullary thyroid carcinoma
NYHA	New York Heart Association
OAD	oral anti-diabetic drug
PG	plasma glucose

PP	per protocol
PPG	postprandial glucose
PPND	pre- and postnatal development
PRO	patient reported outcome
RA	receptor agonist
SAE	serious adverse event
SAP	statistical analysis plan
s.c.	subcutaneous
SD	standard deviation
SDV	source data verification
SMBG	self-measured blood glucose
SMPG	self-measured plasma glucose
SUSAR	suspected unexpected serious adverse reaction
TMM	Trial Materials Manual
TEAE	treatment emergent adverse event
TVP	trial validation plan
UACR	urinary albumin to creatinine ratio
UTN	universal trial number
V	visit

1 Summary

Objectives and endpoints:

Primary objective

To compare the effect of once-weekly dosing of two dose levels of semaglutide versus sitagliptin 100 mg once-daily on glycaemic control after 30 weeks of treatment

Primary endpoint

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

Secondary objectives

To compare the effects of once-weekly dosing of two dose levels of semaglutide versus sitagliptin 100 mg once-daily after 30 weeks of treatment on:

- Inducing and maintaining weight loss
- Other parameters of efficacy, safety and tolerability

Key secondary endpoint

Confirmatory secondary endpoint

- Change from baseline to week 30 in body weight

Supportive secondary endpoints:

Change from baseline to week 30 in:

- Fasting plasma glucose (FPG)
- Systolic and diastolic blood pressure
- Patient reported outcome (PRO) questionnaire: Diabetes Treatment Satisfaction Questionnaire status (DTSQs) score

Subjects who after 30 weeks treatment achieve (yes/no):

- $HbA_{1c} \leq 6.5\%$ (48 mmol/mol) - American Association of Clinical Endocrinologists (AACE) target

Trial design:

This is a 30-week randomised, double-blind, double-dummy, active-controlled, multi-centre, multi-national four-armed, parallel-group trial comparing semaglutide 0.5 mg and 1.0 mg once-weekly against sitagliptin 100 mg once-daily.

Subjects with type 2 diabetes inadequately controlled on metformin will be randomised in a 2:2:1:1 manner to receive either:

- semaglutide 0.5 mg once-weekly + sitagliptin placebo once-daily
- semaglutide 1.0 mg once-weekly + sitagliptin placebo once-daily
- sitagliptin 100 mg once-daily + semaglutide placebo (0.5) mg once-weekly
- sitagliptin 100 mg once-daily + semaglutide placebo (1.0) mg once-weekly

Trial product will be add-on to subject's stable pre-trial metformin.

Key inclusion criteria:

- Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial
- Male or female, age ≥ 18 years at the time of signing informed consent
- Subjects diagnosed with type 2 diabetes and on stable treatment in a period of 60 days prior to screening with metformin ≥ 1500 mg (or maximum tolerated dose ≥ 1000 mg). Stable is defined as unchanged medication and unchanged daily dose
- HbA_{1c} 7.0 – 10.5 % (53-91 mmol/mol) (both inclusive)

Key exclusion criteria:

- Female who is pregnant, breast-feeding or intends to become pregnant or is of childbearing potential not using an adequate contraceptive method throughout the trial including the 5 week follow-up period (adequate contraceptive measure as required by local regulation or practice).
- Any disorder which, in the opinion of the investigator, might jeopardise subject's safety or compliance with the protocol
- Treatment with glucose lowering agent(s) other than stated in the inclusion criteria in a period of 60 days before screening. An exception is short-term treatment (≤7 days in total) with insulin in connection with inter-current illness
- History of chronic or idiopathic acute pancreatitis
- Screening calcitonin value ≥ 50 ng/L (pg/mL)
- Personal or family history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia syndrome type 2 (MEN 2)
- Impaired renal function defined as estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2 per modification of diet in renal disease (MDRM) formula (4 variable version)
- Acute coronary or cerebrovascular event within 90 days before randomisation
- Heart failure, New York Heart Association (NYHA) class IV

Assessments:

Efficacy:

- Glucose metabolism
- Body measurements (body weight, body mass index (BMI) and waist circumference)
- Systolic and diastolic blood pressure
- Blood lipids
- Patient reported outcome (PRO) questionnaires (SF-36v2™ and DTSQs)

Safety:

- Adverse events and serious adverse events
- Hypoglycaemic episodes
- Biochemistry and haematology
- Anti-semaglutide antibodies
- Physical examination (including electrocardiogram (ECG))

Trial products:

Novo Nordisk A/S will supply the following trial products:

- Semaglutide 1.34 mg/mL, solution for injection, 1.5 mL pre-filled PDS290 pen-injector
- Semaglutide placebo, solution for injection, 1.5 mL pre-filled PDS290 pen-injector
- Sitagliptin (Januvia®) 100 mg tablets for oral administration
- Sitagliptin placebo tablets for oral administration

2 Flow chart

Trial Periods	Screen	Rand	Treatment period						End of Treatment[1]	Follow Up[1]	End of Treatment premature discontinuation[2]	Follow Up premature discontinuation[2]
Visit (V) or Phone (P) number	V1	V2	V3	P4	V5	V6	V7	V8	V9	V10	V9A	V10A
Time of visit Weeks	-2	0	4	6	8	12	16	23	30	35		
Visit window Days	±7		±3	±3	±3	±3	±3	±3	±7	+7		
SUBJECT RELATED INFO /ASSESSMENTS												
Informed consent 18.1	x											
In/exclusion criteria 6.2 and 6.3	x	x										
Randomisation 8.1.3		x										
Withdrawal criterion 6.5			x	x	x	x	x	x	x		X	
Demography 8.2.1	x											
Diagnosis of diabetes 8.2.2	x											
Diabetes treatment history 8.2.3	x											
Diabetes complications 8.2.4	x											
Concomitant illness 8.2.5	x											
Medical History 8.2.5	x											
History of cardiovascular disease 8.2.6	x											
History of[9] gallbladder disease 8.2.7	x											
Smoking habits 8.2.8	x											
Concomitant medication 8.2.9	x	x	x	x	x	x	x	x	x	x	X	x
Fundoscopy/fundus photography[3] 8.2.10		x										
Height 8.2.11		x										
EFFICACY												
Body weight 8.3.1		x	x		x	x	x	x	x		X	
Waist circumference 8.3.2		x	x		x	x	x	x	x		X	
Systolic blood pressure, sitting 8.3.4	x	x	x		x	x	x	x	x		X	

Trial Periods	Screen	Rand	Treatment period						End of Treatment[1]	Follow Up[1]	End of Treatment premature discontinuation[2]	Follow Up premature discontinuation[2]
Visit (V) or Phone (P) number	V1	V2	V3	P4	V5	V6	V7	V8	V9	V10	V9A	V10A
Time of visit **Weeks**	-2	0	4	6	8	12	16	23	30	35		
Visit window **Days**	±7		±3	±3	±3	±3	±3	±3	±7	+7		
Diastolic blood pressure, sitting 8.3.4	x	x	x		x	x	x	x	x		X	
HbA_{1c} 8.5.1.1	x	x	x		x	x	x	x	x		X	
Fasting plasma glucose 8.5.1.1		x	x		x	x	x	x	x		X	
Fasting insulin 8.5.1.1		x					x		x		X	
Fasting proinsulin 8.5.1.1		x					x		x		X	
Fasting C-peptide 8.5.1.1		x					x		x		X	
Fasting glucagon 8.5.1.1		x					x		x		X	
Lipids 8.5.1.3		x					x		x		X	
hsCRP (highly sensitive CRP)8.5.1.2		x					x		x		X	
SMPG 7 point profile 8.5.1.4		x					x		x		X	
SAFETY												
Adverse events 8.4.1		x	x	x	x	x	x	x	x	x	X	x
Hypoglycaemic episodes 8.4.2		x	x	x	x	x	x	x	x	x	X	x
ECG 8.4.3		x							x	x	X	x
Physical examination 8.4.4	x								x		X	
Pulse, sitting 8.4.5	x	x	x		x	x	x	x	x		X	
Anti-semaglutide antibodies[4] 8.5.2.1		x					x		x	x	X	x
Creatinine 8.5.2.2	x		x		x	x	x	x	x		X	
Biochemistry 8.5.2.2		x	x		x	x	x	x	x		X	
Haematology 8.5.2.3		x	x		x	x	x	x	x		X	
Calcitonin 8.5.2.4	x						x		x		X	
Pregnancy test[5] 8.5.2.5	x	x	x		x	x	x	x	x	x	X	x
Urinalysis 8.5.2.6		x					x		x		X	
Urinalysis, Albumin : creatinine ratio 8.5.2.6		x					x		x		X	

Trial Periods	Screen	Rand	Treatment period						End of Treatment[1]	Follow Up[1]	End of Treatment premature discontinuation[2]	Follow Up premature discontinuation[2]
Visit (V) or Phone (P) number	V1	V2	V3	P4	V5	V6	V7	V8	V9	V10	V9A	V10A
Time of visit **Weeks**	-2	0	4	6	8	12	16	23	30	35		
Visit window **Days**	±7		±3	±3	±3	±3	±3	±3	±7	+7		
OTHER ASSESSMENTS												
PRO questionnaire: SF-36v2™ 8.6.1.1		x							x		X	
PRO questionnaire: DTSQs 8.6.1.2		x							x		X	
TRIAL MATERIAL												
Drug accountability 9.4					x		x		x		X	
IV/IWRS call 10	x	x			x		x		x		X	
Dispensing visit 9.1		x			x		x					
REMINDERS												
Training in trial product, pen handling and dispense Direction for Use 9.1		x			x		x					
End of trial										x		
Supply & instruction in BG meter use 8.5.1.4	x											
Dispense and instruction in diary[6] 8.6.2	x	x	x		x	x	x	x	x	x[6]	X	x[6]
Attend visit fasting[7] 8.1.2		x	x		x	x	x	x	x	x[8]	X	x[8]
Dispense trial identity card 8.1.1	x											

2.1 Flow chart explanatory descriptions

Footer	Description
x[1]	V9 (End of Treatment) and V10 (Follow Up) are applicable for all randomised subjects. Subjects who have discontinued trial product prematurely should also attend V9 and V10 according to their initially scheduled week 30 and Week 35 visits.
x[2]	Subjects discontinuing trial product prematurely will be asked to attend two additional visits to undergo assessments: End of Treatment-premature discontinuation (V9A) and Follow Up -premature discontinuation (V10A). V9A should be scheduled at discontinuation of the trial product. V10A should be scheduled 5 weeks after discontinuation of trial product (+ 7 days visit window).
x[3]	Fundoscopy/fundus photography performed within 90 days before visit 2 is acceptable if results are available for evaluation at the visit 2 and no deterioration in visual function since last assessment.
x[4]	Antibody sampling should preferably be done pre-dose. For fasting and non-fasting visit, where the injection takes place on the day of site visit, trial product must not be taken before blood sampling. For visit 9 and 10: Not applicable if taken at a premature discontinuation visit
x[5]	For women of child bearing potential: For all site visits a serum pregnancy test must be performed. Urine pregnancy test should be performed at any time during the trial if a menstrual period is missed, or as required by local law.
x[6]	At V10 and V10A collect diary only.
x[7]	Fasting is defined as having consumed only water since midnight. Glucose lowering agents and trial product cannot be taken until after blood sampling has been performed but other prescribed medication should be taken.
x[8]	For the follow-up visit (V10/V10A) attend fasting is defined as having consumed only water within the last 2 hours prior to the visit.
x[9]	pancreatitis and

3 Background information and rationale for the trial

The trial will be conducted in compliance with this protocol, ICH GCP [1] and applicable regulatory requirements, and in accordance with the Declaration of Helsinki [2].

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 Type 2 diabetes

Type 2 diabetes is a progressive metabolic disease primarily characterised by abnormal glucose metabolism. The pathogenesis is not fully understood but seems to be heterogeneous, involving environmental, lifestyle, and genetic factors leading to chronic hyperglycaemia caused by peripheral tissue insulin resistance, impaired insulin secretion due to abnormal beta-cell function and abnormal glucose metabolism in the liver [3].

Optimal glycaemic control is the treatment goal in subjects with type 2 diabetes, in order to prevent long-term complications associated with chronic hyperglycaemia [4,5]. Despite the availability of several oral anti-diabetic drugs (OADs) and insulin, a significant proportion of subjects with type 2 diabetes do not achieve the recommended blood glucose target levels [6-9].

In addition to the need for new effective and safe glucose lowering agents, it is important to establish the benefits of the available marketed glucose lowering agents in order to optimise the individual treatment in the best possible way.

3.2 Glucagon-like peptide-1

Glucagon-like peptide-1 (GLP-1) is an incretin hormone secreted from the L-cells in the small intestine. An incretin hormone is a gut-derived peptide with important physiological function in augmenting post-prandial insulin secretion in response to ingestion of a meal. GLP-1 has a glucose-dependent stimulatory effect on insulin- and inhibitory effect on glucagon secretion from the pancreatic islets (i.e. when plasma glucose levels are above normal) [10,11]. Both these effects are considered of importance for the glucose lowering effect of GLP-1 [12]. Physiologically GLP-1 has a pronounced inhibitory effect on gastric emptying [13]. This effect seems to diminish upon chronic exposure to GLP-1 [14,15]. GLP-1 also lowers body weight due to a decreased energy intake induced by a lowered appetite [16].

Patients with diabetes have a decreased incretin effect [17-20]). However, the insulinotropic action of GLP-1 and thus, the ability to lower blood glucose is preserved in subjects with type 2 diabetes when administered at supra physiological levels [21].

The mechanism of action makes GLP-1 a potent blood glucose lowering agent [22] and thus an attractive pharmacological tool for treatment of type 2 diabetes [23-25]. However, the very short

elimination half-life (t½) of endogenous GLP-1 (t½ < 1.5 minutes after intravenous (iv) administration) due to rapid degradation by ubiquitous dipeptidyl peptidase (DPP-4) [26] makes endogenous GLP-1 an unattractive treatment option. Clinical trials have revealed that 24-hour infusion of endogenous GLP-1 would be necessary to achieve satisfactory glycaemic control. Therefore, to benefit from the potentials of GLP-1 in treatment of diabetes it has been necessary to develop GLP-1 receptor agonists with longer half-life.

3.3 Semaglutide

Semaglutide is a potent human GLP-1 receptor agonist (RA) for once-weekly subcutaneous (s.c.) administration. It is structurally similar to liraglutide (Victoza®), a once-daily GLP-1 RA developed by Novo Nordisk and approved worldwide for the treatment of type 2 diabetes.

For the semaglutide molecule the principal mechanism of protraction is albumin binding facilitated by a large fatty acid derived chemical moiety attached to the lysine in position 26. The specific modifications in the molecule are: 1) a modification in position 8 (Alanine to 2-aminoisobutyric acid) of the peptide backbone in order to further increase stability against DPP-4, and a change in position 34 from a lysine to an arginine in order to only have one lysine in the sequence; 2) a large hydrophilic linker 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. The latter two contribute to increased albumin binding which results in decreased renal clearance. In addition to slowed degradation in plasma and decreased renal clearance, delayed absorption from subcutis also contributes to a prolonged half-life of approximately 160 hours making semaglutide suitable for once-weekly s.c. administration.

In vitro receptor studies have shown that semaglutide is a potent and selective GLP-1 RA, and animal studies using non-diabetic rats, non-diabetic pigs and diabetic mice have shown lowering of blood glucose and inhibition of food intake.

3.3.1 Non-clinical data

The non-clinical programme for semaglutide was designed according to the ICH M3 [27] guideline to support the clinical development. The standard non-clinical 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.

3.3.1.1 Thyroid C-cell tumours in rodents

Treatment-related non-genotoxic proliferative changes in the thyroid C-cells of mice and rats were observed in 2-year carcinogenicity studies with semaglutide. Early C-cell changes were also identified in repeated dose toxicity studies with semaglutide in mice. However, this was not the case in other species including a 52-week repeat dose study in non-human primates at exposure levels up to 36-fold above the expected clinical exposure. The observed pattern of effects in mice and rats (thyroid C-cell proliferation preceded by increase in serum calcitonin) and lack of these effects in the non-human primate and in man suggest that the mechanism by which semaglutide acts on the thyroid C-cells in rodents is the same as has been demonstrated for other GLP-1 RAs, including liraglutide. The relevance for human subjects is unknown.

3.3.1.2 Teratogenicity in rats

Semaglutide has been concluded teratogenic in rats, with exposure at no observable adverse effect level (NOAEL) below expected human exposure. This effect is regarded to be caused by impairment of nutrient supply to the embryo across the inverted yolk sac with placental function which is specific to rats.

Non-human primates and humans do not depend on a yolk sac with placental function to supply nutrients to the embryo early in pregnancy. The effect on rat embryo-foetal development is therefore not likely to be relevant to humans. Preliminary and main embryo-foetal development (EFD) and pre- and postnatal development (PPND) studies with doses corresponding to 12-15 fold expected clinical exposure in cynomolgus monkeys have been finalised. In the main EFD study sporadic abnormalities were reported across all dose groups and in the PPND study a dose-dependent increase in early pregnancy losses were observed. The findings observed across the three studies in cynomolgus monkeys are not indicative of a teratogenic potential of semaglutide in this species. The increase in early pregnancy losses is indicative of embryo-toxicity, which may be related to the maternal effect of semaglutide (marked body weight loss). A developmental toxicity NOAEL was determined at an exposure 1- to 2 fold the expected clinical exposure (1 mg/week). A risk for the developing human embryo or foetus cannot be definitely ruled out, but the absence of findings indicative of teratogenicity in the EFD and PPND studies in cynomolgus monkey decrease the level of concern.

A comprehensive review of results from the non-clinical studies can be found in Investigator's Brochure, semaglutide (NN9535) (subcutaneous administration), Type 2 Diabetes and any updates hereof[28].

3.3.2 Clinical data

As of 09 January 2014, 5 clinical pharmacology trials (Trials 1820, 3679, 3633, 3616 and 3819) and 1 phase 2 trial (Trial 1821) have been completed with semaglutide. Four trials are under reporting/on-going: Trial 4010, phase 1 bioequivalence, Trial 3744, phase 3 therapeutic

confirmatory trial to assess cardiovascular risk and long term safety, Trial 3626, phase 3 confirmatory trial to assess parameters of efficacy and safety compared with sitagliptin and Trial 3624, phase 3 confirmatory trial to assess parameters of efficacy and safety compared with exenatide extended release. In the completed trials 525 subjects have been exposed to semaglutide: 164 healthy subjects (both single and multiple dosing), 313 subjects with T2DM (up to 12 weeks of treatment) and 48 subjects (four subjects had T2DM) with varying degrees of renal impairment (single dosing). In addition, 22 healthy subjects were exposed to semaglutide (s.c.) in the oral semaglutide administration project (Trials NN9924 3691 and NN9924 3692).

3.3.2.1 Pharmacokinetics

Results from one single dose trial (NN9535-3616) and from 1 multi-dose trial (NN9535-3819) based on the LC-MS/MS assay confirm that semaglutide has pharmacokinetic (PK) properties compatible with once-weekly administration, with a median time to maximum concentration (t_{max}) of 24-36 hours post dosing and an elimination half-life ($t_{½}$) in the range of 166-184 hours (~7-8 days). Overall, the PK properties of semaglutide appear similar in Caucasian and Japanese subjects, and also in healthy subjects and subjects with type 2 diabetes. In a trial with subjects with different degrees of renal impairment (NN9535-3616), data suggested that subjects with severe renal impairment had a slightly higher exposure compared to subjects with normal renal function. Area under curve ($AUC_{0-\infty}$) increased by approximately 22% in subjects with severe renal impairment, whereas subjects with mild or moderate renal impairment and subjects on haemodialysis had exposure similar to subjects with normal renal function. No safety signals were identified in either of the renal groups, and tolerability profiles appeared similar across renal groups; thus, a dose-reduction in subjects with severe renal impairment does not appear to be warranted.

Interaction with oral contraceptives was assessed at semaglutide 1.0 mg steady-state exposures in postmenopausal women with type 2 diabetes (NN9535-3819). Steady-state exposures (AUC0-24h) of ethinylestradiol (EE) and levonorgestrel (LN) were slightly increased, with bioequivalence established for EE but not for LN; the increase was seen when oral contraceptives were co-administered with semaglutide compared to oral contraceptives alone. Bioequivalence was demonstrated for C_{max} of both EE and LN. These data indicate that semaglutide does not decrease the exposure of oral contraceptives, and suggest that no adjustments of oral contraceptive dose are warranted for women of childbearing potential using a low-dose oral contraceptive.

3.3.2.2 Efficacy

As of 06 April 2013, efficacy of semaglutide in the target population - subjects with type 2 diabetes has been investigated in one phase 2 dose range finding trial (NN9535-1821). The trial was a 12-week, randomised, double-blind, placebo- and active-controlled trial in which 411 adults with type 2 diabetes received once-weekly subcutaneous (c) injection of 1 of 5 semaglutide dose levels (0.1-1.6 mg) once-daily s.c. injection of open-label liraglutide (1.2 mg or 1.8 mg) or once-weekly placebo.

12 weeks of treatment, equivalent to 5-7 weeks in steady state on maintenance dose, provided statistically significant and clinically relevant improvement in glycaemic control for dose levels of 0.2 mg and above. Changes in glycosylated haemoglobin (HbA_{1c}) from baseline was up to -1.19 % (placebo adjusted estimated treatment difference). Dose-dependent improvements in fasting plasma glucose (FPG) and postprandial plasma glucose were also observed. The improvement in glycaemic control was accompanied by weight loss for semaglutide doses of 0.8 mg and above (placebo adjusted estimated treatment difference up to -3.64 kg).

3.3.2.3 Safety

From the clinical trials conducted so far the following safety observations have been made. Consistent with findings with other GLP-1 RAs, common adverse events (AEs) included nausea and vomiting; most of them were mild to moderate in intensity. Hypoglycaemia has occurred in subjects receiving semaglutide and these events have mainly been minor. An increase in heart rate has been observed in subjects exposed to semaglutide in line with the increase seen with other GLP-1 analogous. The implications of this increase are unknown. As is the case with all protein based pharmaceuticals, subjects treated with semaglutide may develop immunogenic and allergic reactions. Few allergic reactions have been reported in connection with semaglutide. These have mainly been mild and transient however, more generalised reactions may occur, including urticaria, rash, pruritus and a single case of angioedema which have been observed. Injection site reactions have been infrequently reported. These have mainly been mild and transient in nature.

Please see Investigator's Brochure, semaglutide (NN9535) (subcutaneous administration), Type 2 Diabetes and any updates hereof [28].

3.4 Sitagliptin

Sitagliptin is an oral antihyperglycemic agent of the dipeptidyl peptidase-4 (DPP-4) inhibitor class suitable for once-daily oral administration. It was developed and marketed by Merck & Co as sitagliptin phosphate under the trade name Januvia®

Sitagliptin works by inhibition of the enzyme dipeptidyl peptidase 4 (DPP-4). This enzyme breaks down the incretin hormones GLP-1 and gastric inhibitory polypeptide (GIP). By preventing GLP-1 and GIP inactivation, secretion of insulin is increased and release of glucagon is suppressed. The obvious advantage with a convenient route of administration is however counterbalanced by a significantly lower effect of the DPP-4 inhibitors on glycaemic control and body weight as compared to GLP-1 RAs. This has also been demonstrated for sitagliptin when compared to liraglutide (NN2211-1860).

Adverse reactions reported in >5% of patients treated with sitagliptin and more commonly than in patients treated with placebo are: upper respiratory tract infection, nasopharyngitis and headache. In

add-on to sulfonylurea and add-on to insulin studies, hypoglycaemia was also more commonly reported in patients treated with sitagliptin compared to placebo. (For more information see label [29])

3.5 Risk and benefits assessment

This assessment is based on the safety and efficacy data for semaglutide and sitagliptin presented above as well as potential risk identified as drug class effects.

3.5.1 Semaglutide risks and precautions

The nonclinical safety programme of semaglutide reveals no identified safety issues for humans based on conventional studies of safety pharmacology, repeat-dose toxicity or genotoxicity (see section 3.3.1).

The human relevance of the proliferative C-cell changes found in rodents described in section 3.3.1.1 is unknown, but data suggest that rodents are more sensitive to the mode of action for induction of C-cell tumours with GLP-1 analogues. However, as a precaution subjects with a family or personal history of multiple endocrine neoplasia type 2 (MEN2) or medullary thyroid carcinoma, and subjects with a screening calcitonin ≥50 ng/L will be excluded from trial. During the trial calcitonin will be measured on a regular basis and guidance for investigators of further evaluation and action on elevated plasma calcitonin concentrations will be carried out by an independent group of thyroid experts, the Calcitonin Monitoring Committee (CMC). This will ensure appropriate and consistent handling of elevated calcitonin levels across trials.

Semaglutide has been concluded teratogenic in rats as described in section 3.3.1.2. The mechanism resulting in this effect is not considered relevant for humans. However as a risk for the developing foetus cannot be completely ruled out, subjects fulfilling the following exclusion criteria will be excluded: females of childbearing potential who are pregnant, breast-feeding or intend to become pregnant and females who are not using adequate contraceptive methods (adequate contraceptive measures as required by local law or practice) throughout the trial including the 5 week follow-up period.

Safety data from clinical trials are consistent with findings from other GLP-1 RAs. The most frequently reported AEs in the clinical trials with semaglutide thus far have been gastrointestinal (GI) disorders (nausea, vomiting, diarrhoea, dyspepsia and constipation). A new dose escalation regiment was tested in a phase 1 trial (NN9535-3819) in order to further improve GI tolerability. As the GI tolerability profile was substantially improved this regimen will be implemented in future clinical trials with semaglutide.

As it is the case with all protein based pharmaceuticals subjects treated with semaglutide risk developing immunogenic and allergic reactions. These may include localised reactions or

generalised reactions including urticaria, rash or pruritus. Severe allergic reactions such as anaphylactic reactions could potentially also pose a risk for subjects treated with semaglutide.

As the mode of action of GLP-1 is glucose dependent[10,11] the risk of development of hypoglycaemic event is low. However, hypoglycaemia has occurred in subjects receiving semaglutide and experience from the GLP-1 RA drugs class warrants special caution when semaglutide is combined with sulfonylureas.

Based on current knowledge about the GLP-1 RA drug class two potential risks have been found relevant.

Firstly untoward effects of volume depletion including acute renal failure resulting from nausea, vomiting and dehydration have been observed in subjects treated with GLP-1 RAs. Semaglutide is not metabolised by the kidneys, and treatment has not been associated with impaired renal function in preclinical or clinical studies. However, as a precaution serum creatinine is measured regularly. Impaired renal function may increase the risk of metformin associated lactic acidosis when GLP-1 RAs are co-administered with metformin. If semaglutide and metformin are co-administered, investigator should evaluate subjects with prolonged or severe nausea and vomiting, monitor serum creatinine, if clinically indicated and withhold metformin until resolution of the renal dysfunction.

Secondly acute pancreatitis, including reports of severe necrotising and haemorrhagic forms, has been associated with other GLP-1 RAs. However data from observational studies suggest an increased frequency of pancreatitis among diabetics and a relationship between pancreatitis and GLP-1 RAs can neither be established nor excluded[30,31] . However, as a precaution subjects with a history of acute idiopathic or chronic pancreatitis will be excluded from clinical trials with semaglutide. Subjects will be monitored for elevated levels of amylase and lipase and be informed of the characteristic symptoms of acute pancreatitis.

3.5.2 Sitagliptin risk and precautions

Sitagliptin is generally considered to be well tolerated. The most commonly reported side effect is upper respiratory tract infection and headache. Some of the potential risk associated with GLP-1 RA treatment has also been associated with treatment with the DPP-4 inhibitors as sitagliptin i.e. pancreatitis, acute renal impairment, hypersensitivity reactions and hypoglycaemia (US prescribing information[32] and Chinese prescribing information[33])

3.5.3 Benefits

In this trial subjects in all treatment arms will be treated within a regimen anticipated to be more efficacious than the treatment they receive at the time of randomisation into the trial. It is expected that subjects will benefit from the trial treatment with respect to optimised glycaemic control, a reduced risk of long-term diabetic complications and a potential weight loss.

Semaglutide has in a phase 2 trial (NN9535-1821) proven to have a clinically meaningful and dose-dependent effect on HbA_{1c}, FPG and weight. Doses ≥0.8 mg brought more subjects to target with regards to HbA_{1c} and FPG and provided a greater weight loss than liraglutide 1.8 mg.

Sitagliptin has in phase 3 trials where sitagliptin has been given in combination with metformin proven to provide significant improvements in HbA_{1c} and FPG[34].

All subjects in this trial will receive active treatment and will receive trial drug and auxiliary free of charge.

Furthermore it is expected that all subjects participating in the trial will benefit from participation through close contact with the study site and close follow-up of their type 2 diabetes. Such careful medical examination will most likely result in an intensified management of their diabetes.

3.5.4 Risk and benefit conclusion

It is concluded that the potential benefits from participating in the trial outweigh the potential risks. The safety profile of semaglutide generated from the clinical and nonclinical development programme has not revealed any safety issues that would prohibit administration of once-weekly doses of 0.5 mg or 1.0 mg semaglutide in accordance with the planned clinical trial. Sitagliptin is already a marketed drug in the 100 mg dose and approved for the use in type 2 diabetic patients. It is concluded that the risk to the subjects in this trial is low and acceptable in view of the benefits a long-acting GLP-1 analogue would provide to subjects with type 2 diabetes.

3.6 Rationale for the trial

The currently available treatment modalities for type 2 diabetes are still not satisfactory and there is still a large proportion of patients not reaching the treatment targets despite a high level of compliance with the treatment regimens. Furthermore, there is a segment of patients where either compliance with once-daily treatment regimens is an issue resulting in sub-optimal glycaemic control, or where there is a wish for a more convenient treatment regimen.

The rationale for this trial is to compare the efficacy of semaglutide versus sitagliptin in subjects with type-2 diabetes in terms of glycaemic control, weight loss and other efficacy parameters. Furthermore the trial is designed to address and compare safety, tolerability and patient satisfaction. This trial is designed to resemble the main trial NN9535-3626 (SUSTAIN™ 2) in the global SUSTAIN™ programme and will be conducted in China and several other countries . The study design is adjusted to fulfil the Chinese requirements.

4 Objectives and endpoints

4.1 Objective

4.1.1 Primary objective

To compare the effect of once-weekly dosing of two dose levels of semaglutide versus sitagliptin 100 mg once-daily on glycaemic control after 30 weeks of treatment

4.1.2 Secondary objectives

To compare the effects of once-weekly dosing of two dose levels of semaglutide versus sitagliptin 100 mg once-daily after 30 weeks of treatment on:

- Inducing and maintaining weight loss
- Other parameters of efficacy, safety and tolerability

4.2 Endpoints

4.2.1 Primary endpoint

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

4.2.2 Secondary endpoints

4.2.2.1 Confirmatory secondary endpoint

- Change from baseline to week 30 in body weight

4.2.2.2 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)
- Insulin, C-peptide, glucagon, pro-insulin, pro-insulin/insulin ratio, homeostasis model assessment of beta-cell function (HOMA-B) and insulin resistance (HOMA-IR) (all fasting)
- Fasting blood lipids (total cholesterol, low density lipoprotein (LDL) cholesterol, very low density lipoprotein (VLDL) cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides and free fatty acids
- Body mass index (BMI)
- Waist circumference
- Systolic and diastolic blood pressure*

- Highly sensitive C-reactive protein (hsCRP)
- Patient reported outcome (PRO) questionnaire: SF-36v2™ score
- Patient reported outcome (PRO) questionnaire: Diabetes Treatment Satisfaction Questionnaire status (DTSQs) score*

Subjects who after 30 weeks treatment achieve (yes/no):

- $HbA_{1c} < 7.0\%$ (53 mmol/mol) - American Diabetes Association (ADA) target
- $HbA_{1c} \leq 6.5\%$ (48 mmol/mol) - American Association of Clinical Endocrinologists (AACE) target*
- Weight loss $\geq 5\%$
- Weight loss $\geq 10\%$
- $HbA_{1c} < 7.0\%$ (53 mmol/mol) without severe or blood glucose (BG) confirmed symptomatic hypoglycaemia and no weight gain

Supportive secondary safety endpoints

- Number of treatment emergent adverse events (TEAEs) during 30 weeks of treatment
- Number of treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes during 30 weeks of treatment
- Severe or BG confirmed symptomatic hypoglycaemic episodes during 30 weeks of treatment (yes/no)

Change from baseline to week 30 in:

- Haematology
- Biochemistry
- Calcitonin
- Urinalysis
- Urinary albumin to creatinine ratio (UACR)
- Pulse
- Electrocardiogram (ECG) evaluation
- Physical examination

Occurrence of anti-semaglutide antibodies during 30 weeks of study duration (yes/no):

- Anti-semaglutide antibodies with *in vitro* neutralising effect
- Anti-semaglutide antibodies cross reacting with endogenous GLP-1
    - Cross reacting antibodies with *in vitro* neutralising effect to endogenous GLP-1

Antibody level during and after 30 weeks of treatment

*Key supportive secondary endpoint prospectively selected for posting on clinicaltrials.gov.

5 Trial design

5.1 Type of trial

This is a 30-week randomised, double-blind, double-dummy, active-controlled, multi-centre, multi-national trial, four-armed, parallel-group trial comparing semaglutide 0.5 mg and 1.0 mg once-weekly against sitagliptin 100 mg once-daily.

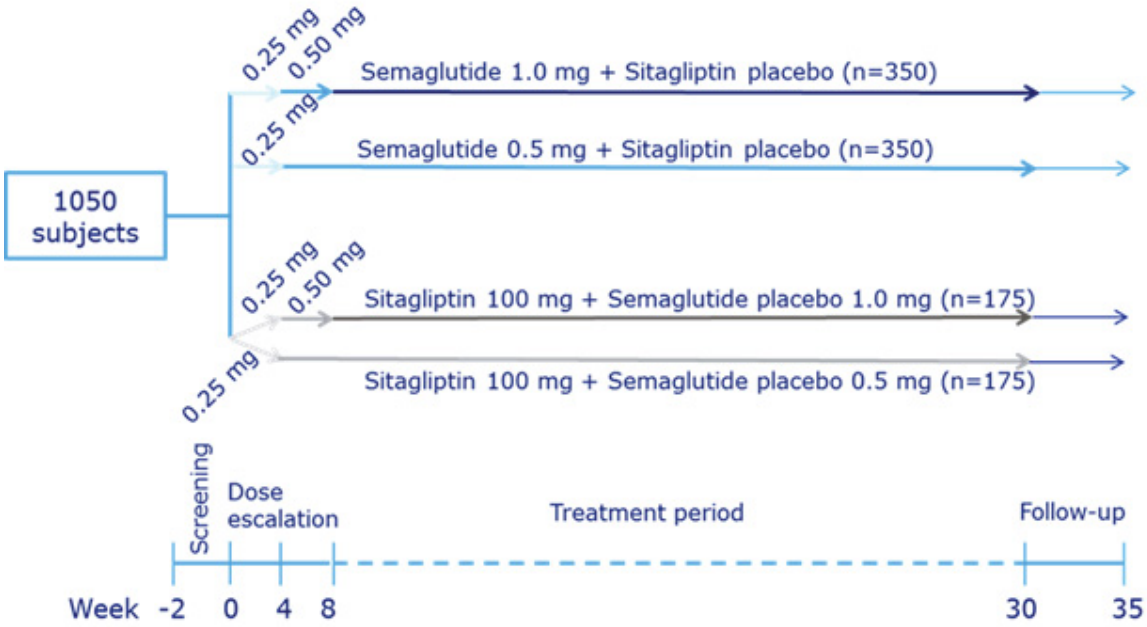


Figure 5–1 Trial design

Subjects with type 2 diabetes inadequately controlled on metformin will be randomised in a 2:2:1:1 manner to receive either:

- semaglutide 0.5 mg once-weekly + sitagliptin placebo once-daily
- semaglutide 1.0 mg once-weekly + sitagliptin placebo once-daily
- sitagliptin 100 mg once-daily + semaglutide placebo (0.5) mg once-weekly
- sitagliptin 100 mg once-daily + semaglutide placebo (1.0) mg once-weekly

The total trial duration for the individual subjects will be approximately 37 weeks. The trial includes a 2-week screening period followed by a 30-week randomised treatment period and a 5 week follow-up period.

A planned total of 1050 subjects will be randomised whereof approximately 792 subjects will be from China. Randomisation will be stratified by country.

5.2 Rationale for trial design

Parallel treatment groups and a randomised double-blind double dummy controlled design have been chosen in accordance with trial objectives and to avoid bias in the trial.

Treatment duration of 30 weeks is considered adequate in terms of assessing efficacy of semaglutide treatment versus sitagliptin treatment on change in HbA_{1c}. Furthermore, 30 weeks is considered sufficient for addressing and comparing the safety, tolerability and patient satisfaction profiles.

5.3 Treatment of subjects

Trial periods		Screening	Period 1	Period 2	Period 3	Follow-up
Alias for trial period		Screening	Dose escalation	Dose escalation/ Maintenance	Maintenance	Follow-up
Visits in each period		Visit 1-2	Visit 2-3	Visit 3-5	Visit 5-9	Visit 9-10
Duration of each period		2 weeks	4 weeks	4 weeks	22 weeks	5 weeks
Treatment arm	**N**					
• Semaglutide 0.5 mg • Sitagliptin placebo	350	Screening	• Semaglutide 0.25 mg, 1.34 mg/mL, 190µL • Sitagliptin placebo	• Semaglutide 0.5 mg, 1.34 mg/mL, 370µL • Sitagliptin placebo	• Semaglutide 0.5 mg, 1.34 mg/mL, 370µL • Sitagliptin placebo	Follow-up
• Semaglutide 1.0 mg • Sitagliptin placebo	350	Screening	• Semaglutide 0.25 mg, 1.34 mg/mL, 190µL • Sitagliptin placebo	• Semaglutide 0.5 mg, 1.34 mg/mL, 370µL • Sitagliptin placebo	• Semaglutide 1.0 mg, 1.34 mg/mL, 740µL • Sitagliptin placebo	Follow-up
• Sitagliptin • Semaglutide placebo (0.5 mg)	175	Screening	• Sitagliptin 100 mg • Semaglutide placebo 0 mg, 190µL	• Sitagliptin 100 mg • Semaglutide placebo 0 mg, 370µL	• Sitagliptin 100 mg • Semaglutide placebo 0 mg, 370µL	Follow-up
• Sitagliptin • Semaglutide placebo (1.0 mg)	175	Screening	• Sitagliptin 100 mg • Semaglutide placebo 0 mg, 190µL	• Sitagliptin 100 mg • Semaglutide placebo 0 mg, 370µL	• Sitagliptin 100 mg • Semaglutide placebo 0 mg, 740µL	Follow-up
All on background medication of metformin ≥ 1500 mg (or maximum tolerated dose ≥ 1000 mg) throughout the trial.						

Table 5–1 Treatment of subjects

After randomisation subjects will follow a fixed dose escalation for semaglutide and semaglutide placebo. The maintenance dose of 0.5 mg will be reached after 4 doses (4 weeks) of 0.25 mg. The maintenance dose of 1.0 mg will be reached after 4 doses (4 weeks) of 0.25 mg, followed by 4

doses (4 weeks) of 0.5 mg. Doses must not be changed during the trial after the maintenance dose has been reached.

Semaglutide injections should be administered in the thigh, abdomen or upper arm, and should be taken on the same day of the week during the trial. Both semaglutide and sitagliptin can be taken any time of day irrespective of meals.

If necessary, the trial product may be discontinued for safety reasons. In case trial product is discontinued, subjects will not be withdrawn from trial but should continue to follow scheduled visits to the extent possible (see section 6.5.1).

Trial product will be add-on in subjects failing on metformin monotherapy.

Subjects must not be prescribed other GLP-1 RA in the period between V9 and V10 or V9A and V10A.

5.3.1 Missed dose

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

5.3.2 Background medication

Subjects should upon inclusion continue pre-trial background medication throughout the entire trial. The background medication should be maintained at the stable, pre-trial dose and frequency during the whole treatment period unless rescue medication is needed (see section 6.4).

Metformin is considered background medication (non-investigational medicinal product) and will not be provided by Novo Nordisk A/S (except for Brazil where Metformin will be provided by Novo Nordisk Farmacêutica do Brasil Ltda). Metformin should be used in accordance with standard of care in the individual country at the discretion of the investigator and the daily dose should be unchanged throughout the trial unless the rescue criteria is met. However the maximum approved dose in the individual country must not be exceeded. Treatment with metformin extended/slow release formulations is allowed.

5.3.3 Treatment after end of trial

When discontinuing trial products the subject should be switched to a suitable marketed product at the discretion of the investigator. (Brazil: After the study ending, if the investigator decides that the study medication is the best treatment option for the subject, the access to the study medication will be assured by the trial sponsor at no costs, according to the current regulations of Brazilian National Council of Health and Health Authority).

5.4 Rationale for treatment

Semaglutide has been developed for s.c. administration. The doses of 0.5 mg and 1.0 mg once-weekly has been chosen based on careful evaluation to strike a satisfactory balance of efficacy and safety that would satisfy the majority of patients. Hence duration and the dose of the randomised treatments are considered adequate for obtaining meaningful information on efficacy and safety in accordance with the trial objectives. Subjects will enrol for a treatment period of 30 weeks in order to be able to evaluate full effect as well as durability of the primary and secondary endpoints as well as a reasonable safety assessment.

For further information please refer to Investigator's Brochure, semaglutide (NN9535) (subcutaneous administration), Type 2 Diabetes and any updates hereof[28].

6 Trial population

6.1 Number of subjects

Planned number of subjects to be screened (i.e. documented informed consent):	Up to 1750
Planned number of subjects to be randomised:	1050
Expected number of subjects to complete the trial:	840
Planned number of Chinese subjects to be randomised:	792
Expected number of Chinese subjects to complete the trial:	636

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. Subjects diagnosed with type 2 diabetes and on stable treatment in a period of 60 days prior to screening with metformin ≥ 1500 mg (or maximum tolerated dose ≥ 1000 mg). Stable is defined as unchanged medication and unchanged daily dose
4. HbA_{1c} 7.0 – 10.5 % (53-91 mmol/mol) (both inclusive)

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 informed consent
3. Female who is pregnant, breast-feeding or intends to become pregnant or is of childbearing potential not using an adequate contraceptive method throughout the trial including the 5 week follow-up period (adequate contraceptive measure as required by local regulation or practice) (China: Sterilization, intrauterine device (IUD), oral contraceptives or barrier methods). (Brazil: For women who expressly declare free of the risk of pregnancy, either by not engaging in sexual activity or by having sexual activity with no birth potential risk, use of contraceptive method will not be mandatory).
4. Receipt of any investigational medicinal product within 90 days before screening (Brazil, Participation in other trials within one year prior to screening visit (V1) unless there is a direct benefit to the research subject at the Investigator´s discretion)

5. Any disorder which, in the opinion of the investigator, might jeopardise subject's safety or compliance with the protocol
6. Treatment with glucose lowering agent(s) other than stated in the inclusion criteria in a period of 60 days before screening. An exception is short-term treatment (≤7 days in total) with insulin in connection with inter-current illness
7. Use of non-herbal Chinese medicine or other non-herbal local medicine with unknown/unspecified content. Herbal traditional Chinese medicine or other local herbal medicines may, at the Investigator's discretion, be continued throughout the trial
8. History of pancreatitis (acute or chronic)
9. Screening calcitonin value ≥ 50 ng/L (pg/mL)
10. Personal or family history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia syndrome type 2 (MEN 2)
11. Impaired renal function defined as eGFR < 60 ml/min/1.73 m2 per MDRD formula (4 variable version)
12. Acute coronary or cerebrovascular event within 90 days before randomisation
13. Heart failure, New York Heart Association (NYHA) class IV
14. Known proliferative retinopathy or maculopathy requiring acute treatment according to the opinion of the investigator
15. Diagnosis of malignant neoplasm in the previous 5 years (except basal cell skin cancer or squamous cell skin cancer)
16. Mental inability, unwillingness or language barrier precluding adequate understanding of or compliance with study procedures

6.4 Rescue criteria

If any of the fasting plasma glucose (FPG) values exceed the limits outlined below and no intercurrent cause of the hyperglycaemia can be identified the subject should be called for an unscheduled visit as soon as possible:

- 15.0 mmol/L (270 mg/dl) from week 0 to end of week 5
- 13.3 mmol/L (240 mg/dl) from week 6 to end of Week 11
- 11.1 mmol/L (200 mg/dl) from week 12 to end of trial

A confirmatory FPG should be obtained. If the confirmatory FPG exceeds the values described above the subject should be offered treatment intensification (rescue medication) at the discretion of the investigator and in accordance with ADA/European Association for the Study of Diabetes (preferably excluding GLP-1 RAs, DPP-4 inhibitors and amylin analogues). Rescue medication (intensification of existing background medication and/or initiation of new medication) and any changes hereto should be captured on the concomitant medication form in the eCRF. Rescue medication should be prescribed as add-on to randomized treatment unless contraindicated according to the local sitagliptin label. In this case trial medication should be discontinued before

initiation of rescue therapy. Subjects should continue to follow the protocol-specified visit schedule even if rescue treatment has been initiated.

6.5 Withdrawal criteria

6.5.1 Discontinuation of trial product

All efforts should be made to keep the subjects on trial product. However in case of a safety concern or unacceptable intolerability the trial product may be discontinued at the investigator's discretion.

Trial product must be discontinued in case of:

- included in the trial in violation of any of the inclusion and/or exclusion criteria
- Pregnancy
- Intention to become pregnant

For procedure to be performed in case of discontinuation of trial product (see section 8.1.6.2). In case of suspicion of acute pancreatitis (see section 8.8.1.4).

Subjects discontinuing trial product prematurely should continue with the scheduled site contact. If necessary, in order to retain the subject in the trial, site visits can be replaced by phone contacts after discontinuation of trial product. As minimum these subjects should be asked to attend the visits end of treatment (V9) and follow up (V10) at the time of the scheduled completion of the trial.

Subjects discontinuing trial product prematurely will be called in for an end of treatment – premature discontinuation visit (V9A), as soon as possible after discontinuation of trial product, and for a follow-up - premature discontinuation visit (V10A) five weeks after last dose of trial product (see section 2 and 8.1.6.2).

Subjects discontinued from trial product should be prescribed alternative therapy at the investigator´s discretion. However subjects must not be prescribed other GLP-1 RA in the period between V9 and V10 or V9A and V10A.

6.5.2 Withdrawal from trial

The subject may withdraw at will at any time. Please see section 8.1.7 for procedure to be performed in case of subject withdrawal.

Subjects should stay in the trial irrespective of lack of adherence to randomised treatment, lack of adherence to visit schedule, missing assessments, trial product discontinuation due to AE (see section 6.5.1), unwillingness to cope with injection regimen, development of co-morbidities or clinical outcomes.

A subject who agrees to provide information concerning morbidities which are relevant for the assessments of cardiovascular outcomes and/or other trial end-points at the planned end of the trial should not be considered withdrawn from the trial.

Subjects who consider withdrawing from the trial should as a minimum be encouraged to have procedures performed according to the end of treatment visit(V9) and the follow up visit(V10), please see 8.1.7.

Only subjects who decline any further contact with the site in relation to the trial, and hence do not agree to report information which is relevant for the assessments of cardiovascular outcomes and/or other trial end-points at the end of trial should be considered as withdrawn from the trial.

6.6 Subject replacement

Subjects who are withdrawn will not be replaced.

6.7 Rationale for trial population

This trial will be carried out in China and several other countries. The aim is to include a broad diabetes population, hence the limited number of exclusion criteria. Subjects with type 2 diabetes who are inadequately controlled on metformin monotherapy will be included in the trial. As sitagliptin is indicated as monotherapy or in combination with metformin in China, subjects on other OADs are not included.

7 Milestones

Planned duration of recruitment period (i.e. FPFV– LPFV): 26 weeks

End of trial is defined as last patient last visit.

Planned date for first patient first visit (FPFV): 28-Apr-2016

Planned date for last patient first visit (LPFV): 27-Oct-2016

Planned date for last patient last visit (LPLV): 13-July-2017

To ensure that only the required number of subjects is randomised, screened subjects will be monitored closely via interactive voice response system/interactive web response system (IV/WRS).

A recruitment strategy will be developed in corporation with the participating countries to secure sufficient number of subjects from China and the other participating countries.

Recruitment will be monitored on an on-going basis by sponsor. Prior to FPFV all sites should have a recruitment strategy in place detailing how many subjects they can recruit within a certain period. If a site has not enrolled the number of subjects according to the recruitment strategy, the remaining subjects may be reallocated.

The screening and randomisation rate will be followed closely via IV/WRS in order to estimate when to stop screening. All investigators will be notified immediately when the enrolment period comes to an end, after which no subjects must be screened, and the IV/WRS will be closed for further screening. All subjects included in the screening period by the time of IV/WRS closure and eligible for randomisation will be randomised.

Trial registration:

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

8 Methods and assessments

8.1 Visit procedures

The following sections describe the assessments and procedures. These are also included in the flow chart (see section 2).

The investigator must keep a subject screening log, a subject identification code list and a subject enrolment log. The subject screening log and subject enrolment log may be combined in one list and may be generated from the IV/WRS.

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

8.1.1 Screening visit 1 (V1)

For procedures and assessments performed at screening, please see flow chart (see section 2).

The IV/WRS must be contacted to register the subject as screened (see section 10). Subject will be assigned a unique number (lowest available number allocated to site) which is maintained throughout the trial. It must be stated in the medical record that the subject is participating in the current trial.

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. The subjects should be reminded to show the card to other health care providers, as applicable.

Once all data relating to screening V1 have been obtained, these must be reviewed by the investigator to ensure that the subject is eligible to continue the trial.

Ability and willingness to self-inject can be tested by administration of injection(s) with a test pen (containing semaglutide placebo) for subjects who do not have prior experience with self-injection.

8.1.1.1 Screen failures

For screening failures the screening failure form 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 case report form eCRF. Follow-up of SAEs must be carried out according to section 12.

A screening failure session must be made in the IV/WRS. The case book must be signed in eCRF.

8.1.1.2 Re-screening

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

8.1.2 Fasting visits

The subjects should attend several visits in a fasting state (see section 2). Fasting is defined as having consumed only water since midnight. Glucose lowering agents and trial product cannot be taken until after blood sampling has been performed but other prescribed medication should be taken. An exception from this is the follow-up visit (V10) and follow-up premature discontinuation visit (V10A) where fasting is defined as having consumed only water within the last two hours prior to the visit. If the subject is not fasting as required, the subject should be called in for a new visit within the visit window to have the fasting procedures done.

8.1.3 Randomisation V2

For procedures and assessments performed at randomisation (see section 2).

Visit 2 will take place two weeks (±7 days) after screening V1.

Eligible subjects will be randomised into one of four treatment arms. The IV/WRS will allocate the dispensing unit number (DUN) of trial product to be dispensed to the subject.

Trial product will be dispensed to the subject by the site, hospital pharmacy or equivalent with different intervals during the trial. Subject will be instructed in administration of sc injection of trial product and the investigator must document that a direction for use (DFU) is given orally and/or in writing at each dispensing visit. Date, time and dose of first administration of trial product will be captured in the eCRF.

Please see section 9 for further information about the trial product.

8.1.4 Visits

For visit numbers, timing of site visits, phone contacts and visit windows during the trial period, please refer to the flow chart (see section 2). Planned visits can be re-scheduled within the allowed visit window.

It is the responsibility of the investigator to ensure that all site visits and phone contacts occur according to the flow chart (2).

8.1.5 Missed visits and unscheduled visits

If a visit is missed and it is not possible to re-schedule, every effort should be made to ensure information is collected at a telephone contact. Subjects will be invited for the next scheduled visit according to visit schedule.

If a subject is unable or unwilling to attend the subsequent visit(s) the investigator should aim to at least have the subject attending the end of treatment visit and follow-up visit as these two visits should be performed for all subjects regardless of compliance with the protocol and adherence to the treatment (see section 8.1.6).

If a subject attends the clinic for a visit not described in the protocol, an unscheduled visit form must be completed. This only applies if assessments are done, hence not for the purpose of re-test of blood- or urine sampling, or re-supply of trial product. In case of re-supply a dispensing session should be made in the IV/WRS selecting additional medication. Re-scheduling of fasting visit samples is not considered as an unscheduled visit.

8.1.6 End of treatment (V9/9A) and Follow-up (V10/10A)

8.1.6.1 Subjects completing the treatment period as per protocol

An end of treatment visit (V9) should be scheduled when the subject has completed the treatment period as described per protocol and a follow-up visit (V10) should be performed at least 5 weeks after (+7 days visit window). Please see the flow chart for details (section 2).

The follow-up visit serves to collect AEs, technical complaints, hypoglycaemic episodes, ECG, concomitant medication and blood sampling for anti-semaglutide antibodies .

8.1.6.2 Subjects who prematurely discontinue trial product

For subjects who discontinue trial product prematurely the visit end of treatment – premature discontinuation (V9A) should be scheduled shortly after subject has discontinued trial product. The visit follow-up – premature discontinuation (V10A) should be scheduled at least 5 weeks after discontinuation of trial product (+7 days visit window). Please see the flow chart for details (section 2).

Subjects discontinuing trial product prematurely should continue with the scheduled site contacts. If necessary, in order to retain the subject in the trial, site visits can be replaced by phone contacts after discontinuation of trial product. However, as a minimum these subjects will be called in for end of treatment (V9) and follow-up (V10) at the time of the scheduled completion of the trial.

8.1.7 Withdrawals

If the subject fulfils the withdrawal criterion, the investigator must ask the subject to attend the End of Treatment visit (visit 9), as soon as possible, and the Follow Up visit (visit 10) at least 5 weeks after but not more than 6 weeks after, if possible.

The End of Trial form must be completed and final drug accountability must be performed even if the subject is not able to come to the site. The case book must be signed by the investigator in eCRF and a premature discontinuation of trial product session must be made in the IV/WRS (see section 10). The case book must be signed by the investigator in the eCRF.

Although a subject is not obliged to give his/her reason(s) for withdrawing from a trial, the investigator must make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights. Where the reasons are obtained, the primary reason for not completing the trial must be specified on the end-of-trial form in the CRF (see section 6.5).

Subjects who withdraw will be asked to allow the investigator to contact their family doctor at planned end of trial by having consented to this.

8.1.8 Investigator's assessment

Review of diaries, patient reported outcomes (PROs), laboratory reports, ECGs, eye examination (fundoscopy/fundus photography), physical examination etc. must be documented either on the front page of the documents and/or in the subject's medical record. The signed documents must be retained at the site as source documentation.

For ECGs, physical examinations and eye examinations the evaluations must follow the categories:

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

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

In case of abnormal clinical significant findings found as a result of screening procedures conducted at V1 or assessments revealing baseline conditions at V2 the investigator must state a comment in the subjects 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 site staff must review the diary to ensure that AEs, including overall change in health and concomitant medication are reported.

If clarification of entries or discrepancies in the diary or patient reported outcomes (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.

8.2 Subject related information

8.2.1 Demography

The following information must to be recorded in the subject's medical record and will be transcribed into eCRF at screening V1:

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

8.2.2 Diagnosis of diabetes

The following information must to be recorded in the subject's medical record and will be transcribed into eCRF at screening V1:

- Date of diagnosis of type 2 diabetes.

8.2.3 Diabetes treatment history

The following information must be recorded in the subject's medical record and will be transcribed into eCRF at screening V1:

- Current diabetes treatment
- Dose of current diabetes treatment
- Start date of current diabetes treatment

8.2.4 Diabetes complications

The following information related to signs or symptoms of microvascular complications of diabetes must be recorded in the subject's medical record and will be transcribed into eCRF at screening V1:

- Diabetic nephropathy
- Diabetic retinopathy
- Diabetic neuropathy
- macroangiopathy including peripheral vascular disease
- other complications where relevant

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.

8.2.5 Concomitant illness and medical history

A **concomitant illness** is any illness that is present at the start of the trial (V1).

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

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

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

Concomitant illness and medical history must be recorded in the subject's medical record and will be transcribed into eCRF .

8.2.6 History of cardiovascular disease

Information related to history of cardiovascular disease (CVD) (i.e. heart failure incl. New York Heart Association class, hypertension or ischaemic stroke) or other risk factors for CVD must be recorded in the subjects medical record and will be transcribed into eCRF at screening V1. Please refer to Appendix A for detailed information of CVD.

8.2.7 History of gallbladder disease

Information related to gallbladder disease(. ie pancreatitis, gallstone disease, cholecystitis) must be recorded in the subjects medical record and will be transcribed into the eCRF at screening V1.

8.2.8 Smoking habits

Details of smoking habit must be recorded in the subject's medical record at V1. Smoking is defined as smoking at least one cigarette, cigar or pipe daily.

It must be recorded whether the subject is a smoker according to the following criteria:

- Never smoked
- Is a previous smoker
  - cessation date
  - average cigarettes per day
  - approximate years of smoking
- Is a current smoker
  - average cigarettes per day
  - approximate years of smoking

8.2.9 Concomitant medication

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

Details of any concomitant medication must be recorded in the eCRF at V1. Changes in concomitant medication, including rescue medication and anti-diabetic medication(s) prescribed at the end of the treatment (follow-up period), must be recorded at each visit as they occur.

The information collected for each concomitant medication includes trade name or generic name, indication, start date and stop date or continuation and for anti-diabetic medication also total daily dose.

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

8.2.10 Fundoscopy/fundus photography

Fundoscopy/fundus photography will be performed as per flow chart by the investigator or according to local practise. Results of the fundoscopy/fundus photography will be interpreted by the investigator (see section 8.1.8). Dilation is not required.

If a fundoscopy/fundus photography has been performed within 90 days before randomisation the procedure does not need to be repeated, unless worsening of visual function since the last examination. The results must be available prior to randomisation.

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

8.2.11 Height

Height is measured without shoes in centimetres or inches and recorded in the eCRF to nearest ½ cm or 1/4 inch.

8.3 Assessments for efficacy

8.3.1 Body weight

Body weight must be measured in kilograms (kg) or pound(lb), with one decimal. The body weight should be measured without shoes and only wearing light clothing.

The same scale should preferably be used throughout the trial.

8.3.2 Waist circumference

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

Three consecutive measurements of waist circumference should be performed and recorded in the eCRF. The waist circumference will be measured in cm to the nearest ½ cm using a non-stretchable measuring tape (measuring tapes will be provided to the sites).

The subject 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 and twists in the tape should be avoided. The subject should be asked to breathe normally and the measurement should be taken when the subject is breathing out gently.

8.3.3 BMI

BMI will be calculated by the eCRF using the equation as listed below:

BMI kg/m^2 = Body weight (kg)/(Height (m) x Height (m)) or (kg/m^2 = [lb/in^2 x 703])

8.3.4 Systolic and diastolic blood pressure

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

- Avoid caffeine, smoking and exercise at least 30 minutes prior to measuring the blood pressure
- The blood pressure should be measured in a sitting position, with the legs uncrossed, the back and arms supported
- Subjects should be sitting for five minutes before the measurement is taken
- Subject or the observer should not talk during the measurement

It is recommended to use the same arm as used at V1 for subsequent measurements.

8.4 Assessments for safety

The timing of the assessments for safety are outlined in the flow chart (see section 2).

8.4.1 Adverse events

AEs must be recorded at each visit in accordance with the procedures outlined in section 12.

Any clinically significant worsening from baseline of a previous finding must be reported as an AE.

8.4.2 Hypoglycaemic episodes

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

All plasma glucose values:

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

should be recorded by the subject in the diary. These must be transcribed into the eCRF (hypoglycaemic episode form) throughout the trial from V1 to V10/10A.

The record should include the following information:

- Date and time of hypoglycaemic episode
- The plasma glucose level before treating the episode (if available)
- Whether the episode was symptomatic
- Whether the subject was able to treat him/herself, if No:
  - What treatment was administered by another person (oral carbohydrates, glucagon, IV glucose, other)
  - Where was the treatment administered (at home, paramedical care, emergency room, hospital, other)
  - What symptoms were associated with the hypoglycaemic episode (sweating, trembling, hunger, palpitations, confusion, drowsiness, speech difficulty, visual disturbances, odd behaviour, impaired balance, incoordination, headache, malaise, seizure, other)

  - Was the subject unconscious/comatose
  - Did the symptoms alleviate after treatment
- Type, date and time of last trial product and other antidiabetic drug(s) administrated prior to episode
  - Whether any of the above were related to a deviation from the prescribed dose of the antidiabetic drug(s)
- Date and time of last main meal prior to episode
- Whether the episode occurred in relation to exercise

The answer to the question: "Was subject able to treat him/herself?" must be answered "No" for an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration [38] .

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

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

8.4.3 Electrocardiogram

12-lead electrocardiograms (ECG) will be performed locally by the investigator or delegated staff during the trial (see section 2). The ECG print out must be interpreted, dated and signed by investigator as described in section 8.1.8. ECG printed is source documentation.

Additional unscheduled ECG recordings can be performed at the investigator´s site at investigator´s discretion at other visits than the planned ECG visits.

8.4.4 Physical examination

A physical examination will be performed by the investigator according to local procedure (see section 2). A physical examination must include:

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

8.4.5 Pulse

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

8.5 Laboratory assessments

For laboratory analysis of efficacy and safety parameters will be drawn during the 37 weeks of the trial. The laboratory analyses will be performed by a central laboratory except for anti-semaglutide antibodies and IgE antibodies where a special laboratory will be used. In the situation described in section (8.8.1.4) and (8.8.1.5) a local laboratory will be used. Laboratory samples comprise both urine and blood samples.

Descriptions of assay methods, laboratory supplies and procedures for collecting, handling, storage and shipping of samples and information regarding who will perform the assessments will be

described in the laboratory manual provided by the central laboratory (for central and special laboratory details, see Attachment I).

Samples will be coded in order to keep subject identity anonymous.

Laboratory samples may be drawn at another day than on the day of the actual visit as long as it is within the visit window outlined in the flow chart (see section 2).Please note that a laboratory sample pertaining to a specific visit must always be reported to that visit.

For some of the samples drawn during the trial it is required for the sensitivity of the analysis, that the subject is fasting.

Central laboratory will provide laboratory results 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 section 12. An exception to this is that anti-semaglutide antibody result will not be available to the investigator during the trial. However these results will be provided to the investigator upon request after the completion of the clinical trial report(CTR).

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 must be reported to the investigator.

All laboratory samples will be destroyed on an on-going basis after analysis and no later than CTR, except for samples taken for anti-semaglutide antibody samples, which will be kept until market authorisation approval or rejection of file. (Brazil, due to local regulation (Resolution 441/11 from National Council of Health), the laboratory samples for Brazilian subjects will be destroyed at the latest at the completion of the CTR, including samples for anti-semaglutide antibody analysis. No sample will be stored after the completion of CTR).

The investigator should ensure that the last samples are shipped to the central laboratory within 24 hours after the last subject visit last at the site.

8.5.1 Laboratory assessments for efficacy

Blood samples be drawn according to flow chart (see section 2) and analysed at the central laboratory to determine levels of the following efficacy laboratory parameters:

8.5.1.1 Glucose metabolism

- HbA_{1c}
- Fasting plasma glucose
- Fasting insulin
- Fasting C-peptide
- Fasting glucagon
- Fasting pro-insulin

8.5.1.2 Biomarker

- hsCRP

8.5.1.3 Lipids (all fasting)

- Total cholesterol
- LDL-cholesterol
- VLDL-cholesterol
- HDL-cholesterol
- Triglycerides
- Free fatty acids

8.5.1.4 Self measured plasma glucose (SMPG) 7 point profile

When using blood glucose meters the measurement is performed with capillary blood calibrated to plasma equivalent glucose values i.e. the measurement is performed on blood while the value is reported as plasma. It is important to be aware of this difference throughout the protocol.

The subject will be instructed to perform a SMPG 7-point profile twice during the trial (see section 2) on a day where the subject does not anticipate unusual strenuous exercise.

At screening V1 subjects will be provided with a blood glucose meter including lancets, plasma-calibrated test strips and control solutions. Oral and written directions for use of the device including the performance of calibrations according to the manufacturer's instructions will be provided to the subject. Sites should as necessary, repeat the directions for use to the subject at subsequent visits.

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

Subjects should be instructed in how to record the results of the SMBGs in the diaries. The record of each SMBG should include date and value. The record of each SMBG measurement should include date, time and value at the following seven time points: before and 90 minutes after the start

of breakfast, lunch, dinner, and at bedtime. All data from the diary must be transcribed into the eCRF during or following the contact.

8.5.2 Laboratory assessments for safety

Blood samples be drawn according to flow chart (see section 2) and analysed at the central laboratory to determine levels of the following safety laboratory parameters: anti-semaglutide antibodies, biochemistry, haematology, calcitonin, pregnancy test and urinalysis.

8.5.2.1 Anti-semaglutide antibodies

Blood samples will be drawn for measurement of serum antibodies to semaglutide at selected visits in randomised subjects. Positive anti-semaglutide antibody samples will be further characterised for cross reactivity to native GLP-1 (see section 2). Samples taken at follow-up which are positive for anti-semaglutide antibodies will be further characterised for in vitro neutralising effect towards semaglutide. In addition, samples taken at follow-up which are positive for cross-reactivity against native GLP-1 will be further analysed for in vitro neutralising effect towards native GLP-1.

Follow-up antibody (taken at the follow-up V10/10A) samples must be taken fasting (as a minimum by only having consumed water for at least two hours).

8.5.2.2 Biochemistry

- Creatinine
- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Alkaline phosphatase
- Sodium
- Potassium
- Albumin
- Bilirubin (total)
- Total protein
- Urea
- Creatine kinase
- Calcium total
- Calcium, albumin corrected (calcium, ionized)
- Lipase
- Amylase

8.5.2.3 Haematology

- Haemoglobin
- Haematocrit
- Thrombocytes
- Erythrocytes
- Leucocytes
- Differential count:
    - eosinophils
    - neutrophils
    - basophils
    - monocytes

- lymphocytes

8.5.2.4 Calcitonin

Blood samples for the measurement of calcitonin concentration will be drawn as per flow chart (see section 2). Calcitonin values ≥20 ng/L will be submitted to an independent committee of thyroid experts. The CMC will provide guidance to the investigator with regards to treatment and further investigations. It is recommended that screening failure subjects with a calcitonin value ≥10 ng/L are referred to a thyroid expert for further evaluation. For details please refer to Appendix B.

8.5.2.5 Pregnancy test

Females of childbearing potential will have a serum pregnancy test (beta-hCG) performed as specified in section 2 or as required by local law.

During the trial urine pregnancy tests must be performed at home for females of childbearing potential, if a menstrual period is missed or as required by local law.

Pregnancy testing will not be required (unless required by local law) for subjects who are postmenopausal (defined as women who have undergone a hysterectomy, bilateral oophorectomy or bilateral tubal ligation or for women above the age of 50, who have been without menstrual period for at least 1 year).

8.5.2.6 Urinalysis

The first morning urine sample will be taken during the trial (see section 2) and analysed at the central laboratory to determine levels of the following parameters:

- Urinary albumin to creatinine ratio (UACR)
- Urinalysis by urine dip-stick: erythrocytes, protein, glucose and ketones, pH

8.6 Other assessments

8.6.1 Patient reported Outcome questionnaires

The following PRO questionnaires will be used in this trial:

- SF-36v2TM
- DTSQs

The questionnaires should be completed by the subject as specified in the flow chart (see section 2), preferably before any other trial related activities. It takes approximately 10 minutes to complete each questionnaire. The assessment must be reviewed as described in section 8.1.8. All results from the PRO questionnaires must be transcribed into the eCRF.

The PRO questionnaire will be used to assess subjects overall Health related Quality of Life and can also be used to estimate Quality Adjusted Life years (QALY) which is used in cost effectiveness calculations.

8.6.1.1 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 QALY which is used in cost effectiveness calculations. This instrument contains 36 items and measures the individual overall health related quality of life on 8 domains; physical functioning, role functioning, bodily pain, general health, vitality, social functioning, role emotional and mental health.

8.6.1.2 DTSQs

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

8.6.2 Subject diary

The subject must be provided with paper diaries at all visits, except the follow-up visit (V10 and V10A). If a subject prematurely discontinues trial product, diaries should not be dispensed and filled out by the subjects after the follow-up – premature discontinuation visit. For these subjects all available data will be collected. Entries in the diaries are only to be made by the subject, unless otherwise specified.

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

- date, time, dose and injection site of first dose of trial product.
- date, time and dose of last injection of trial product prior to each visit/phone contact
- hypoglycaemic episodes
- concomitant medication
- AEs
- SMPG 7-point profile
- Urine pregnancy test for females of childbearing potential

The diaries should be collected at the visit described in the flow chart (see section 2). The recordings must be reviewed as described in section 8.1.8 and transcribed to the eCRF.

8.7 Subject compliance

Throughout the trial the investigator will remind the subjects to follow the trial procedures and requirements to ensure subject compliance. If a subject is found to be non-compliant, the

investigator will remind the subject of the importance of following the instructions given including taking the trial products as prescribed.

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.

If a subject is discovered to be non-compliant, the investigator must inform the subject of the importance of taking trial product as directed.

8.8 In case of specific safety issues

8.8.1 Thyroidectomy

Subjects scheduled for thyroidectomy (partial or total) will be asked to inform the investigator prior to their operation.

8.8.1.1 Thyroidectomy pathology slides

In addition to the examination of the thyroid tissue routinely made by the hospital pathology laboratory, the pathology slides of the thyroid tissue will be sent centrally for a second review by a pathologist with expertise in thyroid and C-cell pathology. The central pathologist will be blinded to both randomised treatment and the diagnosis from the hospital pathology laboratory. Both the hospital pathology report and the central pathology report will be reviewed by an independent event adjudication committee (EAC) (see section 12.7.2). Once the samples are re-examined they will be sent back to the hospital pathology laboratory.

The investigator will be informed of the results of central pathology report and if C-cell pathology is confirmed by the EAC, the CMC will provide guidance to the investigator with regards to treatment and further investigations.

8.8.1.2 Thyroid tissue sample collection in case of thyroidectomy

Prior to the thyroidectomy the subject will be asked to consent to have a sample of the removed thyroid tissue collected and stored in a tissue bank, if allowed by local law. If C-cell pathology is confirmed (i.e. hyperplastic or neoplastic thyroid C-cells) the sample will be tested for RET Y1062 phosphorylation in the thyroid C-cells, if allowed by local law. The tissue sample will be destroyed after examination. (Brazil – All requirements of Resolution 340/04 must be followed. Otherwise genetic tests cannot be done for Brazilian patients).

8.8.1.3 Genetic testing in case of confirmed C-cell pathology

In addition, the subject will also be asked to consent to be tested (blood sample) to identify germline RET gene mutations associated with MEN2 syndrome. This RET gene mutation detection will only

be conducted if the EAC has confirmed c-cell abnormality (medullary carcinoma or C-cell hyperplasia). The genetic testing will only be performed if allowed by local law.

The blood sample should be collected at the first visit to the clinic after the confirmation of C-cell pathology. The extraction of DNA will be performed by the central laboratory whereas the identification of gene mutations will be performed by a specialised laboratory (for details please see Attachment I). The blood sample will be destroyed as soon as the genetic analysis is complete.

8.8.1.4 Assessments in case of suspicion of acute pancreatitis

In case of acute, severe persistent abdominal pain or other relevant symptoms leading to a suspicion of acute pancreatitis, the trial product should promptly be interrupted until pancreatitis is ruled out. Appropriate additional examinations must be performed, including local measurement of amylase and lipase. If acute pancreatitis is ruled out trial product should be re-initiated. Appropriate treatment and careful monitoring of the subject should be initiated if pancreatitis is confirmed (as a minimum 2 of 3):

- severe acute abdominal pain
- amylase and/or lipase >3x upper normal range (UNR)
- characteristic findings on relevant imaging eg computerised axial tomography (CT)/magnetic resonance imaging (MRI)/ultrasound

Trial product should not be re-initiated but subject should remain in the trial. The event should be reported as a MESI and will undergo assessment by the EAC (see section 12.7.2).

8.8.1.5 Assessments in case of suspicion of severe hypersensitivity

If a severe immediate hypersensitivity reaction to the trial product is suspected, blood sampling for assessment of anti-semaglutide IgE antibodies and anti-semaglutide binding antibodies should be collected after a suitable washout period (minimum 5 weeks). In these cases, it is also recommended to test for tryptase (total and/or mature tryptase) within 3 hours of the reaction. In case a tryptase sample was collected within 3 hours of the event, a baseline tryptase sample should be taken at the same time as the IgE sample is obtained. Tryptase concentrations (if measured) as well as results of anti-semaglutide antibody and IgE-isotype anti-semaglutide antibodies will be collected by Novo Nordisk and included in the final MESI report (see section 12.1.

8.8.1.6 Assessments in case of suspicion of immune complex disease

If immune complex disease is suspected, blood sampling for central assessment of complement levels (C3 and C4) should be conducted and results should be included when reporting a MESI.

9 Trial supplies

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

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

9.1 Trial products

The following trial products for subcutaneous injection will be provided by Novo Nordisk, Denmark:

- Semaglutide 1.34 mg/mL, solution for injection, 1.5 mL pre-filled PDS290 pen-injector
- Semaglutide placebo, solution for injection, 1.5 mL pre-filled PDS290 pen-injector

The following trial products for oral administration will be provided by Novo Nordisk, Denmark:

- Sitagliptin (Januvia®) 100 mg, tablet
- Sitagliptin placebo, tablet

For both semaglutide and sitagliptin the placebo and active drug are identical with regard to appearance.

Semaglutide both active drug and placebo are manufactured and supplied by Novo Nordisk, Denmark. Sitagliptin 100 mg and placebo is packed for use in clinical trials and supplied by Novo Nordisk, Denmark.

All trial products are considered investigational medicinal products (IMPs).

Other than trial product, test pens to ensure subject's willingness and ability to self-inject will be supplied at the screening visit. The test pen contains semaglutide placebo, solution for injection, 1.5 mL prefilled PDS290 pen-injector, the test pen is for single use only (using this test pen is optional).

Refer to the appropriate IB or local label for more detailed information regarding the listed trial products.

Each site will be supplied with sufficient trial products for the trial on an on-going basis controlled by the IV/WRS and according to enrolment and randomisation with different intervals during the trial. Subject will be instructed in administration of trial product and the investigator must document that a DFU is given orally and in writing at each dispensing visit.

9.2 Labelling

Labelling of the investigational medicinal products (IMPs) will be in accordance with Annex 13[39], local law and trial requirements. Please refer to the TMM provided by Novo Nordisk for details regarding standard packages for the trial products.

9.3 Storage

Semaglutide preparations (both in-use and not in-use) must not be exposed to excessive heat or direct sunlight. Semaglutide preparations which have been frozen must not be used. Semaglutide must not be used, if it does not appear clear and colourless.

Trial product	Storage conditions (not-in-use)	In-use conditions
Semaglutide 1.34 mg/mL and placebo	• Store in a refrigerator (2°C to 8°C) • Do not freeze • Protect from light	• Store below 30°C • Do not refrigerate • Do not freeze • Protect from light • Use within 1 month*
Semaglutide placebo (test pen)	• Store in a refrigerator (2°C to 8°C) • Do not freeze • Protect from light	For single use only
Sitagliptin 100 mg and placebo	• Do not store above 30°C • Do not freeze • Do not refrigerate • Protect from light and humidity	Not applicable

* In-use time starts when first dose is taken.

The investigator must ensure the availability of proper storage conditions, record and evaluate the temperature. The investigator must inform Novo Nordisk (via the assigned monitor) immediately if

any trial product has been stored outside specified conditions (e.g. outside temperature range). Fifteen minutes outside the indicated range is negligible, and should not be recorded as a deviation.

Trial products stored outside the temperature range are not to be used and must be stored separately within allowed temperature range until after evaluation of condition. Evaluation will be performed by Novo Nordisk. Trial products that have been stored improperly must not be dispensed to any subject before it has been re-evaluated and approved for further use by Novo Nordisk.

Returned trial products (unused, partly used or used including empty packaging material) must be stored separately from non-allocated trial products.

The temperatures during storage should be monitored by a calibrated and stationary system. A temperature log must be kept to document storage within the right temperature interval and storage facilities should be checked frequently. Investigator must take appropriate action to avoid recurrence of the detected temperature deviation.

9.4 Drug accountability and destruction

The trial products will be dispensed to each subject as required according to treatment group. The IV/WRS will allocate trial product to the subject at each dispensing visit, starting at the randomisation visit. The correct DUN(s) must be dispensed to the subject.

The investigator or delegated person is responsible for ensuring that:

- Trial products are not dispensed to any person not included in the trial
- Drug accountability is performed using the IV/WRS drug accountability module
- Subjects are instructed to return all used, partly used and unused trial product including empty packaging material at each dispensing visit and at End of Treatment visit
- All returned trial products (used/partial used and unused including empty packaging material) is kept and stored separately from non-allocated trial products

Destruction of trial products will be done according to local law after accountability is finalised at site and reconciled by monitor. Destruction of trial products must be documented.

9.5 Auxiliary supplies

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

- Needles for pre-filled pen systems
- Blood glucose meters, including lancets, plasma-calibrated test strips and control solutions
- Directions for use for PDS290 pen-injector

10 Interactive voice/web response system

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

IV/WRS is used for:

- Screening
- Screening failure
- Randomisation
- Medication arrival
- Dispensing
- Treatment discontinuation
- Treatment completion
- Drug accountability
- Data change

IV/WRS user manuals will be provided to each trial site.

11 Randomisation procedure and breaking of blinded codes

The trial is a double-blind trial. A randomisation session will be carried out for all subjects by using the IV/WRS. At the randomisation visit subjects meeting all inclusion/exclusion criteria will be randomised in a 2:2:1:1 manner to receive one of four parallel treatments groups:

- Semaglutide 0.5 mg once-weekly + sitagliptin placebo once-daily
- Semaglutide 1.0 mg once-weekly + sitagliptin placebo once-daily
- Sitagliptin 100 mg once-daily + semaglutide placebo (0.5) mg once-weekly
- Sitagliptin 100 mg once-daily + semaglutide placebo (1.0) mg once-weekly

Randomisation will be stratified by country.

11.1 Breaking of blinded codes

If the trial site needs to break the code, Novo Nordisk should if possible, be contacted before the code is broken. The IV/WRS will notify Novo Nordisk (monitor and the Global Safety department) immediately after the code is broken.

The code for a particular subject may be broken in a medical emergency if knowing the actual treatment would influence the treatment of the subject. Whenever a code is broken the person breaking the code must print the code break confirmation notification generated by the IV/WRS, record the reason, and sign and date the document.

If the code has been broken, the subject should be discontinued from trial product but be asked to continue in the trial (see section 8.1.6.2).

If the code has been broken the subject must be discontinued from trial product but be asked to continue in the trial. A treatment discontinuation session should be completed in IV/WRS.

When the code is broken, the treatment allocation will be accessible to the investigator and the Novo Nordisk Global Safety department. If IV/WRS is not accessible at the time of code break monitor should be contacted and if monitor cannot get access the IV/WRS vendor helpdesk should be contacted.

12 Adverse events, and technical complaints and pregnancies

12.1 Definitions

Adverse event

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

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

An AE includes:

- A clinically significant worsening of a concomitant illness.
- A clinical laboratory adverse event (CLAE): a clinical laboratory abnormality which is clinically significant, ie 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 procedures (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 8.4.2).

The following three definitions are used when assessing an AE:

- **Severity assessment**
  - **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 assessment**

The following terms are used when assessing the 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 of an AE**
  - **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.

Serious adverse event

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

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

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 (eg 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 dyscrasiasis or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

Non-serious adverse event

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

Medical event of special interest

A medical event of special interest (MESI) is an event which, in the evaluation of safety, has a special focus. A MESI is an AE (SAE or non-serious AE) which fulfils one or more of the below defined MESI criteria.

1. Medication errors concerning trial products:
   - Administration of wrong drug.
   - Wrong route of administration, such as intramuscular instead of subcutaneous.
   - Administration of an overdose with the intention to cause harm (eg suicide attempt).
   - Accidental administration of a lower or higher dose than intended. That is a dose of semaglutide 10% lower or higher than 1.0 mg week (± 24h) or of sitagliptin that is lower or higher than 100 mg/day; however the administered dose must deviate from the intended dose to an extend where clinical consequences for the trial subject were likely to happen as judged by the investigator, although not necessarily did happen.
2. Fatal events (if not covered by another MESI) (A)
3. Acute coronary syndrome (A)
   - Myocardial infarction
   - Hospitalisation for unstable angina

4. Cerebrovascular event (stroke or transient ischaemic attack) (A)
5. Coronary revascularisation procedure (A)
6. Peripheral arterial revascularisation procedure
7. Heart failure requiring hospital admission (A)
8. Neoplasm (excluding thyroid neoplasm) (A)
9. Thyroid disease (including thyroid neoplasm) (A – if thyroid neoplasm or thyroidectomy)
10. Pancreatitis or clinical symptoms leading to suspicion of pancreatitis (A)
11. Immunogenicity events (allergic reactions, immune complex disease and anti-semaglutide antibody formation)

MESIs marked with an '(A)' in the list above will undergo adjudication by an independent EAC (see section 12.7.2).

Any event confirmed or suspected to be a MESI must be reported as such. In case the sponsor identifies potentially missed MESIs through predefined review of available data, the investigator will be asked to reconsider if this is a MESI. However, MESIs should not be reported for screening failures.

For further information regarding definitions of MESIs and an overview of which events that should undergo adjudication, please refer to Appendix A.

Technical complaint

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 (eg discoloration, particles or contamination)
- The packaging material (eg leakage, cracks, rubber membrane issues or errors in labelling text)
- Problems related to devices (eg to the injection mechanism, dose setting mechanism, push button or interface between the pen and the needle)

12.2 Reporting of adverse events

All events meeting the definition of an AE must be collected and reported. This includes events from the first trial-related activity after the subject has signed the informed consent until the end of the post-treatment follow-up period (see section 2). The events must be recorded in the applicable CRF 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, either observed by the investigator or subject, must be reported by the investigator and evaluated. Novo Nordisk assessment of expectedness is performed according to the following reference documents

- Investigator's Brochure, semaglutide (NN9535) (subcutaneous administration), Type 2 Diabetes and any updates hereof[28]
- Sitagliptin (Januvia®): EU Summary of Product Characteristics (SmPC) [29], current version.

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

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

MESIs, regardless of seriousness, must be reported using both the AE form and the safety information form and a MESI form. The MESI form is a form tailored to collect specific information related to the individual MESI.

For MESIs qualifying for event adjudication, an event adjudication document collection form (adjudication form) will also have to be completed in the eCRF. The event adjudication document collection form is a check list of clinical data to be provided from the site. The investigator should provide relevant medical documentation within 4 weeks of event identification.

The AE form for a non-serious AE should be signed when the event is resolved or at the end of the trial.

Timelines for initial reporting of AEs:

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

- **SAEs**: The AE form **within 24 hours** and the safety information form **within 5 calendar** days of the investigator's first knowledge of the SAE.

Both forms must be signed within 7 calendar days from the date the information was entered in the eCRF.

- **SAEs fulfilling the MESI criteria:** In addition to above, the MESI form **within 14 calendar days** of the investigator's first knowledge of the AE.
- **Non-serious AE fulfilling the MESI criteria:** The AE form, safety information form and MESI form **within 14 calendar days** of the investigator's first knowledge of the event.
- **Events for adjudication**: The event adjudication document collection form must be completed **within 14 calendar days**. The investigator should provide the medical documentation within 4 weeks of event identification.

If the eCRF is unavailable, the concerned AE information must be reported on paper forms 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 re-enter the information on the appropriate forms in the eCRF.

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

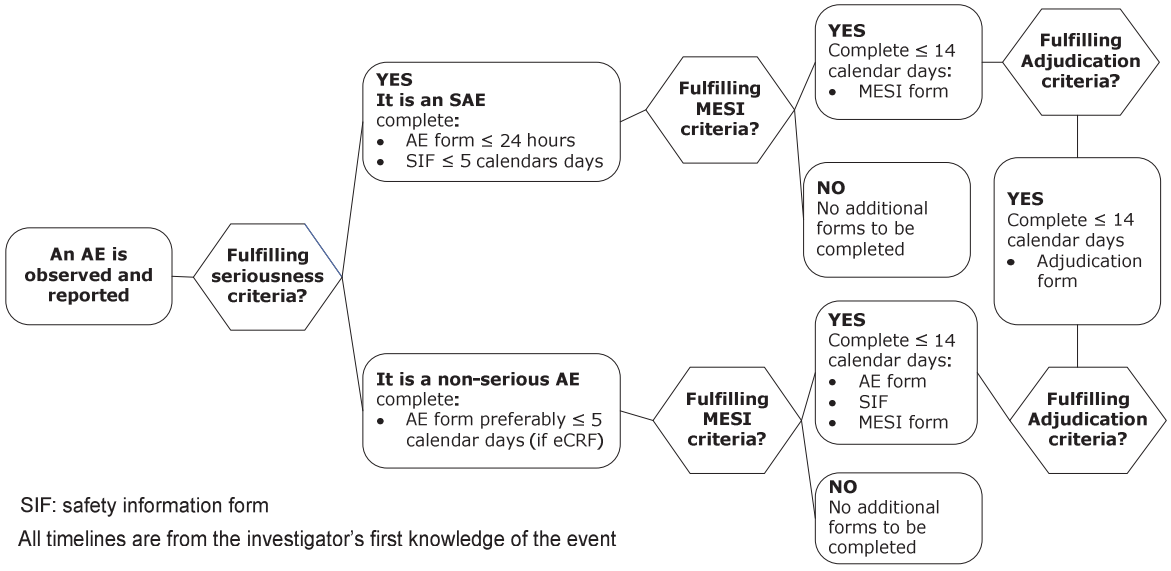


Figure 12–1 Initial reporting of AEs

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

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

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 (eg 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.
- **Non-serious AE fulfilling the MESI criteria:** Follow-up information on MESIs should only include new (eg corrections or additional) information and must be reported **within 14 calendar days** of the investigator's first knowledge of the information. This is also the case for previously reported non-serious AEs which subsequently fulfil the MESI criteria.

The investigator must ensure that 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.

12.4 Technical complaints and technical complaint samples

12.4.1 Reporting of technical complaints

All technical complaints and on any of the following products:

- Semaglutide 1.34 mg/mL solution for injection, 1.5 mL pre-filled PDS290 pen-injector
- Semaglutide placebo, solution for injection, 1.5 mL pre-filled PDS290 pen-injector
- Sitagliptin (Januvia®) 100 mg, tablet
- Sitagliptin placebo, tablet
- Needles for pre-filled pen systems
- Semaglutide placebo, solution for injection, 1.5 mL pre-filled PDS290 pen-injector (test pen)

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, SAEs, and/or MESI.

Technical complaints must be reported on a separate technical complaint form for each product listed. If the technical complaint involves more than one batch, code or lot number or more than one DUN, a technical complaint form for each batch, code or lot number or for each DUN 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.

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 print or copy of the technical complaint form must be sent with the sample.

The investigator must ensure that the technical complaint sample contains the batch or lot number and, if available, the DUN.

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. The shipment of the technical complaint sample should be done in accordance with the same conditions as for storage (see section 9).

12.5 Pregnancies

12.5.1 Pregnancies in female subjects

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

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

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

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

1. **Reporting of pregnancy information**
   Information about the pregnancy and pregnancy outcome/health of the newborn infant(s) has to be reported on maternal form 1A and 1B, respectively.

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

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

2. Reporting of AE information

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

Forms and timelines for reporting AEs:

Non-serious AEs:

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

SAEs:

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

* 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.

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

12.6 Precautions and/or overdose

Semaglutide

Little experience of accidental overdose exists from the semaglutide clinical development programme. Events of nausea, vomiting and headache have been reported in connection with accidental administration of up to 4.0 mg semaglutide. No symptoms of hypoglycaemia have been reported in connection with overdose of semaglutide. In the event of overdose, appropriate supportive treatment should be initiated according to the subject’s clinical signs and symptoms.

For other precautions, please see section 3.5.1.

Sitagliptin

During controlled clinical trials in healthy subjects, single doses of up to 800 mg sitagliptin were generally well tolerated. Minimal increases in QTc, not considered to be clinically relevant, were observed in one study at a dose of 800 mg sitagliptin. There is no experience with doses above 800

mg in clinical studies. In Phase I multiple-dose studies, there were no dose-related clinical adverse reactions observed with sitagliptin with doses of up to 600 mg per day for periods of up to 10 days and 400 mg per day for periods of up to 28 days.

In the event of an overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring (including obtaining an electrocardiogram), and institute supportive therapy if required. Sitagliptin is modestly dialysable. In clinical studies, approximately 13.5 % of the dose was removed over a 3- to 4-hour hemodialysis session. Prolonged hemodialysis may be considered if clinically appropriate. It is not known if sitagliptin is dialysable by peritoneal dialysis.

For other precautions, please see section 3.5.2.

12.7 Committees related to safety

12.7.1 Novo Nordisk safety committee

Novo Nordisk has constituted an internal semaglutide safety committee to perform ongoing safety surveillance. The semaglutide safety committee may recommend unblinding of any data for further analysis.

12.7.2 Event adjudication committee

An external event adjudication committee is established to perform qualitative or quantitative validation of selected AEs according to pre-defined diagnostic criteria. The validation is based on review of pre-defined clinical data related to the specific AE.

Adjudication will be completed based on a review of data collected from the sites. The provided data will be anonymised for subject identifiers.

The events are reviewed by the event adjudication committee in an independent and blinded manner.

The EAC is composed of permanent members covering required medical specialities. EAC members must disclose potential conflicts of interest and must be independent of Novo Nordisk. The role of the EAC is solely to adjudicate events in a blinded manner. The EAC will have no authorisations to impact trial conduct, trial protocol or amendments.

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

The events will be adjudicated according to Food and Drug Administration (FDA) requirements.

The EAC will review copies in English (translated if necessary) of medical documentation received in the adjudication package (for example X-ray, ECGs, ultrasound images, discharge summaries, pathology reports, and death certificates). The investigator should provide medical documentation within 4 weeks of event identification. The supplier of EAC can evaluate an event not initially reported as a MESI for adjudication to be adjudicated. In this case the investigator must provide medical documentation as soon as possible, when receiving a request from Novo Nordisk or the supplier.

The assessment made by the EAC will be included in the CTR as well as assessments made by the investigator. However, the adjudication made by an EAC, given its independence and in-depth analysis of each event, will be attributed with greater importance of the two. The outcomes of adjudication will be kept in the clinical trial database.

The following AEs will be adjudicated in this trial:

- Fatal events (if not covered by another MESI)
- Acute coronary syndrome
- Cerebrovascular event (stroke or transient ischaemic attack)
- Coronary Revascularisation Procedure
- Heart failure requiring hospital admission
- Neoplasms (excluding thyroid neoplasm)
- Thyroid disease (including thyroid neoplasm or resulting in thyroidectomy)
- Pancreatitis or clinical symptoms leading to suspicion of pancreatitis

Please see Appendix A for details.

Event adjudication will not be performed for AEs in screening failures.

AEs for adjudication must be reported according to section 12.2. In addition the specific event adjudication document collection form has to be completed within 14 days and all relevant pre-defined documents has to be provided within 4 weeks of the investigator's first knowledge of the AE, according to instructions in the event adjudication site manual.

12.7.3 Calcitonin monitoring committee(CMC)

The CMC will provide recommendations to the investigators with regards to further investigation and treatment of the individual subject (see Appendix B).

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 supplied by a vendor.

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 (eg is not applicable), indicate this according to the data entry instructions.

The following will be provided as paper CRFs:

- Pregnancy forms

In addition paper AE forms and safety information forms will be provided. These must be used when access to the eCRF is revoked.

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

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

13.2 Case report form flow

13.2.1 Electronic case report form flow

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

At the end of trial the investigator must ensure that all remaining data have been entered into the eCRF no later than 3 days after the last subject’s last visit 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 investigator site after the trial database is released and access to update the trial data on the EDC application has been removed. This data will be retained by the site.

When the final CTR is available the data will be archived by Novo Nordisk.

13.2.2 Paper case report form flow

The pregnancy forms are paper based CRFs.

Also, the SIF, technical complaint form, and AE form will be provided in paper but are only to be used if for any reason the eCRF is unavailable.

The investigator must ensure that data are recorded in these forms as soon as possible and ensure that Novo Nordisk receives these forms within the required timeline (see section 12).

Corrections to the data in the 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 were crossed out. Each correction must be initialled, dated and explained (if necessary) by the investigator or the investigator's authorised staff.

14 Monitoring procedures

During the course of the trial, the monitor will visit the trial site to ensure that the protocol is adhered to, that all issues have been recorded, to perform source data verification and to monitor drug accountability. The first monitoring visit will be performed as soon as possible after FPFV or FSFV and no later than 4 weeks after. The monitoring visit intervals will depend on the outcome of the remote monitoring of the CRFs, the trial site's recruitment rate and the compliance of the trial site to the protocol and GCP, but will not exceed 8 weeks.
The intervals between monitoring visits can be shorter. Factors to be considered in this determination may include objective, endpoints, purpose, design, complexity, blinding, number of subjects and expected recruitment rate.

The monitor must be given direct access to 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 (eg by telephone).

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

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. Considering the electronic source data environment, it is accepted that the earliest practically retainable record should be considered as the location of the source data. Therefore transcription to the diary from the blood glucose meter is considered the source document for BG values.

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 diaries and PROs are considered as source data and must not be removed from the trial site.

The monitor will ensure that the CRFs are completed on an on-going basis within the agreed timelines.

The monitor must ensure that all required eCRF forms for screening failures are completed, (e.g. screening failure form and the case book sign of (affirmation statement) is electronically signed by the investigator).

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

When data has been source verified and all queries have been resolved the case book must be signed by the investigator in the eCRF

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

15 Data management

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

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 from the laboratory performing the analyses. 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 identification number. Appropriate measures such as encryption or leaving out certain identifiers will be enforced to protect the identity of subjects in all presentations and publications as required by local, regional and national requirements.

16 Computerised systems

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

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

17 Statistical considerations

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

Results from the statistical analysis will generally be presented by two-sided confidence intervals with a confidence level of 95%. Superiority will be formulated and tested as one-sided hypotheses at a 2.5% significance level. Non-inferiority between two treatments will be evaluated by comparing the upper limit of the associated two-sided 95% confidence interval for the difference with the pre-defined non-inferiority margin.

Handling of missing data

In the case of missing data no general imputation will be performed for the analyses, unless otherwise specified. If an assessment has been made both at screening and randomisation, the value from the randomisation visit will be used as the baseline value. If the value measured at the randomisation visit is missing and the assessment also has been made at screening, then the screening value will be used as the baseline value.

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

The primary analysis model will be the mixed model for repeated measurements (MMRM), see section 17.3 for further details. One of the assumptions behind (MMRM) is that the missing data mechanism is missing at random (MAR). This means that given the observed data, the mechanism generating missing values is independent of the unobserved data that is the missing data. The MMRM and the negative binomial model both rely on the MAR assumption for generating unbiased estimates of treatment differences.

Based on previous semaglutide trials in subjects with type 2 diabetes, the withdrawal rate from randomised treatment is expected to be about 20%. The treatments in this trial should be effective, given the historical documentation, and this should minimise withdrawals due to ineffective therapy. The main reasons for withdrawal are expected to be AEs, ineffective therapy and non-eligibility (subjects randomised although not fulfilling inclusion/exclusion criteria). Withdrawal due to non-eligibility can be regarded as missing completely at random (MCAR), i.e. it does not depend on the observed or missing data values. This category of missing data is not expected to introduce bias in the estimated treatment differences. Withdrawal due to lack of efficacy is expected to be reflected in the observed data obtained prior to the withdrawal from randomised treatment, and the corresponding missing data can therefore be assumed as MAR to some extent. Missing data due to AEs is expected to be similar between groups except for, potentially, a slightly higher incidence in the semaglutide treatment group due to gastrointestinal side effects. Together with potential

withdrawals due to the own will of the subject, the MAR assumption may be less adequate for this category of drop-outs.

Several different sensitivity analyses will be used to investigate whether the results from the MMRM approach are robust towards deviations from the assumption of MAR.

17.1 Sample size calculation

The primary objective is to compare the effect of two dose levels of semaglutide once-weekly treatment (0.5 mg or 1.0 mg) with sitagliptin 100 mg on the primary endpoint, change from baseline in HbA_{1c} after 30 weeks of treatment. In the calculations determining the sample size it is presumed that in the analysis the two sitagliptin/semaglutide placebo groups will be pooled assuming no correlation between endpoints and placebo volume.

In total 1050 subjects will be randomised in a 2:2:1:1 manner. Assuming 20% of subjects discontinuing randomised treatment, and further taking the assumption that these subjects are excluded from the per protocol (PP) analysis set, 280 subjects in each group are expected to be included in the PP analysis set.

The sample size calculation is based on demonstrating HbA_{1c} non-inferiority for semaglutide 0.5 mg vs. sitagliptin 100 mg and HbA_{1c} non-inferiority for semaglutide 1.0 mg vs. sitagliptin 100 mg.

The two hypothesis tests are assumed to be independent and for each of the hypothesis the power calculation is based on a t-statistic under the assumption of a one-sided test of size 2.5%. Using a non-inferiority margin of 0.3%, and assuming a true HbA_{1c} difference (semaglutide minus sitagliptin) of 0% and a standard deviation (SD) of 1.1%, a total of 280 subjects per group in the PP analysis set will give 90% marginal power to conclude HbA_{1c} non-inferiority for the comparison of a semaglutide dose vs. sitagliptin 100 mg.

Assuming the same HbA_{1c} effect for the two dose levels of semaglutide, the overall power to demonstrate HbA_{1c} non-inferiority for the two dose levels of semaglutide vs. sitagliptin will be at least 80%.

For change in body weight, the power calculation is based on the assumptions of a true difference of -1.5 kg and a SD of 4.0 kg. In addition, 50% efficacy retention is assumed for the anticipated 20% of subjects discontinuing randomised treatment giving an expected treatment difference of -1.35 kg, which is the number used in the power calculation. With the above assumptions, a total of 350 subjects per group in the full analysis set (FAS) will give more than 99% marginal power to conclude superiority in body weight for the comparison of a semaglutide dose vs. sitagliptin 100 mg.

17.2 Definition of analysis sets

The following analysis sets are defined in accordance with the ICH-E9 guideline [40].

Full Analysis Set (FAS): includes all randomised subjects who have received a dose and have any post randomisation data. The statistical evaluation of the FAS will follow the intention-to-treat (ITT) principle and subjects will contribute to the evaluation "as randomised".

Per Protocol (PP) Analysis Set:

Includes all subjects in the FAS who fulfil the following criteria:

- have not violated any inclusion criteria
- have not fulfilled any exclusion criteria
- have a non-missing HbA_{1c} measurement at screening and /or randomisation
- have at least 23 weeks actual treatment weeks of expose
- have at least one non-missing HbA_{1c} measurement after 23 actual weeks of expose

Subjects in the PP Analysis Set will contribute to the analysis "as treated".

Safety Analysis Set (SAS): includes all subjects exposed to at least one dose of randomised semaglutide or stigliptin. Subjects in the SAS will contribute to the evaluation "as treated".

Before data are locked for statistical analysis, a review of all data will take place. Any decision to exclude a subject or single observations from the statistical analysis is the joint responsibility of the members of the internal 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 must be documented and signed by those responsible before database lock. The subjects and observations excluded from analysis sets, and the reason for this, will be described in the CTR.

17.3 Primary endpoint

The primary endpoint is change from baseline in HbA_{1c} after 30 weeks of treatment. In the analysis the two sitagliptin/semaglutide placebo groups will be pooled assuming no correlation between HbA_{1c} change after 30 weeks and placebo volume.

The primary endpoint will be analysed by MMRM where all post baseline HbA_{1c} measurements obtained at planned visits before discontinuation from randomised treatment or initiation of rescue treatment enter as the dependent variables, and visit, treatment, and country are included as fixed factors and baseline HbA_{1c} as covariate. Furthermore, interaction terms of visit by treatment, visit by country and visit by baseline HbA_{1c} will be included. An unstructured covariance matrix for HbA_{1c} measurements within same subject will be employed. Regarding missing data this analysis

approach relies on the assumption that data are missing at random (MAR). At week 30 the estimated differences between each semaglutide dose level and sitagliptin and corresponding two sided p-values and 95% confidence intervals will be presented.

In order to preserve the overall type 1 error the conclusion of non-inferiority and superiority with treatment of each semaglutide dose versus sitagliptin after 30 weeks will be evaluated hierarchically according to the sequence below, and starting with the first. In this testing sequence it is necessary to fulfil the test criteria, which is to reject the corresponding null hypothesis in order to go to the next step. If the corresponding null hypothesis is not rejected, the testing will stop and no further conclusions will be drawn.

The following ordering in the statistical test sequence will be used:

1. Non-inferiority in change in HbA_{1c} for semaglutide 1.0 mg vs. sitagliptin
2. Non-inferiority in change in HbA_{1c} for semaglutide 0.5 mg vs. sitagliptin
3. Superiority in change in HbA_{1c} for semaglutide 1.0 mg vs. sitagliptin
4. Superiority in change in body weight for semaglutide 1.0 mg vs. sitagliptin
5. Superiority in change in body weight for semaglutide 0.5 mg vs. sitagliptin
6. Superiority in change in HbA_{1c} for semaglutide 0.5 mg vs. sitagliptin

Non-inferiority will be concluded if the upper limit of the two-sided 95% confidence interval for the estimated difference in HbA_{1c} between semaglutide and sitagliptin is less than 0.3%. Superiority for either change in HbA_{1c} or change in body weight will be claimed if the upper limit of the two-sided 95% confidence interval for the estimated difference is below 0% or 0 kg respectively.

When establishing non-inferiority the analysis will be based on the full analysis set (FAS) and supplemented by an analysis with the per protocol population as supportive evidence. The FAS population will be used in the analysis when concluding superiority.

Sensitivity analysis

To investigate the sensitivity of the main results, complimentary and separate analyses for primary endpoint and the confirmatory secondary endpoint will be performed, using the FAS only, except for HbA_{1c}, where the PP analysis set will be used in a sensitivity analysis regarding the non-inferiority evaluation. These analyses will investigate the sensitivity of the results due to the impact of missing values.

The primary analysis regarding non-inferiority of the primary endpoint change in HbA_{1c} after 30 weeks will also be performed separately based on the data in the PP analysis set only.

The primary endpoint and the secondary confirmatory endpoint will be evaluated in the following sensitivity analyses:

- An analysis of covariance (ANCOVA) model will be analysed with imputation of missing values according to the last observation carried forward (LOCF) method. The model will include terms for treatment, country, and the corresponding baseline value as a covariate. The response variable will be the last available value obtained within the 30 weeks period of the trial
- The MMRM will be analysed based on all data record after randomisation using also data from subjects who discontinued randomised treatment and /or initiated rescue treatment.
- The MMRM will be analysed based on data only from subjects that completed the trial without receiving rescue treatment.

A pattern mixture model approach mimicking an ITT scenario where withdrawn subjects are assumed to be switched to a treatment inferior to the control treatment after withdrawal will be performed for evaluation of non-inferiority for the primary endpoint change in HbA_{1c} at 30 weeks.

- In the first step 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 treatment group separately and 100 copies of the dataset will be generated.
- In the second step, for each of the 100 copies of the dataset, an analysis of variance model with the same factors as the primary model, and baseline HbA_{1c} and HbA_{1c} at 4 weeks (V3) as covariate is fitted to the change in HbA_{1c} from baseline to 8 weeks (V5) for the sitagliptin group only. The estimated parameters, and their variance, from this model are used to impute missing value at 8 weeks for subjects in all treatment groups, based on country and HbA_{1c} at baseline and 4 weeks.
- In the third step, for each of the 100 copies of the dataset, missing HbA1c values at 12 weeks (V6) are imputed in the same way as for 8 weeks. Now the imputation are based on an analysis of variance model with the same factors and the HbA1c values at baseline, 4 weeks and 8 weeks as covariates, fitted to the control group.

- This stepwise procedure is then repeated sequentially over the available planned visits, adding one visit in each step until the last planned visit at 30 weeks (V9).
- For each withdrawn subject in the investigational treatment group, a value of 0.3% (the non-inferiority limit) is added to the change in HbA_{1c} at 30 weeks.
- For each of the complete data sets, the change from baseline to week 30 is analysed using an analysis of variance model with the same set of factors and the baseline HbA_{1c} value as a covariate.
- The estimates and standard deviations for the 100 data sets are pooled to one estimate and associated standard deviation using Rubin's rule (page 255-257)[41] From these pooled estimates the confidence interval for the treatment differences and the associated p-value are calculated.

A pattern mixture model approach mimicking an ITT scenario where withdrawn subjects are assumed to be switched to the control treatment after withdrawal will be performed separately for the evaluation of superiority in the primary endpoint change in HbA_{1c} and change in body weight at 30 weeks. The same types of approach as used for the non-inferiority assessment in change in HbA_{1c} will be employed, see above. However, the step where 0.3%, the non-inferiority limit, is added to the change in HbA_{1c} at 30 weeks will not be performed in this sensitivity analysis.

Chinese/Korean subgroup analyses

A number of subgroup analyses by country will be performed with the aim to assess the treatment effect in the individual countries including China and Korea. They will be performed in a combined model using all data similar to the main analysis of the respective parameter but with an interaction between treatment and country.

17.4 Secondary endpoints

The planned secondary endpoints used to support the primary objective will be analysed as outlined in this section.

17.4.1 Confirmatory secondary endpoints

Weight loss

A confirmatory secondary variable is change in body weight after 30 weeks of treatment. This variable will be analysed in the same type of model as the primary endpoint although with baseline body weight as covariate.

17.4.2 Supportive secondary endpoints

17.4.2.1 Efficacy endpoints

All efficacy endpoints in this section will be summarised and evaluated using the FAS.

Continuous variables

Change from baseline to week 30 in:

- FPG
- Insulin
- C-peptide
- glucagon
- pro-insulin
- pro-insulin/insulin ratio
- HOMA-B
- HOMA-IR
- fasting blood lipids (total cholesterol, LDL-cholesterol, VLDL-cholesterol, HDL-cholesterol, triglycerides and free fatty acids)
- BMI
- waist circumference
- systolic and diastolic blood pressure
- hsCRP

will all be analysed in the same type of model as the primary endpoint, but with the associated baseline value as a covariate.

Except for FPG, BMI, waist circumference, and blood pressure the values of the variables will be log transformed subject to analysis.

Beta-cell function

Beta-cell function (fasting HOMA-B and fasting HOMA-IR) will be calculated based on fasting insulin and FPG. The calculation will be done at the same time points as for fasting insulin and FPG samples (section 2).

The calculation of the fasting HOMA endpoints will be done as follows:
Fasting HOMA-B (%) = 20 x fasting insulin [µU/ml]/(FPG[mmol/l]-3.5)
Fasting HOMA-IR (%) = fasting insulin [µU/ml] x FPG [mmol/l]/22.5

PRO outcomes

The PRO outcome endpoints:

- PRO questionnaire outcome DTSQs (individual items and treatment satisfaction score (6 of the 8 items summed)), and
- PRO questionnaire outcome SF-36v2™

will be analysed separately with the same type of model as for the primary endpoint, that is, change from baseline to the end of 30 weeks of the randomised treatment. The baseline value of the corresponding endpoint will be used as covariate in the analysis model.

SMPG 7-point profile

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

The endpoints from the 7-point profiles that will be analysed at week 30 are:

- Mean of the 7-point profile, defined as the area under the profile, calculated using the trapezoidal method, divided by the measurement time
- Mean increment over all meals

The mean of the 7-point profile and the mean of the post prandial increments at week 30 will be analysed separately using the ANCOVA model. Factors in the model will be treatment and country. The corresponding endpoint obtained at baseline will be used as covariate.

Response in HbA_{1c} and/or weight loss after 30 weeks

The secondary variables related to fixed response in HbA_{1c} and/or weight loss at 30 weeks will be:

- Responder in HbA_{1c} after 30 weeks of treatment (yes/no) defined as HbA_{1c} <7.0% (<53 mmol/mol) – ADA target
- Responder in HbA_{1c} after 30 weeks of treatment (yes/no) defined as HbA_{1c} ≤6.5% (48 mmol/mol) – AACE target
- Weight loss ≥5%
- Weight loss ≥10%
- HbA_{1c} <7.0% (53 mmol/mol) without severe or confirmed symptomatic hypoglycaemia (plasma glucose ≤3.1 mmol/L) and no weight gain

All these variables will be analysed separately in the same type of logistic regression model. The model will include factors for treatment and country. For the two responder in HbA_{1c} endpoints, baseline HbA_{1c} will be included in the model as a covariate, whereas for the weight responder endpoint (≥5% and ≥10% weight loss), baseline weight will be included instead. For the composite endpoint (cf. last bullet), both baseline HbA_{1c} and baseline weight will be included.

Missing response data at 30 weeks will be imputed from respectively the MMRM used for the primary analysis of HbA_{1c} and the confirmatory secondary endpoint change in body weight at 30 weeks. The results will be described by the odds ratio and the associated 95% confidence interval for the odds ratio.

17.4.2.2 Safety endpoints

The following secondary endpoints are used to support the safety objectives:

- Number of treatment emergent AEs during 30 weeks of treatment
- Number of treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes during 30 weeks of treatment
- Severe or BG confirmed symptomatic hypoglycaemic episodes during 30 weeks of treatment (yes/no)

Change in safety endpoints assessed from baseline to 30 weeks of treatment and/or follow up:

- Haematology
- Biochemistry
- Calcitonin
- Urinalysis
- UACR
- Pulse
- ECG evaluation
- Physical examination evaluation

Occurrence of semaglutide antibodies during 35 weeks of study duration (yes/no):

- Anti-semaglutide antibodies
    - Anti-semaglutide antibodies with in vitro neutralising effect
    - Anti-semaglutide antibodies cross reacting with endogenous GLP-1
        - Cross reacting antibodies with in vitro neutralising effect to endogenous GLP-1

Anti-semaglutide antibody level during and after 30 weeks of treatment

All safety endpoints will be summarised and evaluated by descriptive statistics using the SAS.

Adverse events

All AEs will be coded using the most recent version of the Medical Dictionary for regulatory Activities (MedDRA) coding. A treatment emergent adverse event (TEAE) is defined as an event that has onset date (or increase in severity) on or after the first day of exposure to randomised treatment and no later than the follow-up visit.

TEAEs will be summarised descriptively, whereas non-treatment emergent AE's will be presented in listings. TEAE data will be displayed in terms of the number of subjects with at least one event (N), the percentage of subjects with at least one event (%), the number of events (E) and the event rate per 1000 years (R).

Pulse

Pulse will be analysed separately with the same type of methods as for the primary endpoints but with the pulse value at baseline as a covariate.

Laboratory assessments

Amylase and lipase will be analysed separately with the same type of methods as for pulse with the corresponding baseline assessment as a covariate. The values will be log transformed in the analysis.

Calcitonin

Calcitonin will be displayed in terms of the number of subjects (N), the percentage of subjects (%) and the event rate per 1000 years of exposure (R). The following criteria are defined for tabulations:

Persistent (all post baseline measurements)

- From <upper normal limit (UNL) to persistently ≥UNL
- From <UNL to persistently ≥1.5 UNL
- From <UNL to persistently ≥20 ng/L
- From <UNL to persistently ≥50 ng/L
- From <20 ng/L to persistently ≥20 ng/L
- From <50 ng/L to persistently ≥50 ng/L

Incidental (at least one post baseline measurements)

- From <UNL to ≥UNL
- From <UNL to ≥1.5 UNL
- From <UNL to ≥20 ng/L
- From <UNL to ≥50 ng/L
- From <20 ng/L to ≥20 ng/L
- From <50 ng/L to ≥50 ng/L

Summaries tables of calcitonin continuous measurements, will include number and percentage of observations < and ≥ LLOQ, minimum, Q25, median, Q75 and maximum. Summaries will be presented for all subjects and by gender.

Classification of Hypoglycaemia

Treatment emergent: hypoglycaemic episodes will be defined as treatment emergent if the onset of the episode occurs on or after the first day of trial product administration, and no later than the follow-up visit.

Nocturnal hypoglycaemic episodes: are episodes with time of onset between 00:01 and 05:59 both inclusive.

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

Novo Nordisk classification of hypoglycaemia

In normal physiology, symptoms of hypoglycaemia occur below a plasma glucose level of 3.1 mmol/L (56 mg/dL) [42]. Therefore, Novo Nordisk has included hypoglycaemia with plasma glucose levels below this cut-off point of hypoglycaemia.

In this trial Novo Nordisk use the following classification in addition to the ADA classification (see Figure 17–1):

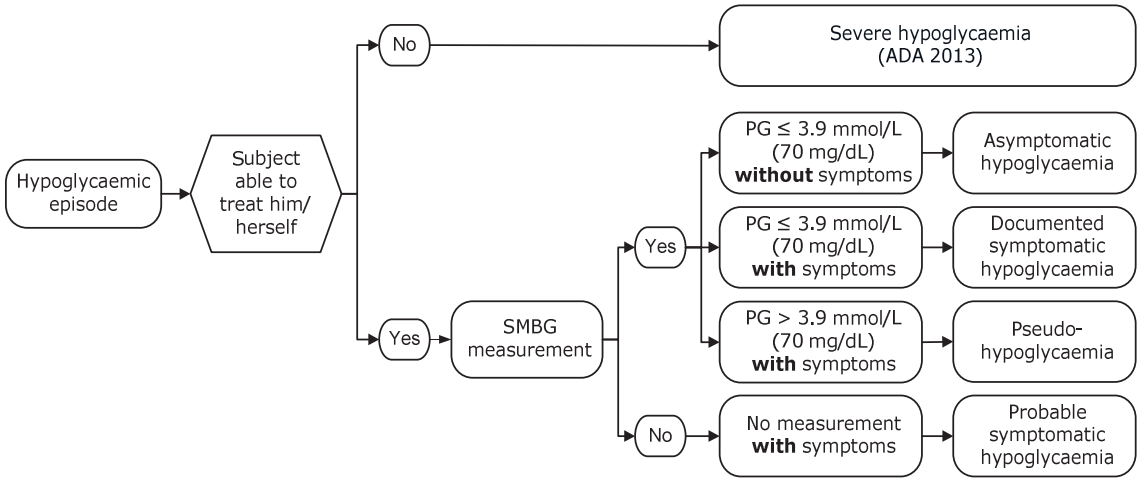
- Severe or BG confirmed symptomatic hypoglycaemia: An episode that is severe according to the ADA classification [38] or BG confirmed by a plasma glucose value <3.1 mmol/L (56 mg/dL) with symptoms consistent with hypoglycaemia.

ADA classification of hypoglycaemia [38]

- Severe hypoglycaemia: An episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take of other corrective actions. Plasma glucose concentration may not be available during an event, but neurological recovery following the

return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

- Asymptomatic hypoglycaemia: An episode not accompanied by typical symptoms of hypoglycaemia, but with a measured plasma glucose concentration ≤ 3.9 mmol/L (70 mg/dL).
- Documented symptomatic hypoglycaemia: An episode during which typical symptoms of hypoglycaemia are accompanied by a measured plasma glucose concentration ≤ 3.9 mmol/L (70 mg/dL).
- Pseudo-hypoglycaemia: An episode during which the person with diabetes reports any of the typical symptoms of hypoglycaemia with a measured plasma glucose concentration > 3.9 mmol/L (70 mg/dL) but approaching that level.
- Probable symptomatic hypoglycaemia: An episode during which symptoms of hypoglycaemia are not accompanied by a plasma glucose determination but that was presumably caused by a plasma glucose concentration ≤ 3.9 mmol/L (70 mg/dL).



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

Figure 17–1 ADA classification of hypoglycaemia

Number of severe or BG confirmed symptomatic hypoglycaemic episodes

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 episodes 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.

The number of severe or BG confirmed symptomatic hypoglycaemic episodes during 30 weeks treatment 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. The model will include factors for treatment, country as fixed factors and baseline HbA_{1c} as covariate.

Number of nocturnal hypoglycaemic episodes

The number of nocturnal (00:01-05:59 am) severe or BG confirmed symptomatic hypoglycaemic episodes during 30 weeks of treatment will be analysed separately in the same type of model as the number of severe or BG confirmed symptomatic hypoglycaemic episodes during 30 weeks treatment.

Severe or BG confirmed symptomatic hypoglycaemic 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 with treatment, country as fixed factors and baseline HbA_{1c} as covariate.

Nocturnal severe or BG confirmed symptomatic hypoglycaemic episodes (yes/no)

The binary endpoint indicating whether a subject has no treatment emergent nocturnal (00:01-05:59 am) severe or BG confirmed symptomatic hypoglycaemic episodes or at least one will be analysed using the same type model as severe or BG confirmed symptomatic hypoglycaemic episodes during 30 weeks treatment.

17.5 Health economics and/or patient reported outcomes

The PRO questionnaires, SF-36v2^{TM} and DTSQs, will be used to evaluate the objective regarding Quality of Life, see section 17.4.2.1for the details of the corresponding statistical analysis.

18 Ethics

The trial will be conducted in compliance with ICH GCP [1] and applicable regulatory requirements, and in accordance with the Declaration of Helsinki [2].

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 treatment. Subjects will be treated within a regimen anticipated to be better than or equal to the treatment they receive at the time of entry into the trial. Subjects will have to spend some extra time, as additional assessments and visits to the clinic are required. It is the responsibility of the investigator to ensure the best possible care according to the principles outlined in Diabetes Care 2013 Standards of Medical Care in Diabetes [43], or any updates thereof.

It is concluded that the potential benefits from participating in the trial outweigh the potential risks. The safety profile of semaglutide generated from the clinical and nonclinical development programme has not revealed any safety issues that would prohibit administration of once weekly doses of 0.5 mg or 1.0 mg semaglutide in accordance with the planned clinical trial. It is concluded that the risk to the subjects in this trial is low and acceptable in view of the benefits a long-acting GLP-1 analogue would provide to people with type 2 diabetes (please see 3.5)

The trial products may be associated with AEs, but relevant precautions have been implemented in the design and planned conduct of the trial in order to minimise the risks and inconveniences of participation in the trial. These precautions include thorough information regarding the correct administration of the trial products and gradual dose adjustment. Furthermore, subjects are fully informed about possible AEs and inconveniences and will be instructed to contact the investigator in case of any concerns regarding the trial participation.

When treatment with trial products ends, the subject and investigator will decide on the best available treatment.

18.1 Informed consent

In seeking and documenting informed consent, the investigator must comply with applicable regulatory requirement(s) and adhere to ICH GCP [1] and the requirements in the Declaration of Helsinki [2].

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 task may be delegated by the investigator 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 case a subject undergoes a thyroidectomy a separate informed consent will be obtained for collection of thyroid tissue sample and genetic testing (see section 8.8.1.2 and 8.8.1.3).

18.2 Data handling

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

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

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

18.3 Information to subject during trial

The site will be offered a communication package to the subject during the conduct of the trial. The package content is issued by Novo Nordisk. The communication package will contain the letters intended for distribution to the subjects. The letters will be translated and adjusted to local requirements and distributed to the subject by discretion of the investigator. The subject may receive a “welcome to the trial letter” and a “thank for your participation letter” at the end of the trial. Further the subject may receive trial letters during the trial period.

All information to the subjects will be submitted to the health authorities and IECs/IRBs for approval according to local regulations.

18.4 Premature termination of the trial and/or trial site

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

If a 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 IRBs/IECs and provide a detailed written explanation. The relevant regulatory authorities must be informed.

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

19 Protocol compliance

Deviations from the protocol should be avoided.

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

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

Documentation on protocol deviations must be kept in the investigator's trial file and Novo Nordisk trial master file.

20 Audits and inspections

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

21 Critical documents

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

- Regulatory approval and/or acknowledgement of notification as required
- Approval/favourable opinion from IRBs/IECs clearly identifying the documents reviewed as follows: protocol, any protocol amendments, subject information/informed consent form, any other written information to be provided to the subject and subject recruitment materials
- List of IRB/IEC members and/or constitution
- Curricula vitae of investigator and sub-investigator(s) (current, dated and signed - must include documented GCP training or a certificate)
- Signed receipt of Investigator's Brochure and local label for comparator
- Signed and dated agreement on the final protocol
- Signed and dated agreement on protocol amendment, if applicable
- Financial agreement(s)
- Source document agreement
- Central laboratory certification and normal ranges
- Insurance statement, if applicable
- Signed and dated Investigator Agreement
- Financial disclosure form from investigator and sub-investigator(s)

Novo Nordisk will analyse and report data from all sites together.

By signing the protocol, each investigator agrees to comply fully with ICH GCP [1], applicable regulatory requirements and the Declaration of Helsinki[2].

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

22 Responsibilities

All staff Novo Nordisk, site, Central Laboratories, CRO etc. must conduct the trial in compliance with ICH GCP [1], applicable regulatory requirements, and in accordance with the Declaration of Helsinki [2]

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

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

The investigator is responsible for filing essential documents (ie those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced) in the investigator's trial file. The documents should be kept in a secure locked facility, so no unauthorized persons can get access to the data. The subject identification code list must be kept securely and separate from the personal 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 (eg 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 Novo Nordisk for regulatory purposes and 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.

One principal investigator will be appointed 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[44].

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.

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 principal 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 [44] (sometimes referred to as the Vancouver Criteria).

At the end of the trial, one or more publications (abstracts, posters, manuscripts) will be prepared for submission to scientific congresses and peer-reviewed journals in collaboration between Novo Nordisk and investigator(s) appointed by Novo Nordisk. These investigator(s) must meet the ICMJE authorship criteria to be named authors on publications.

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 for publication of such primary policy 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 and human biospecimens

24.1 Retention of clinical trial documentation

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

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

The investigator must be able to access his/her trial documents without involving Novo Nordisk in any way. Site-specific CRFs and other subject data (in an electronic readable format or as paper copies or prints) will be provided to the investigator before access is revoked to the systems and/or electronic devices supplied by Novo Nordisk. These data must be retained by the trial site. If the Novo Nordisk provided data (eg 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 as long as the product is on the market plus 20 years.

The files from the investigator site/institution must be retained for 15 years after the completion of the trial, or longer if required by local regulations. The deletion process must ensure confidentiality of data and must be done in accordance with local regulatory requirements.

24.2 Retention of human biospecimens

Antibody samples may be stored until market authorisation in case Health Authorities requests further characterisation of the antibody response.(Brazil, due to local regulation, the laboratory samples for BR subjects will be destroyed at the latest at the completion of the CTR, including samples for anti-semaglutide antibody analysis. No sample will be stored after the completion of CTR).

Thyroid tissue samples will be stored in a tissue bank until testing for RET Y1062 phosphorylation in the thyroid-cells, if allowed by local law.

None of the data will be identified by name. Antibody samples and thyroid tissue will be identified only by a subject number, a visit number and a trial identification number. The trial staff is responsible for maintaining a code list which links to the subject number. The code list must be kept

for at least 15 years. The code list may be reviewed by Novo Nordisk staff including auditors or representatives from regulatory authorities, but no copies will be made of this list.

25 Institutional Review Boards/Independent Ethics Committees and regulatory authorities

IRB/IEC:

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

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

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

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

The investigator must maintain an accurate and complete record of all submissions made to the IRB/IEC. The records must be filed in the investigator's trial 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 local laws/acts/guidelines.

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Protocol

Trial ID: NN9535-4114

SUSTAIN – CHINA MRCT

Efficacy and safety of semaglutide once-weekly versus sitagliptin once-daily as add-on to metformin in subjects with type 2 diabetes

A 30-week randomised, double-blind, double-dummy, active-controlled, parallel-group, multi-centre and multi-national trial

Trial phase: 3a

Protocol originator

[redacted]

Semaglutide Diabetes & Diabetes Outcomes

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List of abbreviations

AACE	American Association of Clinical Endocrinologists
ADA	American Diabetes Association
AE	adverse event
BG	blood glucose
BMI	Body mass index
CRF	case report form
CRO	contract research organisation
CTR	clinical trial report
CVD	cardiovascular disease
DPP-4	dipeptidyl peptidase 4
DUN	dispensing unit number
DTSQs	Diabetes Treatment Satisfaction Questionnaire status
EAC	event adjudication committee
ECG	electrocardiogram
eCRF	electronic case report form
EE	ethinylestradiol
EFD	embryo-foetal development
eGFR	estimated glomerular filtration rate
FAS	full analysis set
FDAAA	Food and Drug Administration Amendment Act
FPFV	first patient first visit
FPG	fasting plasma glucose
FSFV	first subject first visit
GCP	Good Clinical Practice
GI	gastrointestinal
GIP	gastric inhibitory polypeptide
GLP-1	glucagon-like peptide-1
HbA_{1c}	glycosylated haemoglobin

hCG	human chorionic gonadotrophin
HDL	high density lipoprotein
hsCRP	highly sensitive C-reactive protein
IB	Investigator's Brochure
ICMJE	International Committee of Medical Journal Editors
IEC	independent ethics committee
IMP	investigational medicinal product
IRB	Institutional Review Board
IUD	intrauterine device
IWRS	interactive voice/web response system
LDL	low density lipoprotein
LN	levonorgestrel
LPFV	last patient first visit
LPLV	last patient last visit
LSFV	last subject first visit
LSLV	last subject last visit
MACE	major adverse cardiovascular events
MAR	missing at random
MCAR	missing completely at random
MDRD	modification of diet in renal disease
MEN2	multiple endocrine neoplasia syndrome type 2
MMRM	mixed model for repeated measurements
MTC	medullary thyroid carcinoma
NYHA	New York Heart Association
OAD	oral anti-diabetic drug
PG	plasma glucose
PP	per protocol
PPG	postprandial glucose
PPND	pre- and postnatal development

PRO	patient reported outcome
RA	receptor agonist
SAE	serious adverse event
SAP	statistical analysis plan
s.c.	subcutaneous
SD	standard deviation
SDV	source data verification
SMBG	self-measured blood glucose
SMPG	self-measured plasma glucose
SU	sulphonylurea
SUSAR	suspected unexpected serious adverse reaction
TMM	Trial Materials Manual
TEAE	treatment emergent adverse event
TVP	trial validation plan
UACR	urinary albumin to creatinine ratio
UTN	universal trial number
V	visit

1 Summary

Objectives and endpoints:

Primary objective

To compare the effect of once-weekly dosing of two dose levels of semaglutide versus sitagliptin 100 mg once-daily on glycaemic control after 30 weeks of treatment

Primary endpoint

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

Secondary objectives

To compare the effects of once-weekly dosing of two dose levels of semaglutide versus sitagliptin 100 mg once-daily after 30 weeks of treatment on:

- Inducing and maintaining weight loss
- Other parameters of efficacy, safety and tolerability

Key secondary endpoint

Confirmatory secondary endpoint

- Change from baseline to week 30 in body weight

Supportive secondary endpoints:

Change from baseline to week 30 in:

- Fasting plasma glucose (FPG)
- Systolic and diastolic blood pressure
- Patient reported outcome (PRO) questionnaire: Diabetes Treatment Satisfaction Questionnaire status (DTSQs) score

Subjects who after 30 weeks treatment achieve (yes/no):

- $HbA_{1c} \leq 6.5\%$ (48 mmol/mol) - American Association of Clinical Endocrinologists (AACE) target

Trial design:

This is a 30-week randomised, double-blind, double-dummy, active-controlled, multi-centre, multi-national four-armed, parallel-group trial comparing semaglutide 0.5 mg and 1.0 mg once-weekly against sitagliptin 100 mg once-daily.

Subjects with type 2 diabetes inadequately controlled on metformin will be randomised in a 2:2:1:1 manner to receive either:

- semaglutide 0.5 mg once-weekly + sitagliptin placebo once-daily
- semaglutide 1.0 mg once-weekly + sitagliptin placebo once-daily
- sitagliptin 100 mg once-daily + semaglutide placebo (0.5) mg once-weekly
- sitagliptin 100 mg once-daily + semaglutide placebo (1.0) mg once-weekly

Trial product will be add-on to subject's stable pre-trial metformin.

Key inclusion criteria:

- Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial
- Male or female, age ≥ 18 years at the time of signing informed consent
- Subjects diagnosed with type 2 diabetes and on stable treatment in a period of 60 days prior to screening with metformin ≥ 1500 mg (or maximum tolerated dose ≥ 1000 mg). Stable is defined as unchanged medication and unchanged daily dose
- HbA_{1c} 7.0 – 10.5 % (53-91 mmol/mol) (both inclusive)

Key exclusion criteria:

- Female who is pregnant, breast-feeding or intends to become pregnant or is of childbearing potential not using an adequate contraceptive method throughout the trial including the 5 week follow-up period (adequate contraceptive measure as required by local regulation or practice).
- Any disorder which, in the opinion of the investigator, might jeopardise subject's safety or compliance with the protocol
- Treatment with glucose lowering agent(s) other than stated in the inclusion criteria in a period of 60 days before screening. An exception is short-term treatment (≤7 days in total) with insulin in connection with inter-current illness
- History of chronic or idiopathic acute pancreatitis
- Screening calcitonin value ≥ 50 ng/L (pg/mL)
- Personal or family history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia syndrome type 2 (MEN 2)
- Impaired renal function defined as estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2 per modification of diet in renal disease (MDRM) formula (4 variable version)
- Acute coronary or cerebrovascular event within 90 days before randomisation
- Heart failure, New York Heart Association (NYHA) class IV

Assessments:

Efficacy:

- Glucose metabolism
- Body measurements (body weight, body mass index (BMI) and waist circumference)
- Systolic and diastolic blood pressure
- Blood lipids
- Patient reported outcome (PRO) questionnaires (SF-36v2™ and DTSQs)

Safety:

- Adverse events and serious adverse events
- Hypoglycaemic episodes
- Biochemistry and haematology
- Anti-semaglutide antibodies
- Physical examination (including electrocardiogram (ECG))

Trial products:

Novo Nordisk A/S will supply the following trial products:

- Semaglutide 1.34 mg/mL, solution for injection, 1.5 mL pre-filled PDS290 pen-injector
- Semaglutide placebo, solution for injection, 1.5 mL pre-filled PDS290 pen-injector
- Sitagliptin (Januvia®) 100 mg tablets for oral administration
- Sitagliptin placebo tablets for oral administration

2 Flow chart

Trial Periods		Screen	Rand	Treatment period						End of Treatment[1]	Follow Up[1]	End of Treatment premature discontinuation[2]	Follow Up premature discontinuation[2]
Visit (V) or Phone (P) number		V1	V2	V3	P4	V5	V6	V7	V8	V9	V10	V9A	V10A
Time of visit	**Weeks**	-2	0	4	6	8	12	16	23	30	35		
Visit window	**Days**	±7		±3	±3	±3	±3	±3	±3	±7	+7		
SUBJECT RELATED INFO /ASSESSMENTS													
Informed consent	18.1	x											
In/exclusion criteria	6.2,6.3	x	x										
Randomisation	8.1.3		x										
Withdrawal criterion	6.5			x	x	x	x	x	x	x		x	
Demography	8.2.1	x											
Diabetes history and diabetes complications	8.2.2	x											
Concomitant illness and medical history	8.2.3	x											
History of cardiovascular disease	8.2.3	x											
History of gallbladder disease	8.2.3	x											
Tobacco use	8.2.5	x											
Concomitant medication	8.2.4	x	x	x	x	x	x	x	x	x	x	x	x
Height	8.2.7		x										
EFFICACY													
Body weight	8.3.1		x	x		x	x	x	x	x		x	
Waist circumference	8.3.2		x	x		x	x	x	x	x		x	
BMI	8.3.3		x	x		x	x	x	x	x		x	
Systolic blood pressure, sitting	8.3.4	x	x	x		x	x	x	x	x		x	
Diastolic blood pressure, sitting	8.3.4	x	x	x		x	x	x	x	x		x	

Trial Periods		Screen	Rand	Treatment period						End of Treatment[1]	Follow Up[1]	End of Treatment premature discontinuation[2]	Follow Up premature discontinuation[2]
Visit (V) or Phone (P) number		V1	V2	V3	P4	V5	V6	V7	V8	V9	V10	V9A	V10A
Time of visit	**Weeks**	-2	0	4	6	8	12	16	23	30	35		
Visit window	**Days**	±7		±3	±3	±3	±3	±3	±3	±7	+7		
HbA_{1c}	8.5.1.1	x	x	x		x	x	x	x	x		x	
Fasting plasma glucose	8.5.1.1		x	x		x	x	x	x	x		x	
Fasting insulin	8.5.1.1		x					x		x		x	
Fasting proinsulin	8.5.1.1		x					x		x		x	
Fasting C-peptide	8.5.1.1		x					x		x		x	
Fasting glucagon	8.5.1.1		x					x		x		x	
Lipids	8.5.1.3		x					x		x		x	
hsCRP (highly sensitive CRP)	8.5.1.2		x					x		x		x	
7 point profile	8.5.1.4		x					x		x		x	
SAFETY													
Adverse events	8.4.1		x	x	x	x	x	x	x	x	x	x	x
Hypoglycaemic episodes	8.4.4		x	x	x	x	x	x	x	x	x	x	x
ECG	8.4.5		x							x	x	x	x
Physical examination	8.4.6	x								x		x	
Pulse, sitting	8.4.7	x	x	x		x	x	x	x	x		x	
Anti-semaglutide antibodies[4]	8.5.2.1		x					x		x	x	x	x
Creatinine	8.5.2.2	x		x		x	x	x	x	x		x	
Biochemistry	8.5.2.2		x	x		x	x	x	x	x		x	
Haematology	8.5.2.3		x	x		x	x	x	x	x		x	
Calcitonin	8.5.2.4	x						x		x		x	
Pregnancy test[5]	8.5.2.5	x	x	x		x	x	x	x	x	x	x	x
Urinalysis	8.5.2.6		x					x		x		x	
Eye examination[3]	8.4.8		x							x		x	
OTHER ASSESSMENTS													

Trial Periods		Screen	Rand	Treatment period						End of Treatment[1]	Follow Up[1]	End of Treatment premature discontinuation[2]	Follow Up premature discontinuation[2]
Visit (V) or Phone (P) number		V1	V2	V3	P4	V5	V6	V7	V8	V9	V10	V9A	V10A
Time of visit	**Weeks**	-2	0	4	6	8	12	16	23	30	35		
Visit window	**Days**	±7		±3	±3	±3	±3	±3	±3	±7	+7		
PRO questionnaires	8.6.1		x							x		x	
TRIAL MATERIAL													
Drug accountability	9.4					x		x		x		x	
IWRS call	10	x	x			x		x		x		x	
Dispensing visit	9.1		x			x		x					
REMINDERS													
Training in trial product, and pen handling	9.1		x	x		x							
Hand-out Directions for Use (DFU)	9.5		x										
End of treatment	8.1.6									x[9]		x[9]	
End of trial	8.1.6										x[9]		
Hand-out and instruct in BG meter use	8.5.1.4	x											
Hand-out and /or collect diary[6]	8.6.2	x	x	x		x	x	x	x	x	x[6]	x	x[6]
Attend visit fasting[7]	8.1.2		x	x		x	x	x	x	x	x[8]	x	x[8]
Hand-out ID card	8.1.1	x											

2.1 Flow chart explanatory descriptions

Footer	Description
x[1]	V9 (End of Treatment) and V10 (Follow Up) are applicable for all randomised subjects. Subjects who have discontinued trial product prematurely should also attend V9 and V10 according to their initially scheduled week 30 and Week 35 visits.
x[2]	Subjects discontinuing trial product prematurely will be asked to attend two additional visits to undergo assessments: End of Treatment-premature discontinuation (V9A) and Follow Up -premature discontinuation (V10A). V9A should be scheduled at discontinuation of the trial product. V10A should be scheduled 5 weeks after discontinuation of trial product (+ 7 days visit window).
x[3]	Fundus photography/dilated fundoscopy performed within 90 days before visit 2 is acceptable if results are available for evaluation at the visit 2 and no deterioration in visual function since last assessment.
x[4]	Antibody sampling should preferably be done pre-dose. For fasting and non-fasting visit, where the injection takes place on the day of site visit, trial product must not be taken before blood sampling. For visit 9 and 10: Not applicable if taken at a premature discontinuation visit
x[5]	For women of child bearing potential: For all site visits a serum pregnancy test must be performed. Urine pregnancy test should be performed at any time during the trial if a menstrual period is missed, or as required by local law.
x[6]	At V10 and V10A collect diary only.
x[7]	Fasting is defined as having consumed only water within the last 6 hours prior to the visit. Glucose lowering agents and trial product cannot be taken until after blood sampling has been performed but other prescribed medication should be taken.
x[8]	For the follow-up visit (V10/V10A) attend fasting is defined as having consumed only water within the last 2 hours prior to the visit.
x[9]	If premature discontinuation occurs, End of Treatment form must be filled-in when the discontinuation happens and End of Trial form at scheduled V10. 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 V10. In case of subject withdrawal, both End of Treatment form and End of Trial form must be filled-in at the time they withdraw from the trial.

3 Background information and rationale for the trial

The trial will be conducted in compliance with this protocol, ICH GCP[1] and applicable regulatory requirements, and in accordance with the Declaration of Helsinki[2].

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 Type 2 diabetes

Type 2 diabetes (T2D) is a progressive metabolic disease primarily characterised by abnormal glucose metabolism. The pathogenesis is not fully understood but seems to be heterogeneous, involving environmental, lifestyle, and genetic factors leading to chronic hyperglycaemia caused by peripheral tissue insulin resistance, impaired insulin secretion due to abnormal beta-cell function and abnormal glucose metabolism in the liver[3].

Optimal glycaemic control is the treatment goal in subjects with type 2 diabetes, in order to prevent long-term complications associated with chronic hyperglycaemia[4,5]. Despite the availability of several anti-diabetic drugs, a significant proportion of subjects with type 2 diabetes do not achieve the recommended blood glucose target levels[6-9].

3.2 Glucagon-like peptide-1

Glucagon-like peptide-1 (GLP-1) is an incretin hormone with a glucose-dependent stimulatory effect on insulin and inhibitory effect on glucagon secretion from the pancreatic islets[10, 11]. Subjects with T2D have a decreased response to GLP-1[12-15] . However, the insulinotropic action of GLP-1 and thus, the ability to lower BG levels, is preserved when GLP-1 is administered at supraphysiological levels[16]. In addition, supraphysiological levels of GLP-1 induce reduction in body weight[17]. GLP-1 is a physiological regulator of appetite and food intake and GLP-1 receptors are present in several areas of the brain involved in appetite regulation and food intake[18, 19]. Physiologically, GLP-1 also has a pronounced inhibitory effect on gastric emptying; however this effect seems to diminish upon chronic exposure[17-19]. These mechanisms of action make glucagon-like peptide-1 receptor agonists (GLP-1 RAs) an attractive pharmacological treatment for T2D[20-22]. Due to the very short half-life of <1.5 minutes after i.v. administration, native GLP-1 is not suitable for therapeutic use. To realise the full therapeutic potential of GLP-1, the pharmacokinetic and hence the pharmacodynamic effect needs to be protracted.

3.3 Semaglutide

Semaglutide is a potent human GLP-1 receptor agonist (RA) for once-weekly subcutaneous (s.c.) administration. It is structurally similar to liraglutide (Victoza®), a once-daily GLP-1 RA developed by Novo Nordisk and approved worldwide for the treatment of type 2 diabetes. The extended half-life of the semaglutide molecule is primarily obtained due to binding to albumin, which is facilitated

by a large fatty acid derived chemical moiety attached to the lysine in position 26. The specific modifications in the molecule are: 1) a modification in position 8 (alanine to 2-aminoisobutyric acid) of the peptide backbone to increase stability against 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 diacid with a terminal acidic group[23, 24]. The spacer and the fatty acid both contribute to increased albumin binding, which results in decreased renal clearance resulting in a prolonged half-life of approximately 1 week, making semaglutide suitable for once-weekly s.c. administration.

3.3.1 Non-clinical data

The non-clinical programme for semaglutide was designed according to the ICH M3[25] guideline to support the clinical development. The standard non-clinical 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.

3.3.1.1 Thyroid C-cell tumours in rodents

Thyroid C-cell neoplasia was seen in mice and rat 2-year carcinogenicity studies. Proliferative C cell changes in rodents are a known effect following GLP-1 receptor activation by GLP-1 receptor agonists. The finding in rodents is caused by a non-genotoxic, specific GLP-1 receptor-mediated mechanism to which rodents are particularly sensitive. Recently published data have shown that the GLP-1 receptor is not expressed in the normal human thyroid, and accordingly, the risk of GLP-1 receptor mediated C-cell changes in humans is considered to be low[26].

3.3.1.2 Embryo−foetal development toxicity

Semaglutide adversely affected embryo−foetal development in the rat by a GLP-1 receptor mediated impaired function of the inverted yolk sac placenta during a period of gestation when the rat embryo is entirely dependent on the inverted yolk sac placenta for its nutrient supply. In primates, the yolk sac does not invert to fully enclose the embryo, and it does not come in direct contact with the uterine wall to form a placenta as in rodents. Accordingly, the mechanism by which semaglutide adversely affects embryo-foetal development in the rat, is not likely to be of relevance to humans. Studies in cynomolgus monkeys confirmed that maternal dosing of semaglutide does not affect embryo−foetal development in this species. However, the initial maternal body weight loss caused by the pharmacological effect of semaglutide coincided with increased early pregnancy loss in one of three studies. In cynomolgus monkeys, the overall developmental no observable adverse

effect level (NOAEL) was determined to be 0.015 mg/kg/3 days, which provides an exposure equivalent to the human exposure at 1.0 mg/week based on area under the curve (AUC).

A comprehensive review of results from the nonclinical studies can be found in the current edition of semaglutide (NN9535) investigator's brochure (IB)[27], or any updates hereof.

3.3.2 Clinical data

As of 1 August 2016, 16 clinical pharmacology trials (trials NN9535-1820, 3679, 3633, 3616, 3819, 4010, 3789, 3652, 3685, 3634, 3687, 3817,3818, 3684, 3651 and 3635), 1 phase 2 trial (NN9535-1821) and 8 phase 3a trials (NN9535-3623, 3624, 3625,3626, 3627, 3744, 4091, 4092) have been completed with semaglutide s.c. once-weekly. Clinical pharmacology trials were conducted in healthy subjects, in subjects with T2D, in subjects with obesity and in subjects with renal- and hepatic impairment. The phase 2 dose-finding trial was conducted in subjects with T2D. The 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-hyperglycaemic therapies and compared semaglutide with the most important comparators at the time of initiating the phase 3a programme. In addition, the phase 3a programme included a long-term (104-week) cardiovascular outcomes trial (trial 3744) in a T2D population at high risk of cardiovascular events.

3.3.2.1 Pharmacokinetics

The results from the completed clinical pharmacology trials confirm that semaglutide has PK properties compatible with once-weekly administration, having a flat concentration profile over time, with a median time to maximum concentration (tmax) of 1−3 days post-dosing and an elimination half-life (t½) of approximately 1 week. The PK properties of semaglutide appear comparable between healthy subjects, subjects with T2D and subjects with renal failure. Results from drug-interaction studies with warfarin, metformin, atorvastatin and digoxin indicate that no dose adjustment of the co-administered drugs is warranted when administered together with semaglutide. In addition, semaglutide does not decrease the exposure of oral contraceptives and hence, is not anticipated to decrease the effectiveness of oral contraceptives.

3.3.2.2 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 receptor agonists, semaglutide caused a minor delay of early postprandial gastric emptying.

Both as monotherapy and as combination therapy, semaglutide significantly reduced HbA1c 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 HbA1c 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 HbA1c <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 HbA1c were substantiated by improvements in secondary glycaemia-related supportive endpoints[28-31].

3.3.2.3 Safety

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

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

The effect of semaglutide on major adverse cardiovascular events (MACE) was evaluated in a T2D population at high risk for CV events, in the cardiovascular outcome trial, SUSTAIN 6 (NN9535-3744)[32]. SUSTAIN 6 trial achieved its primary objective by showing non-inferiority of once-weekly s.c. semaglutide versus placebo on cardiovascular outcomes; moreover, s.c. semaglutide statistically significantly reduced cardiovascular risk versus placebo[32]. In addition, results from the recently completed LEADER® trial (EX2211-3748) showed that treatment with the once daily liraglutide does not increase the risk of MACE as compared to placebo. In fact, treatment with liraglutide reduced the risk of the primary composite outcome consisting of death from cardiovascular causes, non-fatal myocardial infarction (MI) and non-fatal stroke by 13% versus placebo[32]. The overall safety profile of semaglutide in the SUSTAIN 6 trial (NN9535-3744) was consistent with previous

semaglutide clinical studies. However, in this trial, the diabetic retinopathy complications were reported more frequently in the semaglutide-treated subjects compared with placebo.

Please see the current edition of semaglutide s.c. (NN9535) IB or any updates hereof for further details[27].

3.4 Sitagliptin

Sitagliptin is an oral antihyperglycemic agent of the dipeptidyl peptidase-4 (DPP-4) inhibitor class suitable for once-daily oral administration. It was developed and marketed by Merck & Co as sitagliptin phosphate under the trade name Januvia®

Sitagliptin works by inhibition of the enzyme dipeptidyl peptidase 4 (DPP-4). This enzyme breaks down the incretin hormones GLP-1 and gastric inhibitory polypeptide (GIP). By preventing GLP-1 and GIP inactivation, secretion of insulin is increased and release of glucagon is suppressed. The obvious advantage with a convenient route of administration is however counterbalanced by a significantly lower effect of the DPP-4 inhibitors on glycaemic control and body weight as compared to GLP-1 RAs. This has also been demonstrated for sitagliptin when compared to liraglutide[33-35].

Adverse reactions reported in >5% of patients treated with sitagliptin and more commonly than in patients treated with placebo are: upper respiratory tract infection, nasopharyngitis and headache. In add-on to sulfonylurea and add-on to insulin studies, hypoglycaemia was also more commonly reported in patients treated with sitagliptin compared to placebo[36].

3.5 Risk and benefits assessment

This assessment is based on the safety and efficacy data for semaglutide and sitagliptin presented above as well as potential risk identified as drug class effects.

3.5.1 Semaglutide risks and precautions

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

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

3.5.2 Identified risks

Gastrointestinal adverse events

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

Diabetic retinopathy complications

A transient worsening of diabetic retinopathy is a recognised complication in selected patients with diabetes after initiation of intensive anti-diabetic treatment[37]. 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[38, 39] even in intensively treated patients who experienced early worsening[40]. In a cardiovascular outcomes trial with s.c. semaglutide, results indicate an increased risk of events related to diabetic retinopathy complications in subjects treated with semaglutide compared to placebo. As a precaution in this trial, all subjects are required to have a fundus photography or dilated 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[41].

3.5.3 Potential risks

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 MEN 2 or MTC will not be enrolled in the trial. During the trial, calcitonin will be measured on a regular basis, and the guidance for investigators on further evaluation and action on elevated calcitonin concentrations is included in appendix A.

Acute pancreatitis

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

Pancreatic cancer

Patients with T2D have an increased risk of certain types of cancer such as pancreatic cancer. There is currently no support from nonclinical studies or clinical trials or post marketing data that GLP-1-based therapies increase the risk of pancreatic cancer. However, pancreatic cancer has been included as a separate potential risk due to the scientific debate surrounding a potential association to GLP-1-based therapies and the unknown long-term effects of stimulation of β-cells and suppression of α-cells. Pancreatic cancer has been classified as a potential class risk of GLP-1 RAs by EMA.

Allergic reactions and injection site reaction

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

Hypoglycaemia

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

Acute renal impairment

In subjects treated with GLP-1 RAs, including semaglutide, gastrointestinal AEs such as nausea, vomiting and diarrhoea may lead to significant dehydration and secondary acute renal impairment. 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.

3.5.4 Other safety considerations

Teratogenicity (embryo-foetal development toxicity)

Semaglutide caused embryo-foetal malformations in the rat through a GLP-1 receptor mediated effect on the inverted yolk sac placenta leading to impaired nutrient supply to the developing embryo. Primates do not have an inverted yolk sac placenta which makes this mechanism unlikely to be of relevance to humans. However, as a precaution, females who are pregnant, breast-feeding or intend to become pregnant or are of childbearing potential and not using an adequate contraceptive method will not be enrolled in the trial. In addition, pregnancy tests will be performed 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[42, 43] (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 2016 Standards of Medical Care in Diabetes[44].

Further details with regards to safety of trial product are described in the current edition of the IB for semaglutide (NN9535)[27], or any updates thereto.

3.5.5 Sitagliptin risk and precautions

Sitagliptin is generally considered to be well tolerated. The most commonly reported side effect is upper respiratory tract infection, nasopharyngitis and headache. Some of the potential risk associated with GLP-1 RA treatment has also been associated with treatment with the DPP-4 inhibitors as sitagliptin i.e. pancreatitis, acute renal impairment, hypersensitivity reactions and hypoglycaemia (US prescribing information[45] and Chinese prescribing information[46])

3.5.6 Benefits

In this trial subjects in all treatment arms will be treated within a regimen anticipated to be more efficacious than the treatment they receive at the time of randomisation into the trial. It is expected that subjects will benefit from the trial treatment with respect to optimised glycaemic control, a reduced risk of long-term diabetic complications and a potential weight loss.

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.

Furthermore, data from two cardiovascular outcomes trials investigating treatment with GLP-1 RAs compared to placebo have indicated a beneficial effect of these drugs on cardiovascular outcomes when added to standard of care in subjects with T2D at high risk of cardiovascular events (see Section 3.3.2.3).

Sitagliptin has in phase 3 trials where sitagliptin has been given in combination with metformin proven to provide significant improvements in HbA_{1c} and FPG[47].

All subjects in this trial will receive active treatment and will receive trial drug and auxiliary free of charge.

Finally, it is expected that all subjects participating in the trial will benefit from participation through close contact with the study site and close follow-up of their type 2 diabetes. Such careful medical examination will most likely result in an intensified management of their diabetes.

3.5.7 Risk and benefit conclusion

It is concluded that the potential benefits from participating in the trial outweigh the potential risks. The safety profile of semaglutide generated from the clinical and nonclinical development programme has not revealed any safety issues that would prohibit administration of once-weekly doses of 0.5 mg or 1.0 mg semaglutide in accordance with the planned clinical trial. Sitagliptin is already a marketed drug in the 100 mg dose and approved for the use in type 2 diabetic patients. Safety and efficacy will be monitored regularly and acceptable glycaemic control will be reinforced at all times during the trial.

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

3.6 Rationale for the trial

The currently available treatment modalities for type 2 diabetes are still not satisfactory and there is still a large proportion of patients not reaching the treatment targets. In the 5 global phase 3a trials (3623, 3624, 3625, 3626 and 3627), reductions in HbA1c and body weight with semaglutide was superior to sitagliptin, exenatide ER and insulin glargine demonstrating semaglutide as a highly efficacious treatment option.

The rationale for this trial is to compare the efficacy of semaglutide versus sitagliptin in subjects with type-2 diabetes in terms of glycaemic control, weight loss and other efficacy parameters. Furthermore the trial is designed to address and compare safety, tolerability and patient satisfaction. This trial is designed to resemble the main trial NN9535-3626 (SUSTAIN 2) in the global

SUSTAIN programme and will be conducted in China and several other countries. The study design is adjusted to fulfil the Chinese requirements.

4 Objectives and endpoints

4.1 Objective

4.1.1 Primary objective

To compare the effect of once-weekly dosing of two dose levels of semaglutide versus sitagliptin 100 mg once-daily on glycaemic control after 30 weeks of treatment

4.1.2 Secondary objectives

To compare the effects of once-weekly dosing of two dose levels of semaglutide versus sitagliptin 100 mg once-daily after 30 weeks of treatment on:

- Inducing and maintaining weight loss
- Other parameters of efficacy, safety and tolerability

4.2 Endpoints

4.2.1 Primary endpoint

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

4.2.2 Secondary endpoints

4.2.2.1 Confirmatory secondary endpoint

- Change from baseline to week 30 in body weight

4.2.2.2 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)
- Insulin, C-peptide, glucagon, pro-insulin, pro-insulin/insulin ratio, homeostasis model assessment of beta-cell function (HOMA-B) and insulin resistance (HOMA-IR) (all fasting)
- Fasting blood lipids (total cholesterol, low density lipoprotein (LDL) cholesterol, very low density lipoprotein (VLDL) cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides and free fatty acids
- Body mass index (BMI)
- Waist circumference
- Systolic and diastolic blood pressure*

- Highly sensitive C-reactive protein (hsCRP)
- Patient reported outcome (PRO) questionnaire: SF-36v2™ score
- Patient reported outcome (PRO) questionnaire: Diabetes Treatment Satisfaction Questionnaire status (DTSQs) score*

Subjects who after 30 weeks treatment achieve (yes/no):

- $HbA_{1c} < 7.0\%$ (53 mmol/mol) - American Diabetes Association (ADA) target
- $HbA_{1c} \leq 6.5\%$ (48 mmol/mol) - American Association of Clinical Endocrinologists (AACE) target*
- Weight loss $\geq 5\%$
- Weight loss $\geq 10\%$
- $HbA_{1c} < 7.0\%$ (53 mmol/mol) without severe or blood glucose (BG) confirmed symptomatic hypoglycaemia and no weight gain

Supportive secondary safety endpoints

- Number of treatment emergent adverse events (TEAEs) during 30 weeks of treatment
- Number of treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes during 30 weeks of treatment
- Severe or BG confirmed symptomatic hypoglycaemic episodes during 30 weeks of treatment (yes/no)

Change from baseline to week 30 in:

- Haematology
- Biochemistry
- Calcitonin
- Urinalysis
- Urinary albumin to creatinine ratio (UACR)
- Pulse
- Electrocardiogram (ECG) evaluation
- Physical examination
- Eye examination

Occurrence of anti-semaglutide antibodies during 30 weeks of study duration (yes/no):

- Anti-semaglutide antibodies with *in vitro* neutralising effect
- Anti-semaglutide antibodies cross reacting with endogenous GLP-1
    - Cross reacting antibodies with *in vitro* neutralising effect to endogenous GLP-1

Antibody level during and after 30 weeks of treatment

*Key supportive secondary endpoint prospectively selected for posting on clinicaltrials.gov.

5 Trial design

5.1 Type of trial

This is a 30-week randomised, double-blind, double-dummy, active-controlled, multi-centre, multi-national trial, four-armed, parallel-group trial comparing semaglutide 0.5 mg and 1.0 mg once-weekly against sitagliptin 100 mg once-daily.

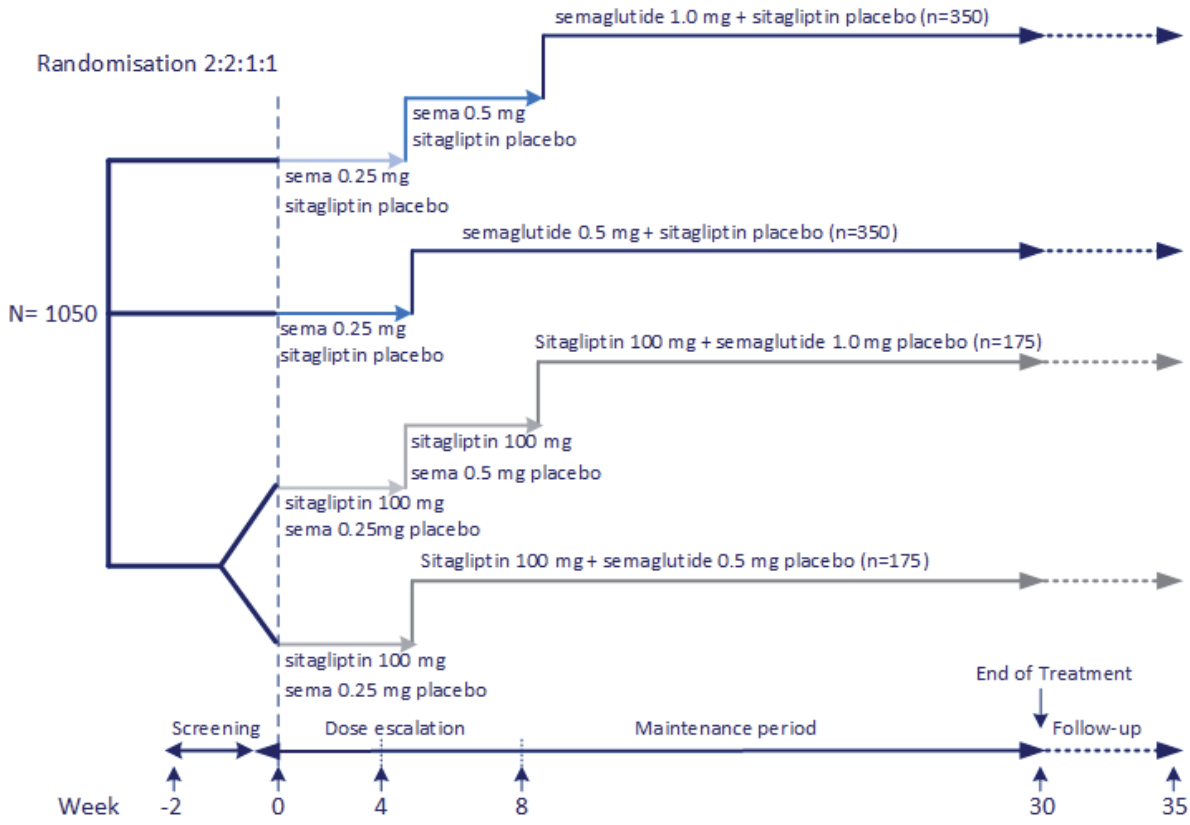


Figure 5–1 Trial design

Subjects with type 2 diabetes inadequately controlled on metformin will be randomised in a 2:2:1:1 manner to receive either:

- semaglutide 0.5 mg once-weekly + sitagliptin placebo once-daily
- semaglutide 1.0 mg once-weekly + sitagliptin placebo once-daily
- sitagliptin 100 mg once-daily + semaglutide placebo (0.5) mg once-weekly
- sitagliptin 100 mg once-daily + semaglutide placebo (1.0) mg once-weekly

The total trial duration for the individual subjects will be approximately 37 weeks. The trial includes a 2-week screening period followed by a 30-week randomised treatment period and a 5 week follow-up period.

A planned total of 1050 subjects will be randomised whereof approximately 792 subjects will be from China. Randomisation will be stratified by country.

5.2 Rationale for trial design

Parallel treatment groups and a randomised double-blind double dummy controlled design have been chosen in accordance with trial objectives and to avoid bias in the trial.

Treatment duration of 30 weeks is considered adequate in terms of assessing efficacy of semaglutide treatment versus sitagliptin treatment on change in HbA_{1c}. Furthermore, 30 weeks is considered sufficient for addressing and comparing the safety, tolerability and patient satisfaction profiles.

5.3 Treatment of subjects

Table 5–1 Treatment of subjects

Trial periods		**Screening**	**Period 1**	**Period 2**	**Period 3**	**Follow-up**
Alias for trial period		Screening	Dose escalation	Dose escalation/ Maintenance	Maintenance	Follow-up
Visits in each period		Visit 1-2	Visit 2-3	Visit 3-5	Visit 5-9	Visit 9-10
Duration of each period		2 weeks	4 weeks	4 weeks	22 weeks	5 weeks
Treatment arm	**N**					
• Semaglutide 0.5 mg • Sitagliptin placebo	350	Screening	• Semaglutide 0.25 mg, 1.34 mg/mL, 190µL • Sitagliptin placebo	• Semaglutide 0.5 mg, 1.34 mg/mL, 370µL • Sitagliptin placebo	• Semaglutide 0.5 mg, 1.34 mg/mL, 370µL • Sitagliptin placebo	Follow-up
• Semaglutide 1.0 mg • Sitagliptin placebo	350	Screening	• Semaglutide 0.25 mg, 1.34 mg/mL, 190µL • Sitagliptin placebo	• Semaglutide 0.5 mg, 1.34 mg/mL, 370µL • Sitagliptin placebo	• Semaglutide 1.0 mg, 1.34 mg/mL, 740µL • Sitagliptin placebo	Follow-up
• Sitagliptin • Semaglutide placebo (0.5 mg)	175	Screening	• Sitagliptin 100 mg • Semaglutide placebo 0 mg, 190µL	• Sitagliptin 100 mg • Semaglutide placebo 0 mg, 370µL	• Sitagliptin 100 mg • Semaglutide placebo 0 mg, 370µL	Follow-up
• Sitagliptin • Semaglutide placebo (1.0 mg)	175	Screening	• Sitagliptin 100 mg • Semaglutide placebo 0 mg, 190µL	• Sitagliptin 100 mg • Semaglutide placebo 0 mg, 370µL	• Sitagliptin 100 mg • Semaglutide placebo 0 mg, 740µL	Follow-up
All on background medication of metformin ≥ 1500 mg (or maximum tolerated dose ≥ 1000 mg) throughout the trial.						

After randomisation subjects will follow a fixed dose escalation for semaglutide and semaglutide placebo. The maintenance dose of 0.5 mg will be reached after 4 doses (4 weeks) of 0.25 mg. The

maintenance dose of 1.0 mg will be reached after 4 doses (4 weeks) of 0.25 mg, followed by 4 doses (4 weeks) of 0.5 mg. Doses must not be changed during the trial after the maintenance dose has been reached.

Semaglutide injections should be administered in the thigh, abdomen or upper arm, and should be taken on the same day of the week during the trial. Both semaglutide and sitagliptin can be taken any time of day irrespective of meals.

If necessary, the trial product may be discontinued for safety reasons. In case trial product is discontinued, subjects will not be withdrawn from trial but should continue to follow scheduled visits to the extent possible (see section 6.5.1).

Trial product will be add-on in subjects failing on metformin monotherapy.

Subjects must not be prescribed other GLP-1 RA in the period between V9 and V10 or V9A and V10A.

5.3.1 Missed dose

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

5.3.2 Background medication

Subjects should upon inclusion continue pre-trial background medication throughout the entire trial. The background medication should be maintained at the stable, pre-trial dose and frequency during the whole treatment period unless rescue medication is needed (see section 6.4).

Metformin is considered background medication (non-investigational medicinal product) and will not be provided by Novo Nordisk A/S (except for Brazil where Metformin will be provided by Novo Nordisk Farmacêutica do Brasil Ltda). Metformin should be used in accordance with standard of care in the individual country at the discretion of the investigator and the daily dose should be unchanged throughout the trial unless the rescue criteria are met. However the maximum approved dose in the individual country must not be exceeded. Treatment with metformin extended/slow release formulations is allowed.

5.3.3 Treatment after end of trial

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

(Brazil: After the study ending, if the investigator decides that the study medication is the best treatment option for the subject, the access to the study medication will be assured by the trial sponsor at no costs, according to the current regulations of Brazilian National Council of Health and Health Authority).

5.4 Rationale for treatment

Semaglutide has been developed for s.c. administration. The doses of 0.5 mg and 1.0 mg once-weekly has been chosen based on careful evaluation to strike a satisfactory balance of efficacy and safety that would satisfy the majority of patients. Hence duration and the dose of the randomised treatments are considered adequate for obtaining meaningful information on efficacy and safety in accordance with the trial objectives. Subjects will enrol for a treatment period of 30 weeks in order to be able to evaluate full effect as well as durability of the primary and secondary endpoints as well as a reasonable safety assessment.

For further information please refer to Investigator's Brochure, semaglutide (NN9535) (subcutaneous administration), Type 2 Diabetes and any updates hereof[27].

6 Trial population

6.1 Number of subjects

Planned number of subjects to be screened (i.e. documented informed consent):	Up to 1750
Planned number of subjects to be randomised:	1050
Expected number of subjects to complete the trial:	840
Planned number of Chinese subjects to be randomised:	792
Expected number of Chinese subjects to complete the trial:	636

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
   (For Korea: Male or female, age above or equal to 19 years at the time of signing informed consent.)
3. Subjects diagnosed with type 2 diabetes and on stable treatment in a period of 60 days prior to screening with metformin ≥ 1500 mg (or maximum tolerated dose ≥ 1000 mg). Stable is defined as unchanged medication and unchanged daily dose
4. HbA_{1c} 7.0 – 10.5 % (53-91 mmol/mol) (both inclusive)

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 informed consent
3. Female who is pregnant, breast-feeding or intends to become pregnant or is of childbearing potential not using an adequate contraceptive method throughout the trial including the 5 week follow-up period (adequate contraceptive measure as required by local regulation or practice)
   (China: Sterilization, intrauterine device (IUD), oral contraceptives or barrier methods).
   (Brazil: For women who expressly declare free of the risk of pregnancy, either by not engaging in sexual activity or by having sexual activity with no birth potential risk, use of contraceptive method will not be mandatory).

4. Receipt of any investigational medicinal product within 90 days before screening *(Brazil: Participation in other trials within one year prior to screening visit (V1) unless there is a direct benefit to the research subject at the Investigator´s discretion)*
5. Any disorder which, in the opinion of the investigator, might jeopardise subject's safety or compliance with the protocol
6. Treatment with glucose lowering agent(s) other than stated in the inclusion criteria in a period of 60 days before screening. An exception is short-term treatment (≤7 days in total) with insulin in connection with inter-current illness
7. Use of non-herbal Chinese medicine or other non-herbal local medicine with unknown/unspecified content. Herbal traditional Chinese medicine or other local herbal medicines may, at the Investigator's discretion, be continued throughout the trial
8. History of pancreatitis (acute or chronic)
9. Screening calcitonin value ≥ 50 ng/L (pg/mL)
10. Personal or family history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia syndrome type 2 (MEN 2)
11. Impaired renal function defined as eGFR < 60 ml/min/1.73 m2 per MDRD formula (4 variable version)
12. Acute coronary or cerebrovascular event within 90 days before randomisation
13. Heart failure, New York Heart Association (NYHA) class IV
14. Proliferative retinopathy or maculopathy requiring acute treatment. Verified by fundus photography or dilated fundoscopy performed within the past 90 days prior to randomisation in accordance with the instructions in Section 8.4.8.
15. Diagnosis of malignant neoplasm in the previous 5 years (except basal cell skin cancer or squamous cell skin cancer)
16. Mental inability, unwillingness or language barrier precluding adequate understanding of or compliance with study procedures

6.4 Rescue criteria

If any of the fasting plasma glucose (FPG) values exceed the limits outlined below and no intercurrent cause of the hyperglycaemia can be identified the subject should be called for an unscheduled visit as soon as possible:

- 15.0 mmol/L (270 mg/dl) from week 0 to end of week 5
- 13.3 mmol/L (240 mg/dl) from week 6 to end of Week 11
- 11.1 mmol/L (200 mg/dl) from week 12 to end of trial

A confirmatory FPG should be obtained. If the confirmatory FPG exceeds the values described above the subject should be offered treatment intensification (rescue medication) at the discretion of the investigator and in accordance with ADA/European Association for the Study of Diabetes[42, 43] (excluding GLP-1 RAs, DPP-4 inhibitors and amylin analogues). Rescue medication

(intensification of existing background medication and/or initiation of new medication) and any changes hereto should be captured on the concomitant medication form in the eCRF. Rescue medication should be prescribed as add-on to randomized treatment unless contraindicated according to the local sitagliptin label. In this case trial medication should be discontinued before initiation of rescue therapy. Subjects should continue to follow the protocol-specified visit schedule even if rescue treatment has been initiated.

6.5 Withdrawal criteria

6.5.1 Discontinuation of trial product

All efforts should be made to keep the subjects on trial product. However in case of a safety concern or unacceptable intolerability the trial product may be discontinued at the investigator's discretion.

Trial product must be discontinued in case of:

- Safety concern related to trial product or unacceptable intolerability
- included in the trial in violation of any of the inclusion and/or exclusion criteria
- Pregnancy
- Intention to become pregnant
- Simultaneous participation in another clinical trial of an approved or non-approved investigational medicinal product
- Calcitonin ≥ 100 ng/L (see appendix A)

For procedures to be performed in case of discontinuation of trial product (see section 8.1.6.2). Subjects discontinuing trial product prematurely should continue with the scheduled site contact. Subjects discontinued from trial product should be prescribed alternative therapy at the investigator´s discretion. However subjects must not be prescribed other GLP-1 RA in the period between V9 and V10 or V9A and V10A.

6.5.2 Withdrawal from trial

The subject may withdraw 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. Please see section 8.1.7 for procedure to be performed in case of subject withdrawal.

Subjects should stay in the trial irrespective of lack of adherence to randomised treatment, lack of adherence to visit schedule, missing assessments, trial product discontinuation due to AE (see section 6.5.1), unwillingness to cope with injection regimen, development of co-morbidities or clinical outcomes.

A subject who agrees to provide information concerning morbidities which are relevant for the assessments of cardiovascular outcomes and/or other trial end-points at the planned end of the trial should not be considered withdrawn from the trial.

Subjects who consider withdrawing from the trial should as a minimum be encouraged to have procedures performed according to the end of treatment visit (V9) and the follow up visit (V10), please see 8.1.7.

Only subjects who decline any further contact with the site in relation to the trial, and hence do not agree to report information which is relevant for the assessments of cardiovascular outcomes and/or other trial end-points at the end of trial should be considered as withdrawn from the trial.

6.6 Subject replacement

Subjects who are withdrawn will not be replaced.

6.7 Rationale for trial population

This trial will be carried out in China and several other countries. The aim is to include a broad diabetes population, hence the limited number of exclusion criteria. Subjects with type 2 diabetes who are inadequately controlled on metformin monotherapy will be included in the trial. As sitagliptin is indicated as monotherapy or in combination with metformin in China, subjects on other oral anti-diabetic drugs (OADs) are not included.

7 Milestones

Planned duration of recruitment period (i.e. FPFV– LPFV): 26 weeks

End of trial is defined as last patient last visit.

Planned date for first patient first visit (FPFV): 28-Aug-2017

Planned date for last patient first visit (LPFV): 26-Feb-2018

Planned date for last patient last visit (LPLV): 05-Nov-2018

To ensure that only the required number of subjects is randomised, screened subjects will be monitored closely via interactive voice response system/interactive web response system (IWRS).

A recruitment strategy will be developed in corporation with the participating countries to secure sufficient number of subjects from China and the other participating countries.

Recruitment will be monitored on an on-going basis by sponsor. Prior to FPFV all sites should have a recruitment strategy in place detailing how many subjects they can recruit within a certain period. If a site has not enrolled the number of subjects according to the recruitment strategy, the remaining subjects may be reallocated.

The screening and randomisation rate will be followed closely via IWRS in order to estimate when to stop screening. All investigators will be notified immediately when the enrolment period comes to an end, after which no subjects must be screened, and the IWRS will be closed for further screening. All subjects included in the screening period by the time of IWRS closure and eligible for randomisation will be randomised.

Trial registration:

Information of the trial will be disclosed at clinicaltrials.gov, chinadrugtrials.org.cn and novonordisk-trials.com. According to the Novo Nordisk Code of Conduct for Clinical Trial Disclosure, it will also be disclosed according to other requirements such as those of the International Committee of Medical Journal Editors (ICMJE)[48], the Food and Drug Administration Amendment Act (FDAAA) [49], European Commission Regulation for EudraCT[50] and other relevant recommendations or regulations. If a subject requests to be included in the trial via the Novo Nordisk e-mail contact at these web sites, Novo Nordisk may disclose the investigator's contact details to the subject. As a result of increasing requirements for transparency, some countries require public disclosure of investigator names and their affiliations.

8 Methods and assessments

8.1 Visit procedures

The following sections describe the assessments and procedures. These are also included in the flow chart (see section 2).

The investigator must keep a subject screening log, a subject identification code list and a subject enrolment log. The subject screening log and subject enrolment log may be combined in one list and may be generated from the IWRS.

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

8.1.1 Screening visit 1 (V1)

For procedures and assessments performed at screening, please see flow chart (see section 2).

The IWRS must be contacted to register the subject as screened (see section 10). Subject will be assigned a unique number (lowest available number allocated to site) which is maintained throughout the trial. It must be stated in the medical record that the subject is participating in the current trial.

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. The subjects should be reminded to show the card to other health care providers, as applicable.

Once all data relating to screening V1 have been obtained, these must be reviewed by the investigator to ensure that the subject is eligible to continue the trial.

8.1.1.1 Screen failures

For screening failures the screening failure form 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 case report form eCRF. Follow-up of SAEs must be carried out according to section 12.

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

8.1.1.2 Re-screening

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

8.1.2 Fasting visits

The subjects should attend several 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.. Glucose lowering agents and trial product cannot be taken until after blood sampling has been performed but other prescribed medication should be taken. An exception from this is the follow-up visit (V10) and follow-up premature discontinuation visit (V10A) where fasting is defined as having consumed only water within the last two hours prior to the visit. If the subject is not fasting as required, the subject must be called in for a new visit within the visit window to have the fasting procedures done.

8.1.3 Randomisation V2

For procedures and assessments performed at randomisation (see section 2).

Visit 2 will take place two weeks (±7 days) after screening V1.

Eligible subjects will be randomised into one of four treatment arms. The IWRS will allocate the dispensing unit number (DUN) of trial product to be dispensed to the subject.

Trial product will be dispensed to the subject by the site, hospital pharmacy or equivalent with different intervals during the trial. Subject will be instructed in administration of sc injection of trial product and the investigator must document that a direction for use (DFU) is given orally and/or in writing. Date, time and dose of first administration of trial product will be captured in the eCRF. Please see section 9 for further information about the trial product.

8.1.4 Visits

For visit numbers, timing of site visits, phone contacts and visit windows during the trial period, please refer to the flow chart (see section 2). Planned visits can be re-scheduled within the allowed visit window.

It is the responsibility of the investigator to ensure that all site visits and phone contacts occur according to the flow chart (2).

8.1.5 Missed visits and unscheduled visits

If a visit is missed and it is not possible to re-schedule, every effort should be made to ensure information is collected at a telephone contact. Subjects will be invited for the next scheduled visit according to visit schedule.

If a subject is unable or unwilling to attend the subsequent visit(s) the investigator should aim to at least have the subject attending the end of treatment visit and follow-up visit as these two visits should be performed for all subjects regardless of compliance with the protocol and adherence to the treatment (see section 8.1.6).

If a subject attends the clinic for a visit not described in the protocol, an unscheduled visit form must be completed. This only applies if assessments are done, hence not for the purpose of re-test of blood- or urine sampling, or re-supply of trial product. In case of re-supply a dispensing session should be made in the IWRS selecting additional medication. Re-scheduling of fasting visit samples is not considered as an unscheduled visit.

8.1.6 End of treatment (V9/9A) and Follow-up (V10/10A)

8.1.6.1 Subjects completing the treatment period as per protocol

An end of treatment visit (V9) should be scheduled when the subject has completed the treatment period as described per protocol and a follow-up visit (V10) should be performed at least 5 weeks after (+7 days visit window). Please see the flow chart for details (section 2).

The follow-up visit serves to collect AEs, technical complaints, hypoglycaemic episodes, ECG, concomitant medication and blood sampling for anti-semaglutide antibodies .

8.1.6.2 Subjects who prematurely discontinue trial product

For subjects who discontinue trial product prematurely the visit end of treatment – premature discontinuation (V9A) should be scheduled shortly after subject has discontinued trial product. The visit follow-up – premature discontinuation (V10A) should be scheduled at least 5 weeks after discontinuation of trial product (+7 days visit window). Please see the flow chart for details (section 2).

Subjects discontinuing trial product prematurely should continue with the scheduled site contacts. If necessary, in order to retain the subject in the trial, site visits can be replaced by phone contacts after discontinuation of trial product. However, as a minimum these subjects will be called in for end of treatment (V9) and follow-up (V10) at the time of the scheduled completion of the trial.

8.1.7 Withdrawals

Subjects who consider withdrawing from the trial should as a minimum be encouraged to have procedures performed according to the end of treatment visit (V9) as soon as possible and the follow up visit (V10) at least 5 weeks after but not more than 6 weeks after, if possible. If a subject has already prematurely discontinued from trial product and previously attended visit V9A and visit V10A, no further visits should be attended.

The End of Treatment and End of Trial form must be completed and final drug accountability must be performed even if the subject is not able to come to the site. The case book must be signed by the investigator in eCRF and a premature discontinuation of trial product session must be made in the IWRS (see section 10).

Although a subject is not obliged to give his/her reason(s) for withdrawing from a trial, the investigator must make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights. Where the reasons are obtained, the primary reason for not completing the trial must be specified on the end-of-trial form in the CRF (see section 6.5).

8.1.8 Investigator's assessment

Review of diaries, patient reported outcomes (PROs), laboratory reports, ECGs, eye examination (fundus photography/dilated fundoscopy), physical examination etc. must be documented either on the front page of the documents and/or in the subject's medical record. The signed documents must be retained at the site as source documentation.

For ECGs, physical examinations and eye examinations the evaluations must follow the categories:

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

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

In case of abnormal clinical significant findings found as a result of screening procedures conducted at V1 or assessments revealing baseline conditions at V2 the investigator must state a comment in the subjects' 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 site staff must review the diary to ensure that AEs, including overall change in health and concomitant medication are reported.

If clarification of entries or discrepancies in the diary or 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.

8.2 Subject related information

8.2.1 Demography

The following information must to be recorded in the subject's medical record and will be transcribed into eCRF at screening V1:

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

8.2.2 Diabetes history and diabetes complications

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

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

8.2.3 Concomitant illness and medical history

A **concomitant illness** is any illness that is present at the start of the trial (V1).

Medical history is a medical event that the subject has experienced in the past. Only relevant medical history as judged by the investigator should be reported. Pre-existing conditions, including those found as a result of screening procedures performed at V1 and V2 should be reported as medical history or concomitant illness.

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.

Concomitant illness and medical history must be recorded in the subject's medical record and will be transcribed into eCRF.

The following must be recorded in the eCRF on the disease specific forms only, i.e. not on the medical history/concomitant illness form:

- History of cardiovascular disease (CVD) (e.g. ischaemic heart disease, MI, heart failure incl. NYHA class, hypertension, stroke, peripheral arterial disease)
- History of gallbladder disease (e.g. gallstone, cholecystitis, cholecystectomy)

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 product, which is taken during the trial, including the screening and follow-up periods.

Details of any concomitant medication must be recorded at visit 1. Changes in concomitant medication, including antidiabetic treatment and rescue treatment, must be recorded at each visit as they occur. The eCRF should be updated accordingly.

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

If a change is due to an AE, then this must be reported according to Section12 . If the change influences the subject's eligibility to continue in the trial, the monitor must be informed.

8.2.5 Tobacco use

Details of tobacco use must be recorded at V1. Smoking is defined as smoking at least one cigarette, cigar or pipe daily. The collected information should include whether or not the subject smokes or has smoked.

It must be recorded whether the subject is a smoker according to the following criteria:

- Never smoked
- Is a previous smoker
    - cessation date
    - average cigarettes per day
    - approximate years of smoking
- Is a current smoker
    - average cigarettes per day
    - approximate years of smoking

8.2.6 Childbearing potential

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

Pregnancy testing must be performed on female subjects of childbearing potential as described in Section 8.5.2.5. Female subjects of childbearing potential must be instructed to use adequate contraceptive methods throughout the trial and until 5 weeks after end of treatment.

Female of non-childbearing potential is defined as:

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

For Brazil only: For women who expressly declare free of the risk of pregnancy, either by not engaging in sexual activity or by having sexual activity with no birth potential risk, use of contraceptive method will not be mandatory.

8.2.7 Height

Height is measured without shoes in centimetres or inches and recorded in the eCRF to nearest ½ cm or 1/4 inch.

8.3 Assessments for efficacy

8.3.1 Body weight

Body weight must be measured in kilograms (kg) or pound (lb), with one decimal. The body weight should be measured without shoes and only wearing light clothing.

The same scale should preferably be used throughout the trial.

8.3.2 Waist circumference

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

Three consecutive measurements of waist circumference should be performed and recorded in the eCRF. The waist circumference will be measured in cm to the nearest ½ cm using a non-stretchable measuring tape (measuring tapes will be provided to the sites).

The subject 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 and twists in the tape should

be avoided. The subject should be asked to breathe normally and the measurement should be taken when the subject is breathing out gently.

8.3.3 BMI

BMI will be calculated by the eCRF using the equation as listed below:

BMI kg/m^2 = Body weight (kg)/(Height (m) x Height (m)) or (kg/m^2 = [lb/in^2 x 703])

8.3.4 Systolic and diastolic blood pressure

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

- Avoid caffeine, smoking and exercise at least 30 minutes prior to measuring the blood pressure
- The blood pressure should be measured in a sitting position, with the legs uncrossed, the back and arms supported
- Subjects should be sitting for five minutes before the measurement is taken
- Subject or the observer should not talk during the measurement

It is recommended to use the same arm as used at V1 for subsequent measurements.

8.4 Assessments for safety

The timing of the assessments for safety are outlined in the flow chart (see section 2).

8.4.1 Adverse events

AEs must be recorded at each visit in accordance with the procedures outlined in section 12.

Any clinically significant worsening from baseline of a previous finding must be reported as an AE.

8.4.2 Medication error

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

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

For definition of medication errors, see section 12.1.3

8.4.3 Adverse events requiring additional data collection

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

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

See appendix B for details about the additional information to report. In case any of these events fulfil the criteria for a serious adverse event, please report accordingly, see Section 12.

8.4.4 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 according to the instructions below and section 8.6.2 throughout the trial from V1 to V10/10A.

All information must be transcribed into the eCRF (hypoglycaemic episode form) throughout the trial. For Novo Nordisk classification of hypoglycaemia, see Section

Upon onset of a hypoglycaemic episode the subject is recommended to measure PG 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[51].

A SMPG value ≤ 3.9 mmol/L (70 mg/dL) or hypoglycaemic symptoms must be recorded in the diary at 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/L (70 mg/dL) and/or symptoms have been resolved. One hypoglycaemic episode form is to cover these measurements 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 the PG value is >3.9 mmol/L (70 mg/dL) and/or symptoms have been resolved).
- If a stop date and time is not reported, a hypoglycaemic episode will cover a period of 60 minutes.
- The PG level before treating the episode (if available) and any follow up measurements.
- The lowest value measured during the hypoglycaemic episode will be reported as the PG 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 PG to normal is considered sufficient evidence that the event was induced by a low PG concentration[51].

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

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

- Who assisted in the treatment of the hypoglycaemic episode (i.e. medical person or non-medical person)?
- Where the treatment was administered (in clinic/emergency room/hospital or other. If the subject was treated in clinic/emergency room/hospital, whether they were transported in an ambulance or not)
- Type of treatment provided by another person (i.e. oral carbohydrates, glucagon, IV glucose or other)
- Were symptoms alleviated after administration of treatment?
- Factors contributing to the episode (i.e. physical activity, missed meal, diet change, medication error (i.e. overdose, mix-up between products, incorrect use of device), miscalculation of dose of antidiabetic medication, other factors not listed or unknown)
- Did the subject experience seizure?
- Was the subject unconscious/comatose?
- Did the subject experience any of the following symptoms[52] ?
  – 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[53, 54]. 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.

8.4.5 Electrocardiogram

12-lead electrocardiograms (ECG) will be performed locally by the investigator or delegated staff during the trial (see section 2). The ECG print out must be interpreted, dated and signed by investigator as described in section 8.1.8. ECG printed is source documentation.

Additional unscheduled ECG recordings can be performed at the investigator´s site at investigator´s discretion at other visits than the planned ECG visits.

8.4.6 Physical examination

A physical examination will be performed by the investigator according to local procedure (see section 2). A physical examination must include:

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

8.4.7 Pulse

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

8.4.8 Eye examination

It is allowed to perform the baseline fundus photography or dilated fundoscopy between the screening visit and the randomisation visit.

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

In addition, fundus photography /dilated fundoscopy must be performed at V9. In the case of premature discontinuation, the assessments must be performed both at V9A and at V9. The assessments at V9A and V9 can be performed in the period between V9A and V10A and between V9 and V10, respectively, but the results should be available no later than at V10A and V10, respectively.

The investigator should indicate whether the outcome of the eye examination was normal or abnormal, and, if abnormal, indicate whether clinically significant. Relevant findings as a result of this screening procedure must be recorded as diabetes history and diabetes complications or concomitant illness/medical history in accordance with Section 8.2.2 and 8.2.3 respectively.

8.5 Laboratory assessments

For laboratory analysis of efficacy and safety parameters will be drawn during the 37 weeks of the trial. The laboratory analyses will be performed by a central laboratory except for anti-semaglutide antibodies and IgE antibodies where a special laboratory will be used. In the situation of suspicion of acute pancreatitis or severe hypersensitivity described in appendix B, a local laboratory will be used. Laboratory samples comprise both urine and blood samples.

Descriptions of assay methods, laboratory supplies and procedures for collecting, handling, storage and shipping of samples and information regarding who will perform the assessments will be

described in the laboratory manual provided by the central laboratory (for central and special laboratory details, see Attachment I).

Samples will be coded in order to keep subject identity anonymous.

Laboratory samples may be drawn at another day than on the day of the actual visit as long as it is within the visit window outlined in the flow chart (see section 2).Please note that a laboratory sample pertaining to a specific visit must always be reported to that visit.

For some of the samples drawn during the trial it is required for the sensitivity of the analysis that the subject is fasting.

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 must be reported to the investigator.

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

Central laboratory will provide laboratory results 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 section 12. An exception to this is that anti-semaglutide antibody result will not be available to the investigator during the trial. However these results will be provided to the investigator upon request after the completion of the clinical trial report (CTR).

All laboratory samples will be destroyed on an on-going basis after analysis and no later than CTR, except for samples taken for anti-semaglutide antibody samples, which will be kept until market authorisation approval or rejection of file. *(For Brazil: the laboratory samples for Brazilian subjects will be destroyed at the latest at the completion of the CTR, including samples for anti-semaglutide antibody analysis. No sample will be stored after the completion of CTR).*

The investigator should ensure that the last samples are shipped to the central laboratory within 24 hours after the last subject visit last at the site.

8.5.1 Laboratory assessments for efficacy

Blood samples must be drawn according to flow chart (see section 2) and analysed at the central laboratory to determine levels of the following efficacy laboratory parameters:

8.5.1.1 Glucose metabolism

- HbA_{1c}
- Fasting plasma glucose
- Fasting insulin
- Fasting C-peptide
- Fasting glucagon
- Fasting pro-insulin

8.5.1.2 Biomarker

- hsCRP

8.5.1.3 Lipids (all fasting)

- Total cholesterol
- LDL-cholesterol
- VLDL-cholesterol
- HDL-cholesterol
- Triglycerides
- Free fatty acids

8.5.1.4 Self measured plasma glucose (SMPG)

At screening V1 subjects will be provided with a blood glucose meter including lancets, plasma-calibrated test strips and control solutions. Oral and written directions for use of the device including the performance of calibrations according to the manufacturer's instructions will be provided to the subject. Sites should, as necessary, repeat the directions for use to the subject at subsequent visits.

The blood glucose meters use test strips calibrated to plasma values. Therefore, all measurements performed with capillary blood are automatically calibrated to plasma equivalent glucose values, which will be shown on the display. When using blood glucose meters the measurement is performed with capillary blood calibrated to plasma equivalent glucose values i.e. the measurement is performed on blood while the value is reported as plasma. It is important to be aware of this difference throughout the protocol.

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

Subjects should be instructed in how to record the results of the SMPG values in the diaries. The record of each SMPG value should include date, time and value. All data from the diary must be

transcribed into the eCRF during or following the contact. If obtained via phone and a discrepancy is later detected, the values in the eCRF must be corrected.

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

8.5.1.5 7 point profile

The subject will be instructed to perform a SMPG 7-point profile, preferably within one week prior to the site visit according to the flow chart (see section 2) on a day where the subject does not anticipate unusual strenuous exercise.

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

- before breakfast
- 90 min after start of breakfast
- before lunch
- 90 min after start of lunch
- before dinner
- 90 min after start of dinner
- at bed time

8.5.2 Laboratory assessments for safety

Laboratory samples must be drawn according to flow chart (see section 2) and analysed at the central laboratory to determine levels of the following safety laboratory parameters:

8.5.2.1 Anti-semaglutide antibodies

Blood samples will be drawn for measurement of serum antibodies to semaglutide at selected visits in randomised subjects. Positive anti-semaglutide antibody samples will be further characterised for cross reactivity to native GLP-1 (see section 2). Samples taken at follow-up which are positive for anti-semaglutide antibodies will be further characterised for in vitro neutralising effect towards semaglutide. In addition, samples taken at follow-up which are positive for cross-reactivity against native GLP-1 will be further analysed for in vitro neutralising effect towards native GLP-1.

Follow-up antibody (taken at the follow-up V10/10A) samples must be taken fasting (as a minimum by only having consumed water for at least two hours).

8.5.2.2 Biochemistry

- Creatinine
- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Alkaline phosphatase
- Sodium
- Potassium
- Albumin
- Bilirubin (total)
- Total protein
- Urea
- Creatine kinase
- Calcium total
- Calcium, albumin corrected (calcium, ionized)
- Lipase
- Amylase

8.5.2.3 Haematology

- Haemoglobin
- Haematocrit
- Thrombocytes
- Erythrocytes
- Leucocytes
- Differential count:
    - eosinophils
    - neutrophils
    - basophils
    - monocytes
    - lymphocytes

8.5.2.4 Calcitonin

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

8.5.2.5 Pregnancy test

Females of childbearing potential will have a serum pregnancy test performed at all site visits (see Section 2). At visit 2, 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).

8.5.2.6 Urinalysis

Subjects will be asked to bring the first morning urine during the trial (see section 2). The urine sample will be analysed at the central laboratory to determine levels of the following parameters:

- Urinary albumin to creatinine ratio (UACR)
- Urinalysis by urine dip-stick: erythrocytes, protein, glucose and ketones, pH

8.6 Other assessments

8.6.1 Patient reported Outcome questionnaires

The following PRO questionnaires will be used in this trial:

- SF-36v2TM
- DTSQs

The questionnaires should be completed by the subject as specified in the flow chart (see section 2), preferably before any other trial related activities. It takes approximately 10 minutes to complete each questionnaire. The assessment must be reviewed as described in section 8.1.8. All results from the PRO questionnaires must be transcribed into the eCRF.

The PRO questionnaire will be used to assess subjects overall Health related Quality of Life and can also be used to estimate Quality Adjusted Life years (QALY) which is used in cost effectiveness calculations.

8.6.1.1 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 QALY which is used in cost effectiveness calculations. This instrument contains 36 items and measures the individual overall health related quality of life on 8 domains; physical functioning, role functioning, bodily pain, general health, vitality, social functioning, role emotional and mental health.

8.6.1.2 DTSQs

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

8.6.2 Subject diary

The subject must be provided with paper diaries at all visits, except the follow-up visit (V10 and V10A). If a subject prematurely discontinues trial product, diaries should not be dispensed and filled out by the subjects after the follow-up – premature discontinuation visit. For these subjects all available data will be collected. Entries in the diaries are only to be made by the subject, unless otherwise specified.

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

- date, time and dose of first dose of trial products (injection and tablet)
- date, time and dose of last injection of trial product prior to each visit/phone contact
- hypoglycaemic episodes
- concomitant medication
- AEs
- SMPG 7-point profile
- Urine pregnancy test for females of childbearing potential

The diaries should be collected at the visit described in the flow chart (see section 2). The recordings must be reviewed as described in section 8.1.8 and transcribed to the eCRF.

8.7 Subject compliance

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

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.

If a subject is discovered to be non-compliant, the investigator must inform the subject of the importance of taking trial product as directed.

9 Trial supplies

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

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

9.1 Trial products

The following trial products for subcutaneous injection will be provided by Novo Nordisk, Denmark:

- Semaglutide 1.34 mg/mL, solution for injection, 1.5 mL pre-filled PDS290 pen-injector
- Semaglutide placebo, solution for injection, 1.5 mL pre-filled PDS290 pen-injector

The following trial products for oral administration will be provided by Novo Nordisk, Denmark:

- Sitagliptin (Januvia®) 100 mg, tablet
- Sitagliptin placebo, tablet

For both semaglutide and sitagliptin the placebo and active drug are identical with regard to appearance.

Semaglutide both active drug and placebo are manufactured and supplied by Novo Nordisk, Denmark. Sitagliptin 100 mg and placebo is packed for use in clinical trials and supplied by Novo Nordisk, Denmark.

All trial products are considered investigational medicinal products (IMPs).

Refer to the appropriate IB or local label for more detailed information regarding the listed trial products.

Each site will be supplied with sufficient trial products for the trial on an on-going basis controlled by the IWRS and according to enrolment and randomisation with different intervals during the trial. Subject will be instructed in administration of trial product and the investigator must document that a DFU is given orally and in writing at randomisation visit.

9.2 Labelling

Labelling of the investigational medicinal products (IMPs) will be in accordance with Annex 13[55], local law and trial requirements. Please refer to the TMM provided by Novo Nordisk for details regarding standard packages for the trial products.

9.3 Storage

Semaglutide preparations (both in-use and not in-use) must not be exposed to excessive heat or direct sunlight. Semaglutide preparations which have been frozen must not be used. Semaglutide must not be used, if it does not appear clear and colourless.

Trial product	Storage conditions (not-in-use)	In-use conditions
Semaglutide 1.34 mg/mL and placebo	• Store in a refrigerator (2°C to 8°C) • Do not freeze • Protect from light	• Store below 30°C • Do not refrigerate • Do not freeze • Protect from light • Use within 1 month*
Sitagliptin 100 mg and placebo	• Do not store above 30°C • Do not freeze • Do not refrigerate • Protect from light and humidity	Not applicable

* In-use time starts when first dose is taken.

The investigator must ensure the availability of proper storage conditions, record and evaluate the temperature. The investigator must inform Novo Nordisk (via the assigned monitor) immediately if any trial product has been stored outside specified conditions (e.g. outside temperature range). Fifteen minutes outside the indicated range is negligible, and should not be recorded as a deviation.

Trial products stored outside the temperature range are not to be used and must be stored separately within allowed temperature range until after evaluation of condition. Evaluation will be performed by Novo Nordisk. Trial products that have been stored improperly must not be dispensed to any subject before it has been re-evaluated and approved for further use by Novo Nordisk.

Returned trial products (unused, partly used or used including empty packaging material) must be stored separately from non-allocated trial products.

The temperatures during storage should be monitored by a calibrated and stationary system. A temperature log must be kept to document storage within the right temperature interval and storage facilities should be checked frequently. Investigator must take appropriate action to avoid recurrence of the detected temperature deviation.

9.4 Drug accountability and destruction

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

The investigator or delegated person is responsible for ensuring that:

- Trial products are not dispensed to any person not included in the trial
- Drug accountability is performed using the IWRS drug accountability module
- Subjects are instructed to return all used, partly used and unused trial product including empty packaging material at each dispensing visit and at End of Treatment visit
- All returned trial products (used/partial used and unused including empty packaging material) is kept and stored separately from non-allocated trial products

Destruction of trial products will be done according to local law after accountability is finalised at site and reconciled by monitor. Destruction of trial products must be documented.

9.5 Auxiliary supplies

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

- Needles for pre-filled pen systems
- Blood glucose meters, including lancets, plasma-calibrated test strips and control solutions
- Directions for use for PDS290 pen-injector

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
- Medication arrival
- Dispensing
- Treatment discontinuation
- Treatment completion
- Drug accountability
- Data change
- Dispensing verification (when barcode scanner is used)

IWRS user manuals will be provided to each trial site.

11 Randomisation procedure and breaking of blinded codes

The trial is a double-blind trial. A randomisation session will be carried out for all subjects by using the IWRS. At the randomisation visit subjects meeting all inclusion/exclusion criteria will be randomised in a 2:2:1:1 manner to receive one of four parallel treatments groups:

- Semaglutide 0.5 mg once-weekly + sitagliptin placebo once-daily
- Semaglutide 1.0 mg once-weekly + sitagliptin placebo once-daily
- Sitagliptin 100 mg once-daily + semaglutide placebo (0.5) mg once-weekly
- Sitagliptin 100 mg once-daily + semaglutide placebo (1.0) mg once-weekly

Randomisation will be stratified by country.

11.1 Breaking of blinded codes

If the trial site needs to break the code, Novo Nordisk should if possible, be contacted before the code is broken. The IWRS will notify Novo Nordisk (monitor and the Global Safety department) immediately after the code is broken.

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

If the code has been broken the subject must be discontinued from trial product but be asked to continue in the trial (see section 8.1.6.2). A treatment discontinuation session should be completed in IWRS.

When the code is broken, the treatment allocation will be accessible to the investigator and the Novo Nordisk Global Safety department. If IWRS is not accessible at the time of code break monitor should be contacted and if monitor cannot get access the IWRS vendor helpdesk should be contacted.

12 Adverse events, and technical complaints and pregnancies

12.1 Definitions

Adverse event

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

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

An AE includes:

- A clinically significant worsening of a concomitant illness.
- A clinical laboratory adverse event (CLAE): a clinical laboratory abnormality which is clinically significant, ie 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 procedures (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 8.4.4).

The following three definitions are used when assessing an AE:

- **Severity assessment**
  - **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 assessment**

The following terms are used when assessing the 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.

12.1.1 Serious adverse event

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

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

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

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

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

c. A substantial disruption of a subject's ability to conduct normal life functions (eg 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 dyscrasiasis or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

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

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

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

12.1.2 Non-serious adverse event

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

12.1.3 Medication errors

Medication errors concerning trial products are defined as:

- Administration of wrong drug. Note: Use of wrong DUN is not considered a medication error.
- Wrong route of administration, such as intramuscular instead of subcutaneous.
- Administration of an overdose with the intention to cause harm (eg 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 extend 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 8.4.2.

12.1.4 Adverse events requiring additional data collection

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

In this trial the following AEs require the completion of specific event forms in the eCRF, see Table 12–1

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

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

For details about specific event form, see appendix B

12.1.5 Technical complaint

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 (eg discoloration, particles or contamination)
- The packaging material including labelling

- Problems related to devices (eg to the injection mechanism, dose setting mechanism, push button or interface between the pen and the needle)

12.2 Reporting of adverse events

All events meeting the definition of an AE must be collected and reported. This includes events from the first trial-related activity after the subject has signed the informed consent until the end of the post-treatment follow-up period (see section 2). 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, either observed by the investigator or subject, must be reported by the investigator and evaluated. All AEs must be recorded by the Investigator on an AE form. The investigator should report the diagnosis, if available. If no diagnosis is available, the investigator should record each sign and symptom as individual AEs using separate AE forms.

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

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

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

Timelines for initial reporting of AEs:

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

- **SAEs**: The AE form **within 24 hours** and the safety information form **within 5 calendar** days of the investigator's first knowledge of the SAE.

- **SAEs requiring reporting on a specific event form :** In addition to above, the specific eventI form **within 14 calendar days** of the investigator's first knowledge of the AE.

- **Events for adjudication**: The event adjudication form must be completed **within 14 calendar days of investigator's first knowledge of the AE, see section 12.7.2.** The investigator should provide the medical documentation within 4 weeks of event identification according to instructions in the event adjudication site manual.

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

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

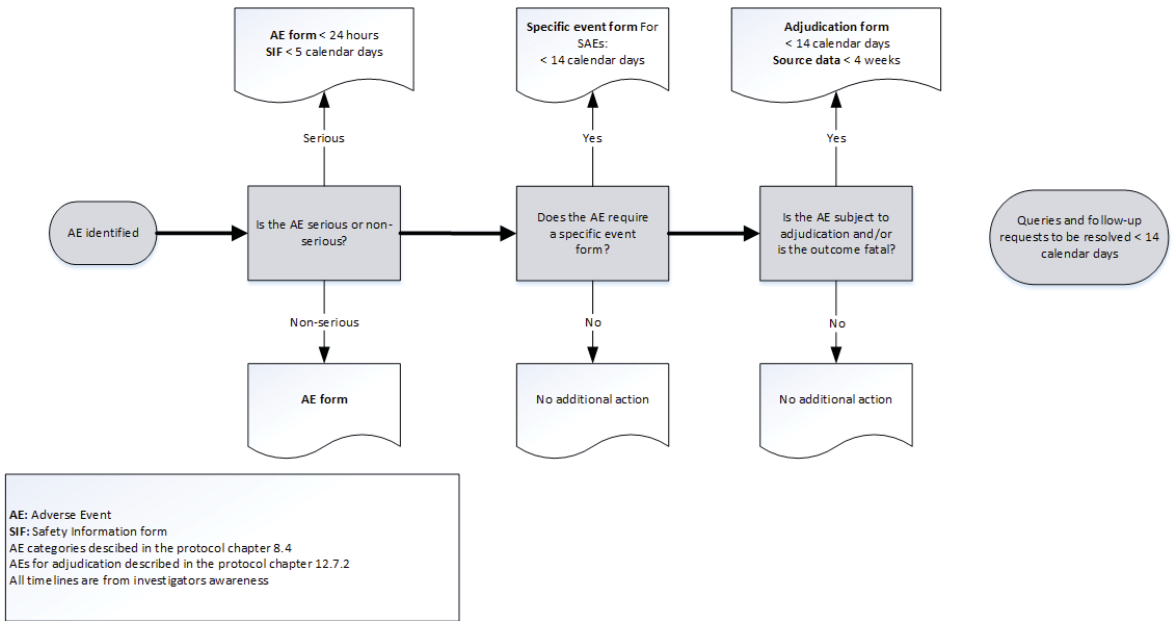


Figure 12–1 Reporting of AEs

Novo Nordisk assessment of AE expectedness:

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

- Semaglutide: NN9535 IB[27] (subcutaneous administration), Type 2 diabetes, current version and any updates thereto
- Sitagliptin (Januvia®): EU Summary of Product Characteristics (SmPC)[56] current version.

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

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

Novo Nordisk products used as concomitant medication

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

12.3 Follow-up of adverse events

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

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

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

  The SAE follow-up information should only include new (eg 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 and on any of the following products:

- Semaglutide 1.34 mg/mL solution for injection, 1.5 mL pre-filled PDS290 pen-injector
- Semaglutide placebo, solution for injection, 1.5 mL pre-filled PDS290 pen-injector
- Sitagliptin (Januvia®) 100 mg, tablet
- Sitagliptin placebo, tablet
- Needles for pre-filled pen systems

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

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

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

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

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

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

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

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

12.4.2 Collection, storage and shipment of technical complaint samples

The investigator must collect the technical complaint sample and notify the monitor **within 5 calendar days** of obtaining the sample at trial site. The monitor must coordinate the shipment to Customer Complaint Center, Novo Nordisk (the address is provided in Attachment I) and ensure that the sample is sent as soon as possible. A print or copy of the technical complaint form must be sent with 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

12.5.1 Pregnancies in female subjects

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

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

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

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

1. **Reporting of pregnancy information**
   Information about the pregnancy and pregnancy outcome/health of the newborn infant(s) has to be reported on maternal form 1A and 1B, respectively.

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

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

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

<u>Forms and timelines for reporting AEs:</u>
Non-serious AEs:

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

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

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

12.6 Precautions and/or overdose

Semaglutide

Events of nausea, vomiting and headache have been reported in connection with accidental administration of up to 4.0 mg semaglutide. No symptoms of hypoglycaemia have been reported in connection with overdose of semaglutide. In the event of overdose, appropriate supportive treatment should be initiated according to the subject's clinical signs and symptoms.

For other precautions, please see section 3.5.1.

Sitagliptin

During controlled clinical trials in healthy subjects, single doses of up to 800 mg sitagliptin were generally well tolerated. Minimal increases in QTc, not considered to be clinically relevant, were observed in one study at a dose of 800 mg sitagliptin. There is no experience with doses above 800 mg in clinical studies. In Phase I multiple-dose studies, there were no dose-related clinical adverse reactions observed with sitagliptin with doses of up to 600 mg per day for periods of up to 10 days and 400 mg per day for periods of up to 28 days.

In the event of an overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring (including obtaining an electrocardiogram), and institute supportive therapy if required. Sitagliptin is modestly dialysable. In clinical studies, approximately 13.5 % of the dose was removed over a 3- to 4-hour hemodialysis session. Prolonged hemodialysis may be considered if clinically appropriate. It is not known if sitagliptin is dialysable by peritoneal dialysis.

For other precautions, please see section 3.5.5.

12.7 Committees related to safety

12.7.1 Novo Nordisk safety committee

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

12.7.2 Event adjudication committee

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

The EAC is composed of permanent members covering required medical specialities. EAC members must disclose potential conflicts of interest and must be independent of Novo Nordisk. The events are reviewed by the EAC in a blinded manner. The EAC will have no authorisations to impact trial conduct, trial protocol or amendments.

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

The events outlined in section 12.1.4 have been selected for adjudication in order to obtain an external independent validation of the diagnosis. In addition, cardiovascular events are being adjudicated according to Standardized Definitions[57].

The EAC will review copies in English (translated if necessary) of medical documentation received in the adjudication package (for example X-ray, ECGs, ultrasound images, discharge summaries, pathology reports, and death certificates). The investigator must provide medical documentation as soon as possible, when receiving a request from Novo Nordisk or the event adjudication vendor.

The AEs for adjudication are listed in Table 12-2

Table 12–2 Adverse events for adjudication

Events	Description	Adjudication outcome
Death*	• All-cause death	• Cardiovascular death (including undetermined cause of death) • Non-Cardiovascular death
Acute Coronary Syndrome	Acute Coronary Syndrome conditions include: • ST-elevation acute myocardial infarction (STEMI) • Non-ST elevation acute myocardial infarction (NSTEMI) • Silent MI • Unstable angina pectoris (UAP) requiring hospitalisation	• Acute myocardial infarction (STEMI or NSTEMI), silent MI • Unstable angina pectoris requiring hospitalisation
Cerebrovascular events	• Episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of haemorrhage or infarction • Transient Ischaemic Attack (TIA) is defined as a transient episode (< 24 hours) of focal neurological dysfunction caused by brain, spinal cord, or retinal ischaemia, without acute infarction	• Ischaemic stroke • Haemorrhagic stroke • Undetermined stroke • TIA
Heart failure requiring hospitalisation	• Hospitalisation with a primary diagnosis of heart failure (new episode or worsening of existing heart failure)	• Heart failure requiring hospitalisation
Acute pancreatitis	The diagnosis of acute pancreatitis requires two of the following three features: • Abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back) • Serum lipase activity (and/or amylase activity) at least three times greater than the upper limit of normal • Characteristic findings of acute pancreatitis on imaging	Acute pancreatitis • Mild • Moderate severe • Severe
Malignant neoplasm	Malignant neoplasms are defined as: • Neoplasms in which abnormal cells divide without control and can invade nearby tissues and/or spread to other parts of the body through the blood and lymph systems • Thyroid neoplasms are excluded in this event category	• Malignant neoplasm
Thyroid disease, if malignant thyroid neoplasm or C-cell hyperplasia	• Malignant thyroid neoplasms are defined as thyroid neoplasms in which abnormal cells divide without control and can invade nearby tissues and/or spread to other parts of the body	• Malignant thyroid neoplasm • C-cell hyperplasia

	through the blood and lymph systems • C-cell hyperplasia, defined as hyperplasia of the parafollicular C-cells of the thyroid gland	

*Death is not a separate event, but an outcome

There are different processes for capturing events for adjudication:

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

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

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

13 Case report forms

Novo Nordisk will provide a system for the electronic case report forms (eCRF). This system and support services to the system will be supplied by a vendor.

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 (eg is not applicable), indicate this according to the data entry instructions.

The following will be provided as paper CRFs:

- Pregnancy forms

In addition paper AE forms and safety information forms will be provided. These must be used when access to the eCRF is revoked.

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

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

13.2 Case report form flow

13.2.1 Electronic case report form flow

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

At the end of trial the investigator must ensure that all remaining data have been entered into the eCRF no later than 3 days after the last subject’s last visit 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 investigator site after the trial database is released and access to update the trial data on the EDC application has been removed. This data will be retained by the site.

When the final CTR is available the data will be archived by Novo Nordisk.

13.2.2 Paper case report form flow

The pregnancy forms are paper based CRFs.

Also, the SIF, technical complaint form, and AE form will be provided in paper but are only to be used if for any reason the eCRF is unavailable.

The investigator must ensure that data are recorded in these forms as soon as possible and ensure that Novo Nordisk receives these forms within the required timeline (see section 12).

Corrections to the data in the 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 were crossed out. Each correction must be initialled, dated and explained (if necessary) by the investigator or the investigator's authorised staff.

14 Monitoring procedures

During the course of the trial, the monitor will visit the trial site to ensure that the protocol is adhered to, that all issues have been recorded, to perform source data verification and to monitor drug accountability. The first monitoring visit will be performed as soon as possible after FPFV or FSFV and no later than 4 weeks after. The monitoring visit intervals will depend on the outcome of the remote monitoring of the CRFs, 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 intervals between monitoring visits can be shorter. Factors to be considered in this determination may include objective, endpoints, purpose, design, complexity, blinding, number of subjects and expected recruitment rate.

The monitor must be given direct access to 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 (eg by telephone).

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

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. Considering the electronic source data environment, it is accepted that the earliest practically retainable record should be considered as the location of the source data. Therefore transcription to the diary from the blood glucose meter is considered the source document for BG values.

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 diaries and PROs are considered as source data and must not be removed from the trial site.

The monitor will ensure that the CRFs are completed on an on-going basis within the agreed timelines.

The monitor must ensure that all required eCRF forms for screening failures are completed, (e.g. screening failure form and the case book sign of (affirmation statement) is electronically signed by the investigator).

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

When data has been source verified and all queries have been resolved the case book must be signed by the investigator in the eCRF.

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

15 Data management

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

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 from the laboratory performing the analyses. 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 identification number. Appropriate measures such as encryption or leaving out certain identifiers will be enforced to protect the identity of subjects in all presentations and publications as required by local, regional and national requirements.

16 Computerised systems

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

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

17 Statistical considerations

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

Results from the statistical analysis will generally be presented by two-sided confidence intervals with a confidence level of 95% and associated p-value. Superiority will be formulated and tested as one-sided hypotheses at a 2.5% significance level. Non-inferiority between two treatments will be evaluated by comparing the upper limit of the associated two-sided 95% confidence interval for the difference with the pre-defined non-inferiority margin.

Handling of missing data

In the case of missing data no general imputation will be performed for the analyses, unless otherwise specified. If an assessment has been made both at screening and randomisation, the value from the randomisation visit will be used as the baseline value. If the value measured at the randomisation visit is missing and the assessment also has been made at screening, then the screening value will be used as the baseline value.

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

The primary analysis model will be the mixed model for repeated measurements (MMRM), see section 17.3 for further details. One of the assumptions behind (MMRM) is that the missing data mechanism is missing at random (MAR). This means that given the observed data, the mechanism generating missing values is independent of the unobserved data that is the missing data. The MMRM and the negative binomial model both rely on the MAR assumption for generating unbiased estimates of treatment differences.

Based on previous semaglutide trials in subjects with type 2 diabetes, the treatment discontinuation rate from randomised treatment and trial withdrawal is expected to be about 20%. The treatments in this trial should be effective, given the historical documentation, and this should minimise treatment discontinuation due to ineffective therapy. The main reasons for treatment discontinuation are expected to be AEs, ineffective therapy and non-eligibility (subjects randomised although not fulfilling inclusion/exclusion criteria). Treatment discontination due to non-eligibility can be regarded as missing completely at random (MCAR), i.e. it does not depend on the observed or missing data values. This category of missing data is not expected to introduce bias in the estimated treatment differences. Treatment discontinuation due to lack of efficacy is expected to be reflected in the observed data obtained prior to the discontinuation from randomised treatment, and the corresponding missing data can therefore be assumed as MAR to some extent. Missing data due to AEs is expected to be similar between groups except for, potentially, a slightly higher incidence in the semaglutide treatment group due to gastrointestinal side effects. Together with potential

withdrawals from trial due to the own will of the subject, the MAR assumption may be less adequate for this category of drop-outs.

Several different sensitivity analyses will be used to investigate whether the results from the MMRM approach are robust towards deviations from the assumption of MAR.

17.1 Sample size calculation

The primary objective is to compare the effect of two dose levels of semaglutide once-weekly treatment (0.5 mg or 1.0 mg) with sitagliptin 100 mg on the primary endpoint, change from baseline in HbA_{1c} after 30 weeks of treatment. In the calculations determining the sample size it is presumed that in the analysis the two sitagliptin/semaglutide placebo groups will be pooled assuming no correlation between endpoints and placebo volume.

In total 1050 subjects will be randomised in a 2:2:1:1 manner. Assuming 20% of subjects discontinuing randomised treatment, and further taking the assumption that these subjects are excluded from the per protocol (PP) analysis set, 280 subjects in each group are expected to be included in the PP analysis set.

The sample size calculation is based on demonstrating HbA_{1c} non-inferiority for semaglutide 0.5 mg vs. sitagliptin 100 mg and HbA_{1c} non-inferiority for semaglutide 1.0 mg vs. sitagliptin 100 mg.

The two hypothesis tests are assumed to be independent and for each of the hypothesis the power calculation is based on a t-statistic under the assumption of a one-sided test of size 2.5%. Using a non-inferiority margin of 0.3%, and assuming a true HbA_{1c} difference (semaglutide minus sitagliptin) of 0% and a standard deviation (SD) of 1.1%, a total of 280 subjects per group in the PP analysis set will give 90% marginal power to conclude HbA_{1c} non-inferiority for the comparison of a semaglutide dose vs. sitagliptin 100 mg.

Assuming the same HbA_{1c} effect for the two dose levels of semaglutide, the overall power to demonstrate HbA_{1c} non-inferiority for the two dose levels of semaglutide vs. sitagliptin will be at least 80%.

For change in body weight, the power calculation is based on the assumptions of a true difference of -1.5 kg and a SD of 4.0 kg. In addition, 50% efficacy retention is assumed for the anticipated 20% of subjects discontinuing randomised treatment giving an expected treatment difference of -1.35 kg, which is the number used in the power calculation. With the above assumptions, a total of 350 subjects per group in the full analysis set (FAS) will give more than 99% marginal power to conclude superiority in body weight for the comparison of a semaglutide dose vs. sitagliptin 100 mg.

17.2 Definition of analysis sets

The following analysis sets are defined in accordance with the ICH-E9 guideline[58] .

Full Analysis Set (FAS): includes all randomised subjects. Subjects in the FAS will contribute to the evaluation "as randomised".

Per Protocol (PP) Analysis Set:

Includes all subjects in the FAS who fulfil the following criteria:

- have not violated any inclusion criteria
- have not fulfilled any exclusion criteria
- have a non-missing HbA_{1c} measurement at screening and /or randomisation
- have at least 23 weeks actual treatment weeks of expose
- have at least one non-missing HbA_{1c} measurement after 23 actual weeks of expoures

Subjects in the PP Analysis Set will contribute to the analysis "as treated".

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".

Before data are locked for statistical analysis, a review of all data will take place. Any decision to exclude a subject or single observations from the statistical analysis is the joint responsibility of the members of the internal 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 must be documented and signed by those responsible before database lock. The subjects and observations excluded from analysis sets, and the reason for this, will be described in the CTR.

Data selections and observation periods

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

- Firstly, subjects will be selected based on the specified analysis set

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

Definition of the observation periods:

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

- The last direct subject-site contact, which is scheduled to take place 5 weeks after planned last dose of trial product at a follow-up visit
- Withdrawal for subjects who withdraw their informed consent
- The last subject-investigator contact as defined by the investigator for subjects who are lost to follow-up
- Death for subjects who dies before any of the above

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

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

- the follow-up visit (V10)
- the follow-up prematurely discontinuation visit (V10A)
- the last date on trial product + 42 days
- the end-date for the in-trial observation period

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

For efficacy and other safety assessments (laboratory assessments, physical examination and vital signs) the observation period ends at the last date on trial product + 7 days in accordance with trial flow chart and assessment times. This ascertainment window corresponds to the dosing interval and will be used to avoid attenuation of a potential treatment effect on endpoints for which the effect is

reversible shortly after treatment discontinuation. Hence, for those assessments this period reflects the period in which subjects are treated.

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

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

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

For subjects who have no post-baseline scheduled assessments available in the on-treatment without rescue period, the baseline value will be carried forward to the first scheduled visit for the associated endpoint to ensure that all randomised subjects will contribute to the statistical analysis.

Data points collected outside an observation period will be treated as missing in the analysis. Baseline data will always be included in an observation period. For adjudicated events, the onset date will be the EAC adjudicated onset date.

17.3 Primary endpoint

The primary endpoint is change from baseline in HbA_{1c} after 30 weeks of treatment. In the analysis the two sitagliptin/semaglutide placebo groups will be pooled assuming no correlation between HbA_{1c} change after 30 weeks and placebo volume.

The primary endpoint will be based on FAS using data from the 'on-treatment without rescue medication' observation period in a Mixed Model for Repeated Measures (MMRM). A restricted maximum likelihood (REML) will be used. The model will include all post baseline HbA_{1c} measurements collected at scheduled visits up to and including week 30 data as dependent variables. The independent effects included in the model will be treatment and country as fixed effects and baseline response as covariate, all nested within visit. An unstructured covariance matrix will be employed for measurements within the same subjects, assuming that measurements across subjects are independent. Regarding missing data this analysis approach relies on the assumption that data are missing at random (MAR). From this mode, the two by dose level estimated treatment differences between s.c.semaglutide versus sitagliptin at week 30 will be presented together with associated two-sided 95% confidence intervals and unadjusted two sided p-values (nominal

alpha=0.05) for testing non-inferiority and superiority. In order to preserve the overall type 1 error the conclusion of non-inferiority and superiority with treatment of each semaglutide dose versus sitagliptin after 30 weeks will be evaluated hierarchically according to the sequence below, and starting with the first. In this testing sequence it is necessary to fulfil the test criteria, which is to reject the corresponding null hypothesis in order to go to the next step. If the corresponding null hypothesis is not rejected, the testing will stop and no further conclusions will be drawn.

The following ordering in the statistical test sequence will be used:

1. Non-inferiority in change in HbA_{1c} for semaglutide 1.0 mg vs. sitagliptin
2. Non-inferiority in change in HbA_{1c} for semaglutide 0.5 mg vs. sitagliptin
3. Superiority in change in HbA_{1c} for semaglutide 1.0 mg vs. sitagliptin
4. Superiority in change in body weight for semaglutide 1.0 mg vs. sitagliptin
5. Superiority in change in body weight for semaglutide 0.5 mg vs. sitagliptin
6. Superiority in change in HbA_{1c} for semaglutide 0.5 mg vs. sitagliptin

Non-inferiority will be concluded if the upper limit of the two-sided 95% confidence interval for the estimated difference in HbA_{1c} between semaglutide and sitagliptin is less than 0.3%. Superiority for either change in HbA_{1c} or change in body weight will be claimed if the upper limit of the two-sided 95% confidence interval for the estimated difference is below 0% or 0 kg respectively.

When establishing non-inferiority the analysis will be based on the full analysis set (FAS) and supplemented by an analysis with the per protocol population using the data from the 'on treatment without rescue medication' observation period as supportive evidence. The FAS population will be used in the analysis when concluding superiority.

Sensitivity analysis

To investigate the sensitivity of the main results, complimentary and separate analyses for primary endpoint and the confirmatory secondary endpoint will be performed, using the FAS only, except for HbA_{1c}, where the PP analysis set will be used in a sensitivity analysis regarding the non-inferiority evaluation. These analyses will investigate the sensitivity of the results due to the impact of missing values.

The primary analysis regarding non-inferiority of the primary endpoint change in HbA_{1c} after 30 weeks will also be performed separately based on the data in the PP analysis set only.

The primary endpoint and the secondary confirmatory endpoint will be evaluated in the following sensitivity analyses:

- An analysis of covariance (ANCOVA) model will be analysed with imputation of missing values according to the last observation carried forward (LOCF) method. based on the FAS

using the data from the 'on-treatment without rescue medication' observation period. The model will include terms for treatment, country, and the corresponding baseline value as a covariate. The response variable will be the last available value obtained within the 30 weeks period of the trial

- The MMRM will be analysed based on all data from the 'in-trial' observation period The MMRM will be analysed based on data only from subjects that completed the trial without receiving rescue treatment.

A pattern mixture model based on the FAS using the 'on-treatment without rescue medication' observation period approach mimicking an ITT scenario where withdrawn subjects are assumed to be switched to a treatment inferior to the control treatment after treatment discontinuation will be performed for evaluation of non-inferiority for the primary endpoint change in HbA_{1c} at 30 weeks.

- In the first step 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 treatment group separately and 500 copies of the dataset will be generated.
- In the second step, for each of the 500 copies of the dataset, an analysis of variance model with the same factors as the primary model, and baseline HbA_{1c} and HbA_{1c} at 4 weeks (V3) as covariate is fitted to the change in HbA_{1c} from baseline to 8 weeks (V5) for the sitagliptin group only. The estimated parameters, and their variance, from this model are used to impute missing value at 8 weeks for subjects in all treatment groups, based on country and HbA_{1c} at baseline and 4 weeks.
- In the third step, for each of the 500 copies of the dataset, missing HbA1c values at 12 weeks (V6) are imputed in the same way as for 8 weeks. Now the imputation are based on an analysis of variance model with the same factors and the HbA1c values at baseline, 4 weeks and 8 weeks as covariates, fitted to the control group.
- This stepwise procedure is then repeated sequentially over the available planned visits, adding one visit in each step until the last planned visit at 30 weeks (V9).
- For each withdrawn subject in the investigational treatment group, a value of 0.3% (the non-inferiority limit) is added to the change in HbA_{1c} at 30 weeks.
- For each of the complete data sets, the change from baseline to week 30 is analysed using an analysis of variance model with the same set of factors and the baseline HbA_{1c} value as a covariate.
- The estimates and standard deviations for the 500 data sets are pooled to one estimate and associated standard deviation using Rubin's rule (page 255-257)[59] From these pooled estimates the confidence interval for the treatment differences and the associated p-value are calculated.

A pattern mixture model approach mimicking an ITT scenario where withdrawn subjects are assumed to be switched to the control treatment after treatment discontinuation will be performed

separately for the evaluation of superiority in the primary endpoint change in HbA_{1c} and change in body weight at 30 weeks. The same types of approach as used for the non-inferiority assessment in change in HbA_{1c} will be employed, see above. However, the step where 0.3%, the non-inferiority limit, is added to the change in HbA_{1c} at 30 weeks will not be performed in this sensitivity analysis.

Chinese/Korean subgroup analyses

A number of subgroup analyses by country will be performed with the aim to assess the treatment effect in the individual countries including China and Korea. They will be performed in a combined model using all data similar to the main analysis of the respective parameter but with an interaction between treatment and country.

17.4 Secondary endpoints

The planned secondary endpoints used to support the primary objective will be analysed as outlined in this section.

17.4.1 Confirmatory secondary endpoints

Weight loss

A confirmatory secondary variable is change in body weight after 30 weeks of treatment. This variable will be analysed in the same type of model as the primary endpoint although with baseline body weight as covariate.

17.4.2 Supportive secondary endpoints

17.4.2.1 Efficacy endpoints

All efficacy endpoints in this section will be summarised and evaluated using the FAS.

Continuous variables

Change from baseline to week 30 in:

- FPG
- Insulin
- C-peptide
- glucagon
- pro-insulin
- pro-insulin/insulin ratio
- HOMA-B
- HOMA-IR
- fasting blood lipids (total cholesterol, LDL-cholesterol, VLDL-cholesterol, HDL-cholesterol, triglycerides and free fatty acids)
- BMI
- waist circumference
- systolic and diastolic blood pressure
- hsCRP

will all be analysed based on the same data and type of model as the primary endpoint, but with the associated baseline value as a covariate.

Except for FPG, BMI, waist circumference, and blood pressure the values of the variables will be log transformed subject to analysis.

Beta-cell function

Beta-cell function (fasting HOMA-B and fasting HOMA-IR) will be calculated based on fasting insulin and FPG. The calculation will be done at the same time points as for fasting insulin and FPG samples (section 2).

The calculation of the fasting HOMA endpoints will be done as follows:
Fasting HOMA-B (%) = 20 x fasting insulin [µU/ml]/(FPG[mmol/l]-3.5)
Fasting HOMA-IR (%) = fasting insulin [µU/ml] x FPG [mmol/l]/22.5

PRO outcomes

The PRO outcome endpoints:

- PRO questionnaire outcome DTSQs (individual items and treatment satisfaction score (6 of the 8 items summed)), and
- PRO questionnaire outcome SF-36v2™ short Form health survey: Total scores(physical component and mental component) and scores from the 8 domains

will be analysed separately using the ANCOVA model based on the data from the on-treatment without rescue medication observation period. Factors in the model will be treatment and country. The baseline value of the corresponding endpoint will be used as covariate in the analysis model.

7-point profile

Subjects will be asked to perform SMPG measurements see section 8.5.1.5.

The endpoints from the 7-point profiles that will be analysed at week 30 are:

- Mean of the 7-point profile, defined as the area under the profile, calculated using the trapezoidal method, divided by the measurement time
- Mean increment over all meals

The mean of the 7-point profile and the mean of the post prandial increments at week 30 will be analysed separately with the same data and type of methods as primary endpoint but with the corresponding baseline assessment as a covariate.

Response in HbA_{1c} and/or weight loss after 30 weeks

The secondary variables related to fixed response in HbA_{1c} and/or weight loss at 30 weeks will be:

- Responder in HbA_{1c} after 30 weeks of treatment (yes/no) defined as HbA_{1c} <7.0% (<53 mmol/mol) – ADA target
- Responder in HbA_{1c} after 30 weeks of treatment (yes/no) defined as HbA_{1c} ≤6.5% (48 mmol/mol) – AACE target
- Weight loss ≥5%
- Weight loss ≥10%
- HbA_{1c} <7.0% (53 mmol/mol) without severe or confirmed symptomatic hypoglycaemia (plasma glucose ≤3.1 mmol/L) and no weight gain

All these variables will be analysed based on the 'on-treatment without rescue medication' observation period separately in the same type of logistic regression model. The model will include factors for treatment and country. For the two responder in HbA_{1c} endpoints, baseline HbA_{1c} will be included in the model as a covariate, whereas for the weight responder endpoint (≥5% and ≥10% weight loss), baseline weight will be included instead. For the composite endpoint (cf. last bullet), both baseline HbA_{1c} and baseline weight will be included.

Missing response data at 30 weeks will be imputed from respectively the MMRM used for the primary analysis of HbA_{1c} and the confirmatory secondary endpoint change in body weight at 30 weeks. The results will be described by the odds ratio and the associated 95% confidence interval for the odds ratio.

17.4.2.2 Safety endpoints

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

- Number of treatment emergent AEs during 30 weeks of treatment
- Number of treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes during 30 weeks of treatment
- Severe or BG confirmed symptomatic hypoglycaemic episodes during 30 weeks of treatment (yes/no)

Change in safety endpoints assessed from baseline to 30 weeks of treatment and/or follow up:

- Haematology
- Biochemistry
- Calcitonin
- Urinalysis
- UACR
- Pulse
- ECG evaluation
- Physical examination evaluation
- Eye examination

Occurrence of semaglutide antibodies during 35 weeks of study duration (yes/no):

- Anti-semaglutide antibodies
    - Anti-semaglutide antibodies with in vitro neutralising effect
    - Anti-semaglutide antibodies cross reacting with endogenous GLP-1
        - Cross reacting antibodies with in vitro neutralising effect to endogenous GLP-1

Anti-semaglutide antibody level during and after 30 weeks of treatment

All safety endpoints will be summarised and evaluated by descriptive statistics using the SAS.

Adverse events

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

- Number of treatment emergent adverse events (TEAEs)

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

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

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

Pulse

Pulse will be analysed separately using an analysis similar to the primary analysis of the primary endpoint. However this analysis will be based on FAS using the data from the on-treatment observation period but with the pulse value at baseline as a covariate.

Laboratory assessments

Amylase and lipase will be analysed separately with the same type of methods as for pulse with the corresponding baseline assessment as a covariate. The values will be log transformed in the analysis.

Calcitonin

Calcitonin will be displayed in terms of the number of subjects (N), the percentage of subjects (%) and the event rate per 1000 years of exposure (R). The following criteria are defined for tabulations:

Persistent (all post baseline measurements)

- From <upper normal limit (UNL) to persistently ≥UNL
- From <UNL to persistently ≥1.5 UNL
- From <UNL to persistently ≥20 ng/L
- From <UNL to persistently ≥50 ng/L

- From <20 ng/L to persistently ≥20 ng/L
- From <50 ng/L to persistently ≥50 ng/L

Incidental (at least one post baseline measurements)

- From <UNL to ≥UNL
- From <UNL to ≥1.5 UNL
- From <UNL to ≥20 ng/L
- From <UNL to ≥50 ng/L
- From <20 ng/L to ≥20 ng/L
- From <50 ng/L to ≥50 ng/L

Summaries tables of calcitonin continuous measurements, will include number and percentage of observations < and ≥ LLOQ, minimum, Q25, median, Q75 and maximum. Summaries will be presented for all subjects and by gender.

Classification of Hypoglycaemia

Treatment emergent: hypoglycaemic episodes will be defined as treatment emergent if the onset of the episode occurs within the on-treatment observation period (see definition of observation periods in Section 17.2.

Nocturnal hypoglycaemic episodes: are episodes with time of onset between 00:01 and 05:59 both inclusive.

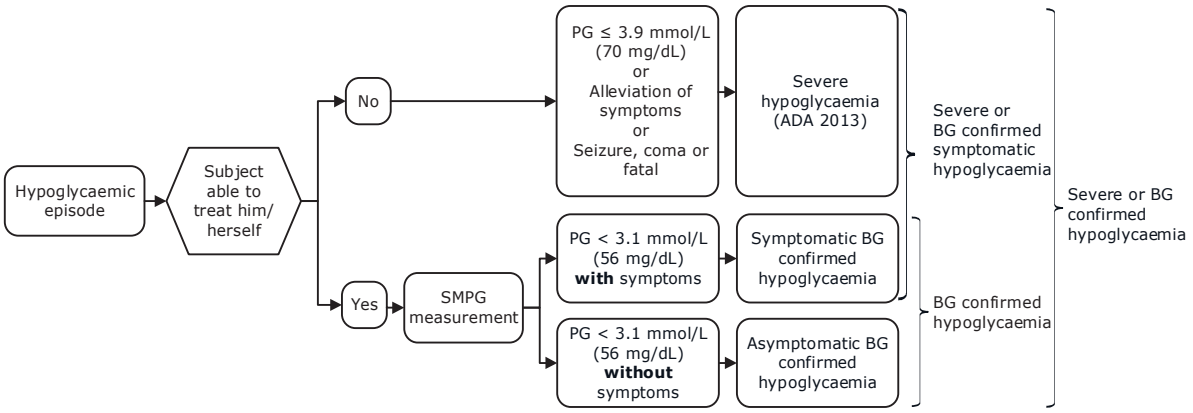
Hypoglycaemic episodes are classified according to the Novo Nordisk classification of hypoglycaemia and the ADA classification of hypoglycaemia (see Figure 17–2).

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)[60]. Therefore, Novo Nordisk has included hypoglycaemia with plasma glucose levels below this cut-off point of hypoglycaemia.

In this trial Novo Nordisk use the following classification in addition to the ADA classification (see Figure 17–1):

- Severe or BG confirmed symptomatic hypoglycaemia: An episode that is severe according to the ADA classification[51] or BG confirmed by a plasma glucose value <3.1 mmol/L (56 mg/dL) with symptoms consistent with hypoglycaemia.



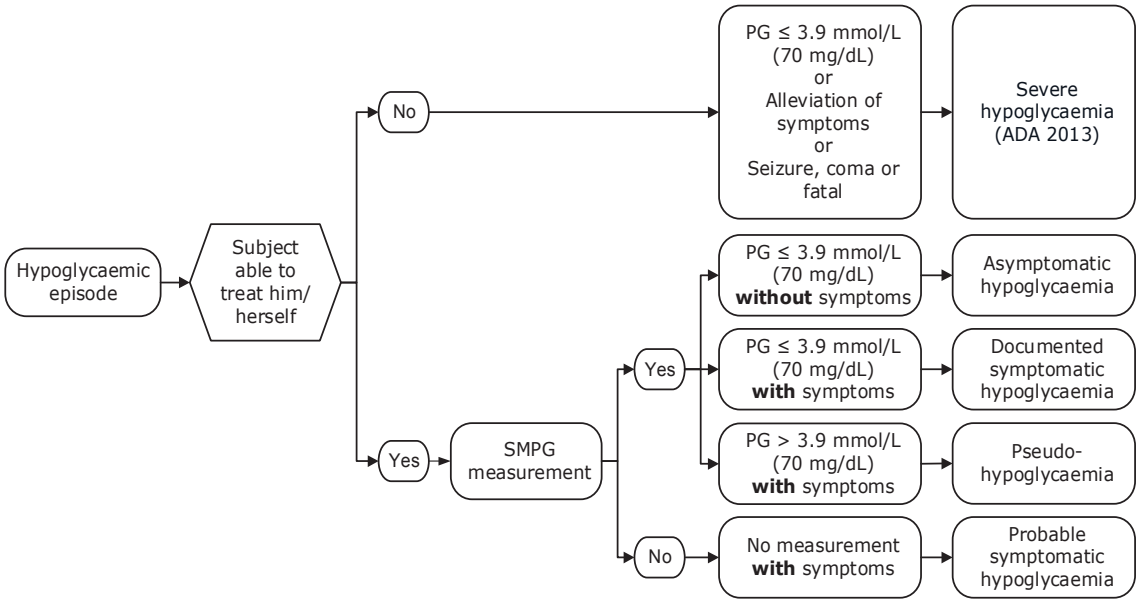
Note: Glucose measurements are performed with capillary blood calibrated to plasma equivalent glucose values

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

Figure 17–1 Novo Nordisk classification of hypoglycaemia

ADA classification of hypoglycaemia[51]

- Severe hypoglycaemia: An episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take of other corrective actions. Plasma glucose concentration 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 17–2 ADA classification of hypoglycaemia

Number of severe or BG confirmed symptomatic hypoglycaemic episodes

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 episodes 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.

The number of severe or BG confirmed symptomatic hypoglycaemic episodes during 30 weeks treatment 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, country as fixed factors and baseline HbA_{1c} as covariate. The SAS will be used for the analysis.

Number of nocturnal hypoglycaemic episodes

The number of nocturnal (00:01-05:59 am) severe or BG confirmed symptomatic hypoglycaemic episodes during 30 weeks of treatment will be analysed separately in the same type of model as the number of severe or BG confirmed symptomatic hypoglycaemic episodes during 30 weeks treatment.

Severe or BG confirmed symptomatic hypoglycaemic 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 with treatment, country as fixed factors and baseline HbA_{1c} as covariate.

Nocturnal severe or BG confirmed symptomatic hypoglycaemic episodes (yes/no)

The binary endpoint indicating whether a subject has no treatment emergent nocturnal (00:01-05:59 am) severe or BG confirmed symptomatic hypoglycaemic episodes or at least one will be analysed using the same type model as severe or BG confirmed symptomatic hypoglycaemic episodes during 30 weeks treatment.

17.5 Health economics and/or patient reported outcomes

The PRO questionnaires, SF-36v2^{TM} and DTSQs, will be used to evaluate the objective regarding Quality of Life, see section 17.4.2.1for the details of the corresponding statistical analysis.

18 Ethics

The trial will be conducted in compliance with ICH GCP[1] and applicable regulatory requirements, and in accordance with the Declaration of Helsinki[2].

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 treatment. Subjects will be treated within a regimen anticipated to be better than or equal to the treatment they receive at the time of entry into the trial. Subjects will have to spend some extra time, as additional assessments and visits to the clinic are required. It is the responsibility of the investigator to ensure the best possible care according to the principles outlined in Diabetes Care 2013 Standards of Medical Care in Diabetes[61], or any updates thereof.

It is concluded that the potential benefits from participating in the trial outweigh the potential risks. The safety profile of semaglutide generated from the clinical and nonclinical development programme has not revealed any safety issues that would prohibit administration of once weekly doses of 0.5 mg or 1.0 mg semaglutide in accordance with the planned clinical trial. It is concluded that the risk to the subjects in this trial is low and acceptable in view of the benefits a long-acting GLP-1 analogue would provide to people with type 2 diabetes (please see 3.5)

The trial products may be associated with AEs, but relevant precautions have been implemented in the design and planned conduct of the trial in order to minimise the risks and inconveniences of participation in the trial. These precautions include thorough information regarding the correct administration of the trial products and gradual dose adjustment. Furthermore, subjects are fully informed about possible AEs and inconveniences and will be instructed to contact the investigator in case of any concerns regarding the trial participation.

When treatment with trial products ends, the subject and investigator will decide on the best available treatment.

18.1 Informed consent

In seeking and documenting informed consent, the investigator must comply with applicable regulatory requirement(s) and adhere to ICH GCP[1] and the requirements in the Declaration of Helsinki[2].

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

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

18.2 Data handling

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

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

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

18.3 Information to subject during trial

The site will be offered a communication package to the subject during the conduct of the trial. The package content is issued by Novo Nordisk. The communication package will contain the letters intended for distribution to the subjects. The letters will be translated and adjusted to local requirements and distributed to the subject by discretion of the investigator. The subject may receive a “welcome to the trial letter” and a “thank for your participation letter” at the end of the trial. Further the subject may receive trial letters during the trial period.

All information to the subjects will be submitted to the health authorities and IECs/IRBs for approval according to local regulations.

18.4 Premature termination of the trial and/or trial site

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

If a 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 IRBs/IECs and provide a detailed written explanation. The relevant regulatory authorities must be informed.

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

19 Protocol compliance

Deviations from the protocol should be avoided.

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

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

Documentation on protocol deviations must be kept in the investigator's trial file and Novo Nordisk trial master file.

20 Audits and inspections

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

21 Critical documents

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

- Regulatory approval and/or acknowledgement of notification as required
- Approval/favourable opinion from IRBs/IECs clearly identifying the documents reviewed as follows: protocol, any protocol amendments, subject information/informed consent form, any other written information to be provided to the subject and subject recruitment materials
- List of IRB/IEC members and/or constitution
- Curricula vitae of investigator and sub-investigator(s) (current, dated and signed - must include documented GCP training or a certificate)
- Signed receipt of Investigator's Brochure and local label for comparator
- Signed and dated agreement on the final protocol
- Signed and dated agreement on protocol amendment, if applicable
- Financial agreement(s)
- Source document agreement
- Central laboratory certification and normal ranges
- Insurance statement, if applicable
- Signed and dated Investigator Agreement
- Financial disclosure form from investigator and sub-investigator(s)

Novo Nordisk will analyse and report data from all sites together.

By signing the protocol, each investigator agrees to comply fully with ICH GCP[1], applicable regulatory requirements and the Declaration of Helsinki[2].

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

22 Responsibilities

All staff Novo Nordisk, site, Central Laboratories, CRO etc. must conduct the trial in compliance with ICH GCP[1], applicable regulatory requirements, and in accordance with the Declaration of Helsinki[2].

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

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

The investigator is responsible for filing essential documents (ie those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced) in the investigator's trial file. The documents should be kept in a secure locked facility, so no unauthorized persons can get access to the data. The subject identification code list must be kept securely and separate from the personal 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 (eg 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 Novo Nordisk for regulatory purposes and 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.

One principal investigator will be appointed 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[62].

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.

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 principal 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[62] (sometimes referred to as the Vancouver Criteria).

At the end of the trial, one or more publications (abstracts, posters, manuscripts) will be prepared for submission to scientific congresses and peer-reviewed journals in collaboration between Novo Nordisk and investigator(s) appointed by Novo Nordisk. These investigator(s) must meet the ICMJE authorship criteria to be named authors on publications.

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 for publication of such primary policy 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 and human biospecimens

24.1 Retention of clinical trial documentation

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

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

The investigator must be able to access his/her trial documents without involving Novo Nordisk in any way. Site-specific CRFs and other subject data (in an electronic readable format or as paper copies or prints) will be provided to the investigator before access is revoked to the systems and/or electronic devices supplied by Novo Nordisk. These data must be retained by the trial site. If the Novo Nordisk provided data (eg 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 as long as the product is on the market plus 20 years.

The files from the investigator site/institution must be retained for 15 years after the completion of the trial, or longer if required by local regulations. The deletion process must ensure confidentiality of data and must be done in accordance with local regulatory requirements.

24.2 Retention of human biospecimens

Antibody samples may be stored until market authorisation in case Health Authorities requests further characterisation of the antibody response.

(For Brazil: the laboratory samples for BR subjects will be destroyed at the latest at the completion of the CTR, including samples for anti-semaglutide antibody analysis. No sample will be stored after the completion of CTR).

None of the data will be identified by name. Antibody samples and thyroid tissue will be identified only by a subject number, a visit number and a trial identification number. The trial staff is responsible for maintaining a code list which links to the subject number. The code list must be kept for at least 15 years. The code list may be reviewed by Novo Nordisk staff including auditors or representatives from regulatory authorities, but no copies will be made of this list.

25 Institutional Review Boards/Independent Ethics Committees and regulatory authorities

IRB/IEC:

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

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

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

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

The investigator must maintain an accurate and complete record of all submissions made to the IRB/IEC. The records must be filed in the investigator's trial 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 local laws/acts/guidelines.

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Protocol

Trial ID: NN9535-4114

SUSTAIN – CHINA MRCT

Efficacy and safety of semaglutide once-weekly versus sitagliptin once-daily as add-on to metformin in subjects with type 2 diabetes

A 30-week randomised, double-blind, double-dummy, active-controlled, parallel-group, multi-centre and multi-national trial

Trial phase: 3a

Protocol originator

[redacted]

Semaglutide Diabetes & Diabetes Outcomes

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List of abbreviations

AACE	American Association of Clinical Endocrinologists
ADA	American Diabetes Association
AE	adverse event
BG	blood glucose
BMI	Body mass index
CRF	case report form
CRO	contract research organisation
CTR	clinical trial report
CVD	cardiovascular disease
DPP-4	dipeptidyl peptidase 4
DUN	dispensing unit number
DTSQs	Diabetes Treatment Satisfaction Questionnaire status
EAC	event adjudication committee
ECG	electrocardiogram
eCRF	electronic case report form
EE	ethinylestradiol
EFD	embryo-foetal development
eGFR	estimated glomerular filtration rate
FAS	full analysis set
FDAAA	Food and Drug Administration Amendment Act
FPFV	first patient first visit
FPG	fasting plasma glucose
FSFV	first subject first visit
GCP	Good Clinical Practice
GI	gastrointestinal
GIP	gastric inhibitory polypeptide
GLP-1	glucagon-like peptide-1
HbA_{1c}	glycosylated haemoglobin

hCG	human chorionic gonadotrophin
HDL	high density lipoprotein
hsCRP	highly sensitive C-reactive protein
IB	Investigator's Brochure
ICMJE	International Committee of Medical Journal Editors
IEC	independent ethics committee
IMP	investigational medicinal product
IRB	Institutional Review Board
IUD	intrauterine device
IWRS	interactive voice/web response system
LDL	low density lipoprotein
LN	levonorgestrel
LPFV	last patient first visit
LPLV	last patient last visit
LSFV	last subject first visit
LSLV	last subject last visit
MACE	major adverse cardiovascular events
MAR	missing at random
MCAR	missing completely at random
MDRD	modification of diet in renal disease
MEN2	multiple endocrine neoplasia syndrome type 2
MMRM	mixed model for repeated measurements
MTC	medullary thyroid carcinoma
NYHA	New York Heart Association
OAD	oral anti-diabetic drug
PG	plasma glucose
PP	per protocol
PPG	postprandial glucose
PPND	pre- and postnatal development

PRO	patient reported outcome
RA	receptor agonist
SAE	serious adverse event
SAP	statistical analysis plan
s.c.	subcutaneous
SD	standard deviation
SDV	source data verification
SMBG	self-measured blood glucose
SMPG	self-measured plasma glucose
SU	sulphonylurea
SUSAR	suspected unexpected serious adverse reaction
TMM	Trial Materials Manual
TEAE	treatment emergent adverse event
TVP	trial validation plan
UACR	urinary albumin to creatinine ratio
UTN	universal trial number
V	visit

1 Summary

Objectives and endpoints:

Primary objective

To compare the effect of once-weekly dosing of two dose levels of semaglutide versus sitagliptin 100 mg once-daily on glycaemic control after 30 weeks of treatment

Primary endpoint

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

Secondary objectives

To compare the effects of once-weekly dosing of two dose levels of semaglutide versus sitagliptin 100 mg once-daily after 30 weeks of treatment on:

- Inducing and maintaining weight loss
- Other parameters of efficacy, safety and tolerability

Key secondary endpoint

Confirmatory secondary endpoint

- Change from baseline to week 30 in body weight

Supportive secondary endpoints:

Change from baseline to week 30 in:

- Fasting plasma glucose (FPG)
- Systolic and diastolic blood pressure
- Patient reported outcome (PRO) questionnaire: Diabetes Treatment Satisfaction Questionnaire status (DTSQs) score

Subjects who after 30 weeks treatment achieve (yes/no):

- $HbA_{1c} \leq 6.5\%$ (48 mmol/mol) - American Association of Clinical Endocrinologists (AACE) target

Trial design:

This is a 30-week randomised, double-blind, double-dummy, active-controlled, multi-centre, multi-national four-armed, parallel-group trial comparing semaglutide 0.5 mg and 1.0 mg once-weekly against sitagliptin 100 mg once-daily.

Subjects with type 2 diabetes inadequately controlled on metformin will be randomised in a 2:2:1:1 manner to receive either:

- semaglutide 0.5 mg once-weekly + sitagliptin placebo once-daily
- semaglutide 1.0 mg once-weekly + sitagliptin placebo once-daily
- sitagliptin 100 mg once-daily + semaglutide placebo (0.5) mg once-weekly
- sitagliptin 100 mg once-daily + semaglutide placebo (1.0) mg once-weekly

Trial product will be add-on to subject's stable pre-trial metformin.

Key inclusion criteria:

- Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial
- Male or female, age ≥ 18 years at the time of signing informed consent
- Subjects diagnosed with type 2 diabetes and on stable treatment in a period of 60 days prior to screening with metformin ≥ 1500 mg (or maximum tolerated dose ≥ 1000 mg). Stable is defined as unchanged medication and unchanged daily dose
- HbA_{1c} 7.0 – 10.5 % (53-91 mmol/mol) (both inclusive)

Key exclusion criteria:

- Female who is pregnant, breast-feeding or intends to become pregnant or is of childbearing potential not using an adequate contraceptive method throughout the trial including the 5 week follow-up period (adequate contraceptive measure as required by local regulation or practice).
- Any disorder which, in the opinion of the investigator, might jeopardise subject's safety or compliance with the protocol
- Treatment with glucose lowering agent(s) other than stated in the inclusion criteria in a period of 60 days before screening. An exception is short-term treatment (≤7 days in total) with insulin in connection with inter-current illness
- History of chronic or idiopathic acute pancreatitis
- Screening calcitonin value ≥ 50 ng/L (pg/mL)
- Personal or family history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia syndrome type 2 (MEN 2)
- Impaired renal function defined as estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2 per modification of diet in renal disease (MDRD) formula (4 variable version)
- Acute coronary or cerebrovascular event within 90 days before randomisation
- Heart failure, New York Heart Association (NYHA) class IV

Assessments:

Efficacy:

- Glucose metabolism
- Body measurements (body weight, body mass index (BMI) and waist circumference)
- Systolic and diastolic blood pressure
- Blood lipids
- Patient reported outcome (PRO) questionnaires (SF-36v2™ and DTSQs)

Safety:

- Adverse events and serious adverse events
- Hypoglycaemic episodes
- Biochemistry and haematology
- Anti-semaglutide antibodies
- Physical examination (including electrocardiogram (ECG))

Trial products:

Novo Nordisk A/S will supply the following trial products:

- Semaglutide 1.34 mg/mL, solution for injection, 1.5 mL pre-filled PDS290 pen-injector
- Semaglutide placebo, solution for injection, 1.5 mL pre-filled PDS290 pen-injector
- Sitagliptin (Januvia®) 100 mg tablets for oral administration
- Sitagliptin placebo tablets for oral administration

2 Flow chart

Trial Periods		Screen	Rand	Treatment period						End of Treatment[1]	Follow Up[1]	End of Treatment premature discontinuation[2]	Follow Up premature discontinuation[2]
Visit (V) or Phone (P) number		V1	V2	V3	P4	V5	V6	V7	V8	V9	V10	V9A	V10A
Time of visit	**Weeks**	-2	0	4	6	8	12	16	23	30	35		
Visit window	**Days**	±7		±3	±3	±3	±3	±3	±3	±7	+7		
SUBJECT RELATED INFO /ASSESSMENTS													
Informed consent	18.1	x											
In/exclusion criteria	6.2,6.3	x	x										
Randomisation	8.1.3		x										
Withdrawal criterion	6.5			x	x	x	x	x	x	x		x	
Demography	8.2.1	x											
Diabetes history and diabetes complications	8.2.2	x											
Concomitant illness and medical history	8.2.3	x											
History of cardiovascular disease	8.2.3	x											
History of gallbladder disease	8.2.3	x											
Tobacco use	8.2.5	x											
Concomitant medication	8.2.4	x	x	x	x	x	x	x	x	x	x	x	x
Height	8.2.7		x										
EFFICACY													
Body weight	8.3.1		x	x		x	x	x	x	x		x	
Waist circumference	8.3.2		x	x		x	x	x	x	x		x	
BMI	8.3.3		x	x		x	x	x	x	x		x	
Systolic blood pressure, sitting	8.3.4	x	x	x		x	x	x	x	x		x	

Trial Periods		Screen	Rand	Treatment period						End of Treatment[1]	Follow Up[1]	End of Treatment premature discontinuation[2]	Follow Up premature discontinuation[2]
Visit (V) or Phone (P) number		V1	V2	V3	P4	V5	V6	V7	V8	V9	V10	V9A	V10A
Time of visit	**Weeks**	-2	0	4	6	8	12	16	23	30	35		
Visit window	**Days**	±7		±3	±3	±3	±3	±3	±3	±7	+7		
Diastolic blood pressure, sitting	8.3.4	x	x	x		x	x	x	x	x		x	
HbA_{1c}	8.5.1.1	x	x	x		x	x	x	x	x		x	
Fasting plasma glucose	8.5.1.1		x	x		x	x	x	x	x		x	
Fasting insulin	8.5.1.1		x					x		x		x	
Fasting proinsulin	8.5.1.1		x					x		x		x	
Fasting C-peptide	8.5.1.1		x					x		x		x	
Fasting glucagon	8.5.1.1		x					x		x		x	
Lipids	8.5.1.3		x					x		x		x	
hsCRP (highly sensitive CRP)	8.5.1.2		x					x		x		x	
7 point profile	8.5.1.4		x					x		x		x	
SAFETY													
Adverse events	8.4.1		x	x	x	x	x	x	x	x	x	x	x
Hypoglycaemic episodes	8.4.4		x	x	x	x	x	x	x	x	x	x	x
ECG	8.4.5		x							x	x	x	x
Physical examination	8.4.6	x								x		x	
Pulse, sitting	8.4.7	x	x	x		x	x	x	x	x		x	
Anti-semaglutide antibodies[4]	8.5.2.1		x					x		x	x	x	x
Creatinine	8.5.2.2	x		x		x	x	x	x	x		x	
Biochemistry	8.5.2.2		x	x		x	x	x	x	x		x	
Haematology	8.5.2.3		x	x		x	x	x	x	x		x	
Calcitonin	8.5.2.4	x						x		x		x	
Pregnancy test[5]	8.5.2.5	x	x	x		x	x	x	x	x	x	x	x
Urinalysis	8.5.2.6		x					x		x		x	

Trial Periods		Screen	Rand	Treatment period						End of Treatment[1]	Follow Up[1]	End of Treatment premature discontinuation[2]	Follow Up premature discontinuation[2]
Visit (V) or Phone (P) number		V1	V2	V3	P4	V5	V6	V7	V8	V9	V10	V9A	V10A
Time of visit	**Weeks**	-2	0	4	6	8	12	16	23	30	35		
Visit window	**Days**	±7		±3	±3	±3	±3	±3	±3	±7	+7		
Eye examination[3]	8.4.8		x							x		x	
OTHER ASSESSMENTS													
PRO questionnaires	8.6.1		x							x		x	
TRIAL MATERIAL													
Drug accountability	9.4					x		x		x		x	
IWRS call	10	x	x			x		x		x		x	
Dispensing visit	9.1		x			x		x					
REMINDERS													
Training in trial product, and pen handling	9.1		x	x		x							
Hand-out Directions for Use (DFU)	9.5		x										
End of treatment	8.1.6									x[9]		x[9]	
End of trial	8.1.6										x[9]		
Hand-out and instruct in BG meter use	8.5.1.4	x											
Hand-out and /or collect diary[6]	8.6.2	x	x	x		x	x	x	x	x	x[6]	x	x[6]
Attend visit fasting[7]	8.1.2		x	x		x	x	x	x	x	x[8]	x	x[8]
Hand-out ID card	8.1.1	x											

2.1 Flow chart explanatory descriptions

Footer	Description
x[1]	V9 (End of Treatment) and V10 (Follow Up) are applicable for all randomised subjects. Subjects who have discontinued trial product prematurely should also attend V9 and V10 according to their initially scheduled week 30 and Week 35 visits.
x[2]	Subjects discontinuing trial product prematurely will be asked to attend two additional visits to undergo assessments: End of Treatment-premature discontinuation (V9A) and Follow Up -premature discontinuation (V10A). V9A should be scheduled at discontinuation of the trial product. V10A should be scheduled 5 weeks after discontinuation of trial product (+ 7 days visit window).
x[3]	Fundus photography/dilated fundoscopy performed within 90 days before visit 2 is acceptable if results are available for evaluation at the visit 2 and no deterioration in visual function since last assessment.
x[4]	Antibody sampling should preferably be done pre-dose. For fasting and non-fasting visit, where the injection takes place on the day of site visit, trial product must not be taken before blood sampling. For visit 9 and 10: Not applicable if taken at a premature discontinuation visit
x[5]	For women of child bearing potential: For all site visits a serum pregnancy test must be performed. Urine pregnancy test should be performed at any time during the trial if a menstrual period is missed, or as required by local law.
x[6]	At V10 and V10A collect diary only.
x[7]	Fasting is defined as having consumed only water within the last 6 hours prior to the visit. Glucose lowering agents and trial product cannot be taken until after blood sampling has been performed but other prescribed medication should be taken.
x[8]	For the follow-up visit (V10/V10A) attend fasting is defined as having consumed only water within the last 2 hours prior to the visit.
x[9]	If premature discontinuation occurs, End of Treatment form must be filled-in when the discontinuation happens and End of Trial form at scheduled V10. 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 V10. In case of subject withdrawal, both End of Treatment form and End of Trial form must be filled-in at the time they withdraw from the trial.

3 Background information and rationale for the trial

The trial will be conducted in compliance with this protocol, ICH GCP[1] and applicable regulatory requirements, and in accordance with the Declaration of Helsinki[2].

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 Type 2 diabetes

Type 2 diabetes (T2D) is a progressive metabolic disease primarily characterised by abnormal glucose metabolism. The pathogenesis is not fully understood but seems to be heterogeneous, involving environmental, lifestyle, and genetic factors leading to chronic hyperglycaemia caused by peripheral tissue insulin resistance, impaired insulin secretion due to abnormal beta-cell function and abnormal glucose metabolism in the liver[3].

Optimal glycaemic control is the treatment goal in subjects with type 2 diabetes, in order to prevent long-term complications associated with chronic hyperglycaemia[4,5]. Despite the availability of several anti-diabetic drugs, a significant proportion of subjects with type 2 diabetes do not achieve the recommended blood glucose target levels[6-9].

3.2 Glucagon-like peptide-1

Glucagon-like peptide-1 (GLP-1) is an incretin hormone with a glucose-dependent stimulatory effect on insulin and inhibitory effect on glucagon secretion from the pancreatic islets[10, 11]. Subjects with T2D have a decreased response to GLP-1[12-15] . However, the insulinotropic action of GLP-1 and thus, the ability to lower BG levels, is preserved when GLP-1 is administered at supraphysiological levels[16]. In addition, supraphysiological levels of GLP-1 induce reduction in body weight[17]. GLP-1 is a physiological regulator of appetite and food intake and GLP-1 receptors are present in several areas of the brain involved in appetite regulation and food intake[18, 19]. Physiologically, GLP-1 also has a pronounced inhibitory effect on gastric emptying; however this effect seems to diminish upon chronic exposure[17-19]. These mechanisms of action make glucagon-like peptide-1 receptor agonists (GLP-1 RAs) an attractive pharmacological treatment for T2D[20-22]. Due to the very short half-life of <1.5 minutes after i.v. administration, native GLP-1 is not suitable for therapeutic use. To realise the full therapeutic potential of GLP-1, the pharmacokinetic and hence the pharmacodynamic effect needs to be protracted.

3.3 Semaglutide

Semaglutide is a potent human GLP-1 receptor agonist (RA) for once-weekly subcutaneous (s.c.) administration. It is structurally similar to liraglutide (Victoza®), a once-daily GLP-1 RA developed by Novo Nordisk and approved worldwide for the treatment of type 2 diabetes. The extended half-life of the semaglutide molecule is primarily obtained due to binding to albumin, which is facilitated

by a large fatty acid derived chemical moiety attached to the lysine in position 26. The specific modifications in the molecule are: 1) a modification in position 8 (alanine to 2-aminoisobutyric acid) of the peptide backbone to increase stability against 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 diacid with a terminal acidic group[23, 24]. The spacer and the fatty acid both contribute to increased albumin binding, which results in decreased renal clearance resulting in a prolonged half-life of approximately 1 week, making semaglutide suitable for once-weekly s.c. administration.

3.3.1 Non-clinical data

The non-clinical programme for semaglutide was designed according to the ICH M3[25] guideline to support the clinical development. The standard non-clinical 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.

3.3.1.1 Thyroid C-cell tumours in rodents

Thyroid C-cell neoplasia was seen in mice and rat 2-year carcinogenicity studies. Proliferative C cell changes in rodents are a known effect following GLP-1 receptor activation by GLP-1 receptor agonists. The finding in rodents is caused by a non-genotoxic, specific GLP-1 receptor-mediated mechanism to which rodents are particularly sensitive. Recently published data have shown that the GLP-1 receptor is not expressed in the normal human thyroid, and accordingly, the risk of GLP-1 receptor mediated C-cell changes in humans is considered to be low[26].

3.3.1.2 Embryo−foetal development toxicity

Semaglutide adversely affected embryo−foetal development in the rat by a GLP-1 receptor mediated impaired function of the inverted yolk sac placenta during a period of gestation when the rat embryo is entirely dependent on the inverted yolk sac placenta for its nutrient supply. In primates, the yolk sac does not invert to fully enclose the embryo, and it does not come in direct contact with the uterine wall to form a placenta as in rodents. Accordingly, the mechanism by which semaglutide adversely affects embryo-foetal development in the rat, is not likely to be of relevance to humans. Studies in cynomolgus monkeys confirmed that maternal dosing of semaglutide does not affect embryo−foetal development in this species. However, the initial maternal body weight loss caused by the pharmacological effect of semaglutide coincided with increased early pregnancy loss in one of three studies. In cynomolgus monkeys, the overall developmental no observable adverse

effect level (NOAEL) was determined to be 0.015 mg/kg/3 days, which provides an exposure equivalent to the human exposure at 1.0 mg/week based on area under the curve (AUC).

A comprehensive review of results from the nonclinical studies can be found in the current edition of semaglutide (NN9535) investigator's brochure (IB)[27], or any updates hereof.

3.3.2 Clinical data

As of 1 August 2016, 16 clinical pharmacology trials (trials NN9535-1820, 3679, 3633, 3616, 3819, 4010, 3789, 3652, 3685, 3634, 3687, 3817,3818, 3684, 3651 and 3635), 1 phase 2 trial (NN9535-1821) and 8 phase 3a trials (NN9535-3623, 3624, 3625,3626, 3627, 3744, 4091, 4092) have been completed with semaglutide s.c. once-weekly. Clinical pharmacology trials were conducted in healthy subjects, in subjects with T2D, in subjects with obesity and in subjects with renal- and hepatic impairment. The phase 2 dose-finding trial was conducted in subjects with T2D. The 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-hyperglycaemic therapies and compared semaglutide with the most important comparators at the time of initiating the phase 3a programme. In addition, the phase 3a programme included a long-term (104-week) cardiovascular outcomes trial (trial 3744) in a T2D population at high risk of cardiovascular events.

3.3.2.1 Pharmacokinetics

The results from the completed clinical pharmacology trials confirm that semaglutide has PK properties compatible with once-weekly administration, having a flat concentration profile over time, with a median time to maximum concentration (tmax) of 1−3 days post-dosing and an elimination half-life (t½) of approximately 1 week. The PK properties of semaglutide appear comparable between healthy subjects, subjects with T2D and subjects with renal failure. Results from drug-interaction studies with warfarin, metformin, atorvastatin and digoxin indicate that no dose adjustment of the co-administered drugs is warranted when administered together with semaglutide. In addition, semaglutide does not decrease the exposure of oral contraceptives and hence, is not anticipated to decrease the effectiveness of oral contraceptives.

3.3.2.2 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 receptor agonists, semaglutide caused a minor delay of early postprandial gastric emptying.

Both as monotherapy and as combination therapy, semaglutide significantly reduced HbA1c 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 HbA1c 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 HbA1c <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 HbA1c were substantiated by improvements in secondary glycaemia-related supportive endpoints[28-31].

3.3.2.3 Safety

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

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

The effect of semaglutide on major adverse cardiovascular events (MACE) was evaluated in a T2D population at high risk for CV events, in the cardiovascular outcome trial, SUSTAIN 6 (NN9535-3744)[32]. SUSTAIN 6 trial achieved its primary objective by showing non-inferiority of once-weekly s.c. semaglutide versus placebo on cardiovascular outcomes; moreover, s.c. semaglutide statistically significantly reduced cardiovascular risk versus placebo[32]. In addition, results from the recently completed LEADER® trial (EX2211-3748) showed that treatment with the once daily liraglutide does not increase the risk of MACE as compared to placebo. In fact, treatment with liraglutide reduced the risk of the primary composite outcome consisting of death from cardiovascular causes, non-fatal myocardial infarction (MI) and non-fatal stroke by 13% versus placebo[32]. The overall safety profile of semaglutide in the SUSTAIN 6 trial (NN9535-3744) was consistent with previous

semaglutide clinical studies. However, in this trial, the diabetic retinopathy complications were reported more frequently in the semaglutide-treated subjects compared with placebo.

Please see the current edition of semaglutide s.c. (NN9535) IB or any updates hereof for further details[27].

3.4 Sitagliptin

Sitagliptin is an oral antihyperglycemic agent of the dipeptidyl peptidase-4 (DPP-4) inhibitor class suitable for once-daily oral administration. It was developed and marketed by Merck & Co as sitagliptin phosphate under the trade name Januvia®

Sitagliptin works by inhibition of the enzyme dipeptidyl peptidase 4 (DPP-4). This enzyme breaks down the incretin hormones GLP-1 and gastric inhibitory polypeptide (GIP). By preventing GLP-1 and GIP inactivation, secretion of insulin is increased and release of glucagon is suppressed. The obvious advantage with a convenient route of administration is however counterbalanced by a significantly lower effect of the DPP-4 inhibitors on glycaemic control and body weight as compared to GLP-1 RAs. This has also been demonstrated for sitagliptin when compared to liraglutide[33-35].

Adverse reactions reported in >5% of patients treated with sitagliptin and more commonly than in patients treated with placebo are: upper respiratory tract infection, nasopharyngitis and headache. In add-on to sulfonylurea and add-on to insulin studies, hypoglycaemia was also more commonly reported in patients treated with sitagliptin compared to placebo[36].

3.5 Risk and benefits assessment

This assessment is based on the safety and efficacy data for semaglutide and sitagliptin presented above as well as potential risk identified as drug class effects.

3.5.1 Semaglutide risks and precautions

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

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

3.5.2 Identified risks

Gastrointestinal adverse events

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

Diabetic retinopathy complications

A transient worsening of diabetic retinopathy is a recognised complication in selected patients with diabetes after initiation of intensive anti-diabetic treatment[37]. 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[38, 39] even in intensively treated patients who experienced early worsening[40]. In a cardiovascular outcomes trial with s.c. semaglutide, results indicate an increased risk of events related to diabetic retinopathy complications in subjects treated with semaglutide compared to placebo. As a precaution in this trial, all subjects are required to have a fundus photography or dilated fundoscopy performe d 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[41].

3.5.3 Potential risks

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 MEN 2 or MTC will not be enrolled in the trial. During the trial, calcitonin will be measured on a regular basis, and the guidance for investigators on further evaluation and action on elevated calcitonin concentrations is included in appendix A.

Acute pancreatitis

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

Pancreatic cancer

Patients with T2D have an increased risk of certain types of cancer such as pancreatic cancer. There is currently no support from nonclinical studies or clinical trials or post marketing data that GLP-1-based therapies increase the risk of pancreatic cancer. However, pancreatic cancer has been included as a separate potential risk due to the scientific debate surrounding a potential association to GLP-1-based therapies and the unknown long-term effects of stimulation of β-cells and suppression of α-cells. Pancreatic cancer has been classified as a potential class risk of GLP-1 RAs by EMA.

Allergic reactions and injection site reaction

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

Hypoglycaemia

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

Acute renal impairment

In subjects treated with GLP-1 RAs, including semaglutide, gastrointestinal AEs such as nausea, vomiting and diarrhoea may lead to significant dehydration and secondary acute renal impairment. 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.

3.5.4 Other safety considerations

Teratogenicity (embryo-foetal development toxicity)

Semaglutide caused embryo-foetal malformations in the rat through a GLP-1 receptor mediated effect on the inverted yolk sac placenta leading to impaired nutrient supply to the developing embryo. Primates do not have an inverted yolk sac placenta which makes this mechanism unlikely to be of relevance to humans. However, as a precaution, females who are pregnant, breast-feeding or intend to become pregnant or are of childbearing potential and not using an adequate contraceptive method will not be enrolled in the trial. In addition, pregnancy tests will be performed 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[42, 43] (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 2016 Standards of Medical Care in Diabetes[44].

Further details with regards to safety of trial product are described in the current edition of the IB for semaglutide (NN9535)[27], or any updates thereto.

3.5.5 Sitagliptin risk and precautions

Sitagliptin is generally considered to be well tolerated. The most commonly reported side effect is upper respiratory tract infection, nasopharyngitis and headache. Some of the potential risk associated with GLP-1 RA treatment has also been associated with treatment with the DPP-4 inhibitors as sitagliptin i.e. pancreatitis, acute renal impairment, hypersensitivity reactions and hypoglycaemia (US prescribing information[45] and Chinese prescribing information[46])

3.5.6 Benefits

In this trial subjects in all treatment arms will be treated within a regimen anticipated to be more efficacious than the treatment they receive at the time of randomisation into the trial. It is expected that subjects will benefit from the trial treatment with respect to optimised glycaemic control, a reduced risk of long-term diabetic complications and a potential weight loss.

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.

Furthermore, data from two cardiovascular outcomes trials investigating treatment with GLP-1 RAs compared to placebo have indicated a beneficial effect of these drugs on cardiovascular outcomes when added to standard of care in subjects with T2D at high risk of cardiovascular events (see Section 3.3.2.3).

Sitagliptin has in phase 3 trials where sitagliptin has been given in combination with metformin proven to provide significant improvements in HbA_{1c} and FPG[47].

All subjects in this trial will receive active treatment and will receive trial drug and auxiliary free of charge.

Finally, it is expected that all subjects participating in the trial will benefit from participation through close contact with the study site and close follow-up of their type 2 diabetes. Such careful medical examination will most likely result in an intensified management of their diabetes.

3.5.7 Risk and benefit conclusion

It is concluded that the potential benefits from participating in the trial outweigh the potential risks. The safety profile of semaglutide generated from the clinical and nonclinical development programme has not revealed any safety issues that would prohibit administration of once-weekly doses of 0.5 mg or 1.0 mg semaglutide in accordance with the planned clinical trial. Sitagliptin is already a marketed drug in the 100 mg dose and approved for the use in type 2 diabetic patients. Safety and efficacy will be monitored regularly and acceptable glycaemic control will be reinforced at all times during the trial.

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

3.6 Rationale for the trial

The currently available treatment modalities for type 2 diabetes are still not satisfactory and there is still a large proportion of patients not reaching the treatment targets. In the 5 global phase 3a trials (3623, 3624, 3625, 3626 and 3627), reductions in HbA1c and body weight with semaglutide was superior to sitagliptin, exenatide ER and insulin glargine demonstrating semaglutide as a highly efficacious treatment option.

The rationale for this trial is to compare the efficacy of semaglutide versus sitagliptin in subjects with type-2 diabetes in terms of glycaemic control, weight loss and other efficacy parameters. Furthermore the trial is designed to address and compare safety, tolerability and patient satisfaction. This trial is designed to resemble the main trial NN9535-3626 (SUSTAIN 2) in the global

SUSTAIN programme and will be conducted in China and several other countries. The study design is adjusted to fulfil the Chinese requirements.

4 Objectives and endpoints

4.1 Objective

4.1.1 Primary objective

To compare the effect of once-weekly dosing of two dose levels of semaglutide versus sitagliptin 100 mg once-daily on glycaemic control after 30 weeks of treatment

4.1.2 Secondary objectives

To compare the effects of once-weekly dosing of two dose levels of semaglutide versus sitagliptin 100 mg once-daily after 30 weeks of treatment on:

- Inducing and maintaining weight loss
- Other parameters of efficacy, safety and tolerability

4.2 Endpoints

4.2.1 Primary endpoint

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

4.2.2 Secondary endpoints

4.2.2.1 Confirmatory secondary endpoint

- Change from baseline to week 30 in body weight

4.2.2.2 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)
- Insulin, C-peptide, glucagon, pro-insulin, pro-insulin/insulin ratio, homeostasis model assessment of beta-cell function (HOMA-B) and insulin resistance (HOMA-IR) (all fasting)
- Fasting blood lipids (total cholesterol, low density lipoprotein (LDL) cholesterol, very low density lipoprotein (VLDL) cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides and free fatty acids
- Body mass index (BMI)
- Waist circumference
- Systolic and diastolic blood pressure*

- Highly sensitive C-reactive protein (hsCRP)
- Patient reported outcome (PRO) questionnaire: SF-36v2™ score
- Patient reported outcome (PRO) questionnaire: Diabetes Treatment Satisfaction Questionnaire status (DTSQs) score*

Subjects who after 30 weeks treatment achieve (yes/no):

- $HbA_{1c} < 7.0\%$ (53 mmol/mol) - American Diabetes Association (ADA) target
- $HbA_{1c} \leq 6.5\%$ (48 mmol/mol) - American Association of Clinical Endocrinologists (AACE) target*
- Weight loss $\geq 5\%$
- Weight loss $\geq 10\%$
- $HbA_{1c} < 7.0\%$ (53 mmol/mol) without severe or blood glucose (BG) confirmed symptomatic hypoglycaemia and no weight gain

Supportive secondary safety endpoints

- Number of treatment emergent adverse events (TEAEs) during 30 weeks of treatment
- Number of treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes during 30 weeks of treatment
- Severe or BG confirmed symptomatic hypoglycaemic episodes during 30 weeks of treatment (yes/no)

Change from baseline to week 30 in:

- Haematology
- Biochemistry
- Calcitonin
- Urinalysis
- Urinary albumin to creatinine ratio (UACR)
- Pulse
- Electrocardiogram (ECG) evaluation
- Physical examination
- Eye examination

Occurrence of anti-semaglutide antibodies during 30 weeks of study duration (yes/no):

- Anti-semaglutide antibodies with *in vitro* neutralising effect
- Anti-semaglutide antibodies cross reacting with endogenous GLP-1
    - Cross reacting antibodies with *in vitro* neutralising effect to endogenous GLP-1

Antibody level during and after 30 weeks of treatment

*Key supportive secondary endpoint prospectively selected for posting on clinicaltrials.gov.

5 Trial design

5.1 Type of trial

This is a 30-week randomised, double-blind, double-dummy, active-controlled, multi-centre, multi-national trial, four-armed, parallel-group trial comparing semaglutide 0.5 mg and 1.0 mg once-weekly against sitagliptin 100 mg once-daily.

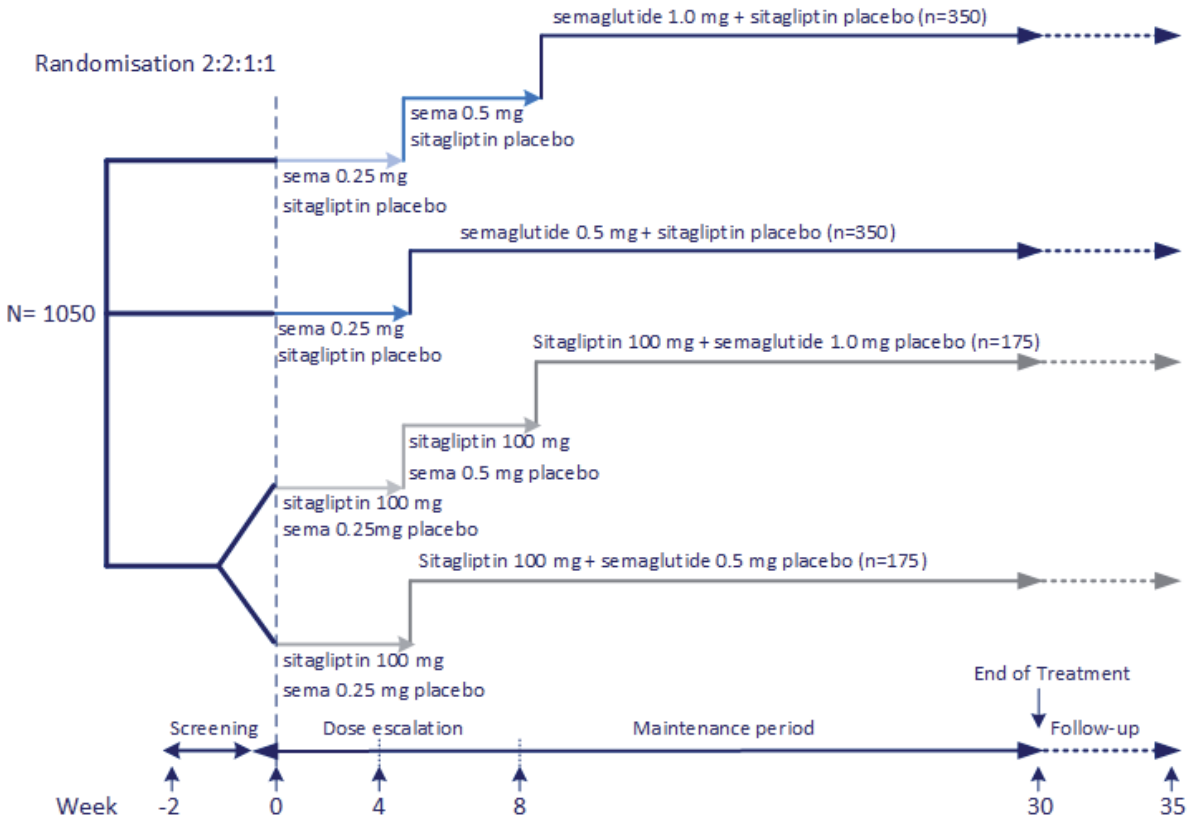


Figure 5–1 Trial design

Subjects with type 2 diabetes inadequately controlled on metformin will be randomised in a 2:2:1:1 manner to receive either:

- semaglutide 0.5 mg once-weekly + sitagliptin placebo once-daily
- semaglutide 1.0 mg once-weekly + sitagliptin placebo once-daily
- sitagliptin 100 mg once-daily + semaglutide placebo (0.5) mg once-weekly
- sitagliptin 100 mg once-daily + semaglutide placebo (1.0) mg once-weekly

The total trial duration for the individual subjects will be approximately 37 weeks. The trial includes a 2-week screening period followed by a 30-week randomised treatment period and a 5 week follow-up period.

A planned total of 1050 subjects will be randomised whereof approximately 792 subjects will be from China. Randomisation will be stratified by country.

5.2 Rationale for trial design

Parallel treatment groups and a randomised double-blind double dummy controlled design have been chosen in accordance with trial objectives and to avoid bias in the trial.

Treatment duration of 30 weeks is considered adequate in terms of assessing efficacy of semaglutide treatment versus sitagliptin treatment on change in HbA_{1c}. Furthermore, 30 weeks is considered sufficient for addressing and comparing the safety, tolerability and patient satisfaction profiles.

5.3 Treatment of subjects

Table 5–1 Treatment of subjects

Trial periods		**Screening**	**Period 1**	**Period 2**	**Period 3**	**Follow-up**
Alias for trial period		Screening	Dose escalation	Dose escalation/ Maintenance	Maintenance	Follow-up
Visits in each period		Visit 1-2	Visit 2-3	Visit 3-5	Visit 5-9	Visit 9-10
Duration of each period		2 weeks	4 weeks	4 weeks	22 weeks	5 weeks
Treatment arm	**N**					
• Semaglutide 0.5 mg • Sitagliptin placebo	350	Screening	• Semaglutide 0.25 mg, 1.34 mg/mL, 190µL • Sitagliptin placebo	• Semaglutide 0.5 mg, 1.34 mg/mL, 370µL • Sitagliptin placebo	• Semaglutide 0.5 mg, 1.34 mg/mL, 370µL • Sitagliptin placebo	Follow-up
• Semaglutide 1.0 mg • Sitagliptin placebo	350	Screening	• Semaglutide 0.25 mg, 1.34 mg/mL, 190µL • Sitagliptin placebo	• Semaglutide 0.5 mg, 1.34 mg/mL, 370µL • Sitagliptin placebo	• Semaglutide 1.0 mg, 1.34 mg/mL, 740µL • Sitagliptin placebo	Follow-up
• Sitagliptin • Semaglutide placebo (0.5 mg)	175	Screening	• Sitagliptin 100 mg • Semaglutide placebo 0 mg, 190µL	• Sitagliptin 100 mg • Semaglutide placebo 0 mg, 370µL	• Sitagliptin 100 mg • Semaglutide placebo 0 mg, 370µL	Follow-up
• Sitagliptin • Semaglutide placebo (1.0 mg)	175	Screening	• Sitagliptin 100 mg • Semaglutide placebo 0 mg, 190µL	• Sitagliptin 100 mg • Semaglutide placebo 0 mg, 370µL	• Sitagliptin 100 mg • Semaglutide placebo 0 mg, 740µL	Follow-up
All on background medication of metformin ≥ 1500 mg (or maximum tolerated dose ≥ 1000 mg) throughout the trial.						

After randomisation subjects will follow a fixed dose escalation for semaglutide and semaglutide placebo. The maintenance dose of 0.5 mg will be reached after 4 doses (4 weeks) of 0.25 mg. The

maintenance dose of 1.0 mg will be reached after 4 doses (4 weeks) of 0.25 mg, followed by 4 doses (4 weeks) of 0.5 mg. Doses must not be changed during the trial after the maintenance dose has been reached.

Semaglutide injections should be administered in the thigh, abdomen or upper arm, and should be taken on the same day of the week during the trial. Both semaglutide and sitagliptin can be taken any time of day irrespective of meals.

If necessary, the trial product may be discontinued for safety reasons. In case trial product is discontinued, subjects will not be withdrawn from trial but should continue to follow scheduled visits to the extent possible (see section 6.5.1).

Trial product will be add-on in subjects failing on metformin monotherapy.

Subjects must not be prescribed other GLP-1 RA in the period between V9 and V10 or V9A and V10A.

5.3.1 Missed dose

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

5.3.2 Background medication

Subjects should upon inclusion continue pre-trial background medication throughout the entire trial. The background medication should be maintained at the stable, pre-trial dose and frequency during the whole treatment period unless rescue medication is needed (see section 6.4).

Metformin is considered background medication (non-investigational medicinal product) and will not be provided by Novo Nordisk A/S (except for Brazil where Metformin will be provided by Novo Nordisk Farmacêutica do Brasil Ltda). Metformin should be used in accordance with standard of care in the individual country at the discretion of the investigator and the daily dose should be unchanged throughout the trial unless the rescue criteria are met. However the maximum approved dose in the individual country must not be exceeded. Treatment with metformin extended/slow release formulations is allowed.

5.3.3 Treatment after end of trial

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

(Brazil: After the study ending, if the investigator decides that the study medication is the best treatment option for the subject, the access to the study medication will be assured by the trial sponsor at no costs, according to the current regulations of Brazilian National Council of Health and Health Authority).

5.4 Rationale for treatment

Semaglutide has been developed for s.c. administration. The doses of 0.5 mg and 1.0 mg once-weekly has been chosen based on careful evaluation to strike a satisfactory balance of efficacy and safety that would satisfy the majority of patients. Hence duration and the dose of the randomised treatments are considered adequate for obtaining meaningful information on efficacy and safety in accordance with the trial objectives. Subjects will enrol for a treatment period of 30 weeks in order to be able to evaluate full effect as well as durability of the primary and secondary endpoints as well as a reasonable safety assessment.

For further information please refer to Investigator's Brochure, semaglutide (NN9535) (subcutaneous administration), Type 2 Diabetes and any updates hereof[27].

6 Trial population

6.1 Number of subjects

Planned number of subjects to be screened (i.e. documented informed consent):	Up to 1750
Planned number of subjects to be randomised:	1050
Expected number of subjects to complete the trial:	840
Planned number of Chinese subjects to be randomised:	792
Expected number of Chinese subjects to complete the trial:	636

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
   (For Korea: Male or female, age above or equal to 19 years at the time of signing informed consent.)
3. Subjects diagnosed with type 2 diabetes and on stable treatment in a period of 60 days prior to screening with metformin ≥ 1500 mg (or maximum tolerated dose ≥ 1000 mg). Stable is defined as unchanged medication and unchanged daily dose
4. HbA_{1c} 7.0 – 10.5 % (53-91 mmol/mol) (both inclusive)

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 informed consent
3. Female who is pregnant, breast-feeding or intends to become pregnant or is of childbearing potential not using an adequate contraceptive method throughout the trial including the 5 week follow-up period (adequate contraceptive measure as required by local regulation or practice)
   (China: Sterilization, intrauterine device (IUD), oral contraceptives or barrier methods).
   (Brazil: For women who expressly declare free of the risk of pregnancy, either by not engaging in sexual activity or by having sexual activity with no birth potential risk, use of contraceptive method will not be mandatory).

4. Receipt of any investigational medicinal product within 90 days before screening *(Brazil: Participation in other trials within one year prior to screening visit (V1) unless there is a direct benefit to the research subject at the Investigator´s discretion)*
5. Any disorder which, in the opinion of the investigator, might jeopardise subject's safety or compliance with the protocol
6. Treatment with glucose lowering agent(s) other than stated in the inclusion criteria in a period of 60 days before screening. An exception is short-term treatment (≤7 days in total) with insulin in connection with inter-current illness
7. Use of non-herbal Chinese medicine or other non-herbal local medicine with unknown/unspecified content. Herbal traditional Chinese medicine or other local herbal medicines may, at the Investigator's discretion, be continued throughout the trial
8. History of pancreatitis (acute or chronic)
9. Screening calcitonin value ≥ 50 ng/L (pg/mL)
10. Personal or family history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia syndrome type 2 (MEN 2)
11. Impaired renal function defined as eGFR < 60 ml/min/1.73 m2 per MDRD formula (4 variable version)
12. Acute coronary or cerebrovascular event within 90 days before randomisation
13. Heart failure, New York Heart Association (NYHA) class IV
14. Proliferative retinopathy or maculopathy requiring acute treatment. Verified by fundus photography or dilated fundoscopy performed within the past 90 days prior to randomisation in accordance with the instructions in Section 8.4.8.
15. Diagnosis of malignant neoplasm in the previous 5 years (except basal cell skin cancer or squamous cell skin cancer)
16. Mental inability, unwillingness or language barrier precluding adequate understanding of or compliance with study procedures

6.4 Rescue criteria

If any of the fasting plasma glucose (FPG) values exceed the limits outlined below and no intercurrent cause of the hyperglycaemia can be identified the subject should be called for an unscheduled visit as soon as possible:

- 15.0 mmol/L (270 mg/dl) from week 0 to end of week 5
- 13.3 mmol/L (240 mg/dl) from week 6 to end of Week 11
- 11.1 mmol/L (200 mg/dl) from week 12 to end of trial

A confirmatory FPG should be obtained. If the confirmatory FPG exceeds the values described above the subject should be offered treatment intensification (rescue medication) at the discretion of the investigator and in accordance with ADA/European Association for the Study of Diabetes[42, 43] (excluding GLP-1 RAs, DPP-4 inhibitors and amylin analogues). Rescue medication

(intensification of existing background medication and/or initiation of new medication) and any changes hereto should be captured on the concomitant medication form in the eCRF. Rescue medication should be prescribed as add-on to randomized treatment unless contraindicated according to the local sitagliptin label. In this case trial medication should be discontinued before initiation of rescue therapy. Subjects should continue to follow the protocol-specified visit schedule even if rescue treatment has been initiated.

6.5 Withdrawal criteria

6.5.1 Discontinuation of trial product

All efforts should be made to keep the subjects on trial product. However in case of a safety concern or unacceptable intolerability the trial product may be discontinued at the investigator's discretion.

Trial product must be discontinued in case of:

- Safety concern related to trial product or unacceptable intolerability
- included in the trial in violation of any of the inclusion and/or exclusion criteria
- Pregnancy
- Intention to become pregnant
- Simultaneous participation in another clinical trial of an approved or non-approved investigational medicinal product
- Calcitonin ≥ 100 ng/L (see appendix A)

For procedures to be performed in case of discontinuation of trial product (see section 8.1.6.2). Subjects discontinuing trial product prematurely should continue with the scheduled site contact. Subjects discontinued from trial product should be prescribed alternative therapy at the investigator´s discretion. However subjects must not be prescribed other GLP-1 RA in the period between V9 and V10 or V9A and V10A.

6.5.2 Withdrawal from trial

The subject may withdraw 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. Please see section 8.1.7 for procedure to be performed in case of subject withdrawal.

Subjects should stay in the trial irrespective of lack of adherence to randomised treatment, lack of adherence to visit schedule, missing assessments, trial product discontinuation due to AE (see section 6.5.1), unwillingness to cope with injection regimen, development of co-morbidities or clinical outcomes.

A subject who agrees to provide information concerning morbidities which are relevant for the assessments of cardiovascular outcomes and/or other trial end-points at the planned end of the trial should not be considered withdrawn from the trial.

Subjects who consider withdrawing from the trial should as a minimum be encouraged to have procedures performed according to the end of treatment visit (V9) and the follow up visit (V10), please see 8.1.7.

Only subjects who decline any further contact with the site in relation to the trial, and hence do not agree to report information which is relevant for the assessments of cardiovascular outcomes and/or other trial end-points at the end of trial should be considered as withdrawn from the trial.

6.6 Subject replacement

Subjects who are withdrawn will not be replaced.

6.7 Rationale for trial population

This trial will be carried out in China and several other countries. The aim is to include a broad diabetes population, hence the limited number of exclusion criteria. Subjects with type 2 diabetes who are inadequately controlled on metformin monotherapy will be included in the trial. As sitagliptin is indicated as monotherapy or in combination with metformin in China, subjects on other oral anti-diabetic drugs (OADs) are not included.

7 Milestones

Planned duration of recruitment period (i.e. FPFV– LPFV): 26 weeks

End of trial is defined as last patient last visit.

Planned date for first patient first visit (FPFV): 28-Aug-2017

Planned date for last patient first visit (LPFV): 26-Feb-2018

Planned date for last patient last visit (LPLV): 19-Nov-2018

To ensure that only the required number of subjects is randomised, screened subjects will be monitored closely via interactive voice response system/interactive web response system (IWRS).

A recruitment strategy will be developed in corporation with the participating countries to secure sufficient number of subjects from China and the other participating countries.

Recruitment will be monitored on an on-going basis by sponsor. Prior to FPFV all sites should have a recruitment strategy in place detailing how many subjects they can recruit within a certain period. If a site has not enrolled the number of subjects according to the recruitment strategy, the remaining subjects may be reallocated.

The screening and randomisation rate will be followed closely via IWRS in order to estimate when to stop screening. All investigators will be notified immediately when the enrolment period comes to an end, after which no subjects must be screened, and the IWRS will be closed for further screening. All subjects included in the screening period by the time of IWRS closure and eligible for randomisation will be randomised.

Trial registration:

Information of the trial will be disclosed at clinicaltrials.gov, chinadrugtrials.org.cn and novonordisk-trials.com. According to the Novo Nordisk Code of Conduct for Clinical Trial Disclosure, it will also be disclosed according to other requirements such as those of the International Committee of Medical Journal Editors (ICMJE)[48], the Food and Drug Administration Amendment Act (FDAAA) [49], European Commission Regulation for EudraCT[50] and other relevant recommendations or regulations. If a subject requests to be included in the trial via the Novo Nordisk e-mail contact at these web sites, Novo Nordisk may disclose the investigator's contact details to the subject. As a result of increasing requirements for transparency, some countries require public disclosure of investigator names and their affiliations.

8 Methods and assessments

8.1 Visit procedures

The following sections describe the assessments and procedures. These are also included in the flow chart (see section 2).

The investigator must keep a subject screening log, a subject identification code list and a subject enrolment log. The subject screening log and subject enrolment log may be combined in one list and may be generated from the IWRS.

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

8.1.1 Screening visit 1 (V1)

For procedures and assessments performed at screening, please see flow chart (see section 2).

The IWRS must be contacted to register the subject as screened (see section 10). Subject will be assigned a unique number (lowest available number allocated to site) which is maintained throughout the trial. It must be stated in the medical record that the subject is participating in the current trial.

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. The subjects should be reminded to show the card to other health care providers, as applicable.

Once all data relating to screening V1 have been obtained, these must be reviewed by the investigator to ensure that the subject is eligible to continue the trial.

8.1.1.1 Screen failures

For screening failures the screening failure form 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 case report form eCRF. Follow-up of SAEs must be carried out according to section 12.

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

8.1.1.2 Re-screening

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

8.1.2 Fasting visits

The subjects should attend several 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.. Glucose lowering agents and trial product cannot be taken until after blood sampling has been performed but other prescribed medication should be taken. An exception from this is the follow-up visit (V10) and follow-up premature discontinuation visit (V10A) where fasting is defined as having consumed only water within the last two hours prior to the visit. If the subject is not fasting as required, the subject must be called in for a new visit within the visit window to have the fasting procedures done.

8.1.3 Randomisation V2

For procedures and assessments performed at randomisation (see section 2).

Visit 2 will take place two weeks (±7 days) after screening V1.

Eligible subjects will be randomised into one of four treatment arms. The IWRS will allocate the dispensing unit number (DUN) of trial product to be dispensed to the subject.

Trial product will be dispensed to the subject by the site, hospital pharmacy or equivalent with different intervals during the trial. Subject will be instructed in administration of sc injection of trial product and the investigator must document that a direction for use (DFU) is given orally and/or in writing. Date, time and dose of first administration of trial product will be captured in the eCRF. Please see section 9 for further information about the trial product.

8.1.4 Visits

For visit numbers, timing of site visits, phone contacts and visit windows during the trial period, please refer to the flow chart (see section 2). Planned visits can be re-scheduled within the allowed visit window.

It is the responsibility of the investigator to ensure that all site visits and phone contacts occur according to the flow chart (2).

8.1.5 Missed visits and unscheduled visits

If a visit is missed and it is not possible to re-schedule, every effort should be made to ensure information is collected at a telephone contact. Subjects will be invited for the next scheduled visit according to visit schedule.

If a subject is unable or unwilling to attend the subsequent visit(s) the investigator should aim to at least have the subject attending the end of treatment visit and follow-up visit as these two visits should be performed for all subjects regardless of compliance with the protocol and adherence to the treatment (see section 8.1.6).

If a subject attends the clinic for a visit not described in the protocol, an unscheduled visit form must be completed. This only applies if assessments are done, hence not for the purpose of re-test of blood- or urine sampling, or re-supply of trial product. In case of re-supply a dispensing session should be made in the IWRS selecting additional medication. Re-scheduling of fasting visit samples is not considered as an unscheduled visit.

8.1.6 End of treatment (V9/9A) and Follow-up (V10/10A)

8.1.6.1 Subjects completing the treatment period as per protocol

An end of treatment visit (V9) should be scheduled when the subject has completed the treatment period as described per protocol and a follow-up visit (V10) should be performed at least 5 weeks after (+7 days visit window). Please see the flow chart for details (section 2).

The follow-up visit serves to collect AEs, technical complaints, hypoglycaemic episodes, ECG, concomitant medication and blood sampling for anti-semaglutide antibodies .

8.1.6.2 Subjects who prematurely discontinue trial product

For subjects who discontinue trial product prematurely the visit end of treatment – premature discontinuation (V9A) should be scheduled shortly after subject has discontinued trial product. The visit follow-up – premature discontinuation (V10A) should be scheduled at least 5 weeks after discontinuation of trial product (+7 days visit window). Please see the flow chart for details (section 2).

Subjects discontinuing trial product prematurely should continue with the scheduled site contacts. If necessary, in order to retain the subject in the trial, site visits can be replaced by phone contacts after discontinuation of trial product. However, as a minimum these subjects will be called in for end of treatment (V9) and follow-up (V10) at the time of the scheduled completion of the trial.

8.1.7 Withdrawals

Subjects who consider withdrawing from the trial should as a minimum be encouraged to have procedures performed according to the end of treatment visit (V9) as soon as possible and the follow up visit (V10) at least 5 weeks after but not more than 6 weeks after, if possible. If a subject has already prematurely discontinued from trial product and previously attended visit V9A and visit V10A, no further visits should be attended.

The End of Treatment and End of Trial form must be completed and final drug accountability must be performed even if the subject is not able to come to the site. The case book must be signed by the investigator in eCRF and a premature discontinuation of trial product session must be made in the IWRS (see section 10).

Although a subject is not obliged to give his/her reason(s) for withdrawing from a trial, the investigator must make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights. Where the reasons are obtained, the primary reason for not completing the trial must be specified on the end-of-trial form in the CRF (see section 6.5).

8.1.8 Investigator's assessment

Review of diaries, patient reported outcomes (PROs), laboratory reports, ECGs, eye examination (fundus photography/dilated fundoscopy), physical examination etc. must be documented either on the front page of the documents and/or in the subject's medical record. The signed documents must be retained at the site as source documentation.

For ECGs, physical examinations and eye examinations the evaluations must follow the categories:

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

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

In case of abnormal clinical significant findings found as a result of screening procedures conducted at V1 or assessments revealing baseline conditions at V2 the investigator must state a comment in the subjects' 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 site staff must review the diary to ensure that AEs, including overall change in health and concomitant medication are reported.

If clarification of entries or discrepancies in the diary or 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.

8.2 Subject related information

8.2.1 Demography

The following information must to be recorded in the subject's medical record and will be transcribed into eCRF at screening V1:

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

8.2.2 Diabetes history and diabetes complications

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

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

8.2.3 Concomitant illness and medical history

A **concomitant illness** is any illness that is present at the start of the trial (V1).

Medical history is a medical event that the subject has experienced in the past. Only relevant medical history as judged by the investigator should be reported. Pre-existing conditions, including those found as a result of screening procedures performed at V1 and V2 should be reported as medical history or concomitant illness.

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.

Concomitant illness and medical history must be recorded in the subject's medical record and will be transcribed into eCRF.

The following must be recorded in the eCRF on the disease specific forms only, i.e. not on the medical history/concomitant illness form:

- History of cardiovascular disease (CVD) (e.g. ischaemic heart disease, MI, heart failure incl. NYHA class, hypertension, stroke, peripheral arterial disease)
- History of gallbladder disease (e.g. gallstone, cholecystitis, cholecystectomy)

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 product, which is taken during the trial, including the screening and follow-up periods.

Details of any concomitant medication must be recorded at visit 1. Changes in concomitant medication, including antidiabetic treatment and rescue treatment, must be recorded at each visit as they occur. The eCRF should be updated accordingly.

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

If a change is due to an AE, then this must be reported according to Section12 . If the change influences the subject's eligibility to continue in the trial, the monitor must be informed.

8.2.5 Tobacco use

Details of tobacco use must be recorded at V1. Smoking is defined as smoking at least one cigarette, cigar or pipe daily. The collected information should include whether or not the subject smokes or has smoked.

It must be recorded whether the subject is a smoker according to the following criteria:

- Never smoked
- Is a previous smoker
    - cessation date
    - average cigarettes per day
    - approximate years of smoking
- Is a current smoker
    - average cigarettes per day
    - approximate years of smoking

8.2.6 Childbearing potential

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

Pregnancy testing must be performed on female subjects of childbearing potential as described in Section 8.5.2.5. Female subjects of childbearing potential must be instructed to use adequate contraceptive methods throughout the trial and until 5 weeks after end of treatment.

Female of non-childbearing potential is defined as:

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

For Brazil only: For women who expressly declare free of the risk of pregnancy, either by not engaging in sexual activity or by having sexual activity with no birth potential risk, use of contraceptive method will not be mandatory.

8.2.7 Height

Height is measured without shoes in centimetres or inches and recorded in the eCRF to nearest ½ cm or 1/4 inch.

8.3 Assessments for efficacy

8.3.1 Body weight

Body weight must be measured in kilograms (kg) or pound (lb), with one decimal. The body weight should be measured without shoes and only wearing light clothing.

The same scale should preferably be used throughout the trial.

8.3.2 Waist circumference

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

Three consecutive measurements of waist circumference should be performed and recorded in the eCRF. The waist circumference will be measured in cm to the nearest ½ cm using a non-stretchable measuring tape (measuring tapes will be provided to the sites).

The subject 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 and twists in the tape should

be avoided. The subject should be asked to breathe normally and the measurement should be taken when the subject is breathing out gently.

8.3.3 BMI

BMI will be calculated by the eCRF using the equation as listed below:

BMI kg/m^2 = Body weight (kg)/(Height (m) x Height (m)) or (kg/m^2 = [lb/in^2 x 703])

8.3.4 Systolic and diastolic blood pressure

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

- Avoid caffeine, smoking and exercise at least 30 minutes prior to measuring the blood pressure
- The blood pressure should be measured in a sitting position, with the legs uncrossed, the back and arms supported
- Subjects should be sitting for five minutes before the measurement is taken
- Subject or the observer should not talk during the measurement

It is recommended to use the same arm as used at V1 for subsequent measurements.

8.4 Assessments for safety

The timing of the assessments for safety are outlined in the flow chart (see section 2).

8.4.1 Adverse events

AEs must be recorded at each visit in accordance with the procedures outlined in section 12.

Any clinically significant worsening from baseline of a previous finding must be reported as an AE.

8.4.2 Medication error

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

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

For definition of medication errors, see section 12.1.3

8.4.3 Adverse events requiring additional data collection

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

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

See appendix B for details about the additional information to report. In case any of these events fulfil the criteria for a serious adverse event, please report accordingly, see Section 12.

8.4.4 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 according to the instructions below and section 8.6.2 throughout the trial from V1 to V10/10A.

All information must be transcribed into the eCRF (hypoglycaemic episode form) throughout the trial. For Novo Nordisk classification of hypoglycaemia, see Section 17.4.2.2.

Upon onset of a hypoglycaemic episode the subject is recommended to measure PG 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[51].

A SMPG value ≤ 3.9 mmol/L (70 mg/dL) or hypoglycaemic symptoms must be recorded in the diary at 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/L (70 mg/dL) and/or symptoms have been resolved. One hypoglycaemic episode form is to cover these measurements 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 the PG value is >3.9 mmol/L (70 mg/dL) and/or symptoms have been resolved).
- If a stop date and time is not reported, a hypoglycaemic episode will cover a period of 60 minutes.
- The PG level before treating the episode (if available) and any follow up measurements.
- The lowest value measured during the hypoglycaemic episode will be reported as the PG 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 PG to normal is considered sufficient evidence that the event was induced by a low PG concentration[51].

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

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

- Who assisted in the treatment of the hypoglycaemic episode (i.e. medical person or non-medical person)?
- Where the treatment was administered (in clinic/emergency room/hospital or other. If the subject was treated in clinic/emergency room/hospital, whether they were transported in an ambulance or not)
- Type of treatment provided by another person (i.e. oral carbohydrates, glucagon, IV glucose or other)
- Were symptoms alleviated after administration of treatment?
- Factors contributing to the episode (i.e. physical activity, missed meal, diet change, medication error (i.e. overdose, mix-up between products, incorrect use of device), miscalculation of dose of antidiabetic medication, other factors not listed or unknown)
- Did the subject experience seizure?
- Was the subject unconscious/comatose?
- Did the subject experience any of the following symptoms[52] ?
  – 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[53, 54]. 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.

8.4.5 Electrocardiogram

12-lead electrocardiograms (ECG) will be performed locally by the investigator or delegated staff during the trial (see section 2). The ECG print out must be interpreted, dated and signed by investigator as described in section 8.1.8. ECG printed is source documentation.

Additional unscheduled ECG recordings can be performed at the investigator´s site at investigator´s discretion at other visits than the planned ECG visits.

8.4.6 Physical examination

A physical examination will be performed by the investigator according to local procedure (see section 2). A physical examination must include:

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

8.4.7 Pulse

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

8.4.8 Eye examination

It is allowed to perform the baseline fundus photography or dilated fundoscopy between the screening visit and the randomisation visit.

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

In addition, fundus photography /dilated fundoscopy must be performed at V9. In the case of premature discontinuation, the assessments must be performed both at V9A and at V9. The assessments at V9A and V9 can be performed in the period between V9A and V10A and between V9 and V10, respectively, but the results should be available no later than at V10A and V10, respectively.

The investigator should indicate whether the outcome of the eye examination was normal or abnormal, and, if abnormal, indicate whether clinically significant. Relevant findings as a result of this screening procedure must be recorded as diabetes history and diabetes complications or concomitant illness/medical history in accordance with Section 8.2.2 and 8.2.3 respectively.

8.5 Laboratory assessments

For laboratory analysis of efficacy and safety parameters will be drawn during the 37 weeks of the trial. The laboratory analyses will be performed by a central laboratory except for anti-semaglutide antibodies and IgE antibodies where a special laboratory will be used. In the situation of suspicion of acute pancreatitis or severe hypersensitivity described in appendix B, a local laboratory will be used. Laboratory samples comprise both urine and blood samples.

Descriptions of assay methods, laboratory supplies and procedures for collecting, handling, storage and shipping of samples and information regarding who will perform the assessments will be

described in the laboratory manual provided by the central laboratory (for central and special laboratory details, see Attachment I).

Samples will be coded in order to keep subject identity anonymous.

Laboratory samples may be drawn at another day than on the day of the actual visit as long as it is within the visit window outlined in the flow chart (see section 2).Please note that a laboratory sample pertaining to a specific visit must always be reported to that visit.

For some of the samples drawn during the trial it is required for the sensitivity of the analysis that the subject is fasting.

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 must be reported to the investigator.

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

Central laboratory will provide laboratory results 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 section 12. An exception to this is that anti-semaglutide antibody result will not be available to the investigator during the trial. However these results will be provided to the investigator upon request after the completion of the clinical trial report (CTR).

All laboratory samples will be destroyed on an on-going basis after analysis and no later than CTR, except for samples taken for anti-semaglutide antibody samples, which will be kept until market authorisation approval or rejection of file. *(For Brazil: the laboratory samples for Brazilian subjects will be destroyed at the latest at the completion of the CTR, including samples for anti-semaglutide antibody analysis. No sample will be stored after the completion of CTR).*

The investigator should ensure that the last samples are shipped to the central laboratory within 24 hours after the last subject visit last at the site.

8.5.1 Laboratory assessments for efficacy

Blood samples must be drawn according to flow chart (see section 2) and analysed at the central laboratory to determine levels of the following efficacy laboratory parameters:

8.5.1.1 Glucose metabolism

- HbA_{1c}
- Fasting plasma glucose
- Fasting insulin
- Fasting C-peptide
- Fasting glucagon
- Fasting pro-insulin

8.5.1.2 Biomarker

- hsCRP

8.5.1.3 Lipids (all fasting)

- Total cholesterol
- LDL-cholesterol
- VLDL-cholesterol
- HDL-cholesterol
- Triglycerides
- Free fatty acids

8.5.1.4 Self measured plasma glucose (SMPG)

At screening V1 subjects will be provided with a blood glucose meter including lancets, plasma-calibrated test strips and control solutions. Oral and written directions for use of the device including the performance of calibrations according to the manufacturer's instructions will be provided to the subject. Sites should, as necessary, repeat the directions for use to the subject at subsequent visits.

The blood glucose meters use test strips calibrated to plasma values. Therefore, all measurements performed with capillary blood are automatically calibrated to plasma equivalent glucose values, which will be shown on the display. When using blood glucose meters the measurement is performed with capillary blood calibrated to plasma equivalent glucose values i.e. the measurement is performed on blood while the value is reported as plasma. It is important to be aware of this difference throughout the protocol.

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

Subjects should be instructed in how to record the results of the SMPG values in the diaries. The record of each SMPG value should include date, time and value. All data from the diary must be

transcribed into the eCRF during or following the contact. If obtained via phone and a discrepancy is later detected, the values in the eCRF must be corrected.

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

8.5.1.5 7 point profile

The subject will be instructed to perform a SMPG 7-point profile, preferably within one week prior to the site visit according to the flow chart (see section 2) on a day where the subject does not anticipate unusual strenuous exercise.

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

- before breakfast
- 90 min after start of breakfast
- before lunch
- 90 min after start of lunch
- before dinner
- 90 min after start of dinner
- at bed time

8.5.2 Laboratory assessments for safety

Laboratory samples must be drawn according to flow chart (see section 2) and analysed at the central laboratory to determine levels of the following safety laboratory parameters:

8.5.2.1 Anti-semaglutide antibodies

Blood samples will be drawn for measurement of serum antibodies to semaglutide at selected visits in randomised subjects. Positive anti-semaglutide antibody samples will be further characterised for cross reactivity to native GLP-1 (see section 2). Samples taken at follow-up which are positive for anti-semaglutide antibodies will be further characterised for in vitro neutralising effect towards semaglutide. In addition, samples taken at follow-up which are positive for cross-reactivity against native GLP-1 will be further analysed for in vitro neutralising effect towards native GLP-1.

Follow-up antibody (taken at the follow-up V10/10A) samples must be taken fasting (as a minimum by only having consumed water for at least two hours).

8.5.2.2 Biochemistry

- Creatinine, including eGFR (per MDRD)
- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Alkaline phosphatase
- Sodium
- Potassium
- Albumin
- Bilirubin (total)
- Total protein
- Urea
- Creatine kinase
- Calcium total
- Calcium, albumin corrected (calcium, ionized)
- Lipase
- Amylase

8.5.2.3 Haematology

- Haemoglobin
- Haematocrit
- Thrombocytes
- Erythrocytes
- Leucocytes
- Differential count:
    - eosinophils
    - neutrophils
    - basophils
    - monocytes
    - lymphocytes

8.5.2.4 Calcitonin

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

8.5.2.5 Pregnancy test

Females of childbearing potential will have a serum pregnancy test performed at all site visits (see Section 2). At visit 2, 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).

8.5.2.6 Urinalysis

Subjects will be asked to bring the first morning urine during the trial (see section 2). The urine sample will be analysed at the central laboratory to determine levels of the following parameters:

- Urinary albumin to creatinine ratio (UACR)
- Urinalysis by urine dip-stick: erythrocytes, protein, glucose and ketones, pH

8.6 Other assessments

8.6.1 Patient reported Outcome questionnaires

The following PRO questionnaires will be used in this trial:

- SF-36v2TM
- DTSQs

The questionnaires should be completed by the subject as specified in the flow chart (see section 2), preferably before any other trial related activities. It takes approximately 10 minutes to complete each questionnaire. The assessment must be reviewed as described in section 8.1.8. All results from the PRO questionnaires must be transcribed into the eCRF.

The PRO questionnaire will be used to assess subjects overall Health related Quality of Life and can also be used to estimate Quality Adjusted Life years (QALY) which is used in cost effectiveness calculations.

8.6.1.1 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 QALY which is used in cost effectiveness calculations. This instrument contains 36 items and measures the individual overall health related quality of life on 8 domains; physical functioning, role functioning, bodily pain, general health, vitality, social functioning, role emotional and mental health.

8.6.1.2 DTSQs

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

8.6.2 Subject diary

The subject must be provided with paper diaries at all visits, except the follow-up visit (V10 and V10A). If a subject prematurely discontinues trial product, diaries should not be dispensed and filled out by the subjects after the follow-up – premature discontinuation visit. For these subjects all available data will be collected. Entries in the diaries are only to be made by the subject, unless otherwise specified.

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

- date, time and dose of first dose of trial products (injection and tablet)
- date, time and dose of last injection of trial product prior to each visit/phone contact
- hypoglycaemic episodes
- concomitant medication
- AEs
- SMPG 7-point profile
- Urine pregnancy test for females of childbearing potential

The diaries should be collected at the visit described in the flow chart (see section 2). The recordings must be reviewed as described in section 8.1.8 and transcribed to the eCRF.

8.7 Subject compliance

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

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.

If a subject is discovered to be non-compliant, the investigator must inform the subject of the importance of taking trial product as directed.

9 Trial supplies

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

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

9.1 Trial products

The following trial products for subcutaneous injection will be provided by Novo Nordisk, Denmark:

- Semaglutide 1.34 mg/mL, solution for injection, 1.5 mL pre-filled PDS290 pen-injector
- Semaglutide placebo, solution for injection, 1.5 mL pre-filled PDS290 pen-injector

The following trial products for oral administration will be provided by Novo Nordisk, Denmark:

- Sitagliptin (Januvia®) 100 mg, tablet
- Sitagliptin placebo, tablet

For both semaglutide and sitagliptin the placebo and active drug are identical with regard to appearance.

Semaglutide both active drug and placebo are manufactured and supplied by Novo Nordisk, Denmark. Sitagliptin 100 mg and placebo is packed for use in clinical trials and supplied by Novo Nordisk, Denmark.

All trial products are considered investigational medicinal products (IMPs).

Refer to the appropriate IB or local label for more detailed information regarding the listed trial products.

Each site will be supplied with sufficient trial products for the trial on an on-going basis controlled by the IWRS and according to enrolment and randomisation with different intervals during the trial. Subject will be instructed in administration of trial product and the investigator must document that a DFU is given orally and in writing at randomisation visit.

9.2 Labelling

Labelling of the investigational medicinal products (IMPs) will be in accordance with Annex 13[55], local law and trial requirements. Please refer to the TMM provided by Novo Nordisk for details regarding standard packages for the trial products.

9.3 Storage

Semaglutide preparations (both in-use and not in-use) must not be exposed to excessive heat or direct sunlight. Semaglutide preparations which have been frozen must not be used. Semaglutide must not be used, if it does not appear clear and colourless.

Trial product	Storage conditions (not-in-use)	In-use conditions
Semaglutide 1.34 mg/mL and placebo	• Store in a refrigerator (2°C to 8°C) • Do not freeze • Protect from light	• Store below 30°C • Do not refrigerate • Do not freeze • Protect from light • Use within 1 month*
Sitagliptin 100 mg and placebo	• Do not store above 30°C • Do not freeze • Do not refrigerate • Protect from light and humidity	Not applicable

* In-use time starts when first dose is taken.

The investigator must ensure the availability of proper storage conditions, record and evaluate the temperature. The investigator must inform Novo Nordisk (via the assigned monitor) immediately if any trial product has been stored outside specified conditions (e.g. outside temperature range). Fifteen minutes outside the indicated range is negligible, and should not be recorded as a deviation.

Trial products stored outside the temperature range are not to be used and must be stored separately within allowed temperature range until after evaluation of condition. Evaluation will be performed by Novo Nordisk. Trial products that have been stored improperly must not be dispensed to any subject before it has been re-evaluated and approved for further use by Novo Nordisk.

Returned trial products (unused, partly used or used including empty packaging material) must be stored separately from non-allocated trial products.

The temperatures during storage should be monitored by a calibrated and stationary system. A temperature log must be kept to document storage within the right temperature interval and storage facilities should be checked frequently. Investigator must take appropriate action to avoid recurrence of the detected temperature deviation.

9.4 Drug accountability and destruction

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

The investigator or delegated person is responsible for ensuring that:

- Trial products are not dispensed to any person not included in the trial
- Drug accountability is performed using the IWRS drug accountability module
- Subjects are instructed to return all used, partly used and unused trial product including empty packaging material at each dispensing visit and at End of Treatment visit
- All returned trial products (used/partial used and unused including empty packaging material) is kept and stored separately from non-allocated trial products

Destruction of trial products will be done according to local law after accountability is finalised at site and reconciled by monitor. Destruction of trial products must be documented.

9.5 Auxiliary supplies

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

- Needles for pre-filled pen systems
- Blood glucose meters, including lancets, plasma-calibrated test strips and control solutions
- Directions for use for PDS290 pen-injector

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
- Medication arrival
- Dispensing
- Treatment discontinuation
- Treatment completion
- Drug accountability
- Data change
- Dispensing verification (when barcode scanner is used)

IWRS user manuals will be provided to each trial site.

11 Randomisation procedure and breaking of blinded codes

The trial is a double-blind trial. A randomisation session will be carried out for all subjects by using the IWRS. At the randomisation visit subjects meeting all inclusion/exclusion criteria will be randomised in a 2:2:1:1 manner to receive one of four parallel treatments groups:

- Semaglutide 0.5 mg once-weekly + sitagliptin placebo once-daily
- Semaglutide 1.0 mg once-weekly + sitagliptin placebo once-daily
- Sitagliptin 100 mg once-daily + semaglutide placebo (0.5) mg once-weekly
- Sitagliptin 100 mg once-daily + semaglutide placebo (1.0) mg once-weekly

Randomisation will be stratified by country. When grouping or analysing data by country, subjects from Hong Kong and Taiwan will be grouped with Chinese subjects if not otherwise specified.

11.1 Breaking of blinded codes

If the trial site needs to break the code, Novo Nordisk should if possible, be contacted before the code is broken. The IWRS will notify Novo Nordisk (monitor and the Global Safety department) immediately after the code is broken.

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

If the code has been broken the subject must be discontinued from trial product but be asked to continue in the trial (see section 8.1.6.2). A treatment discontinuation session should be completed in IWRS.

When the code is broken, the treatment allocation will be accessible to the investigator and the Novo Nordisk Global Safety department. If IWRS is not accessible at the time of code break monitor should be contacted and if monitor cannot get access the IWRS vendor helpdesk should be contacted.

12 Adverse events, and technical complaints and pregnancies

12.1 Definitions

Adverse event

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

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

An AE includes:

- A clinically significant worsening of a concomitant illness.
- A clinical laboratory adverse event (CLAE): a clinical laboratory abnormality which is clinically significant, ie 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 procedures (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 8.4.4).

The following three definitions are used when assessing an AE:

- **Severity assessment**
  - **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 assessment**

The following terms are used when assessing the 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.

12.1.1 Serious adverse event

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

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

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

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

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

c. A substantial disruption of a subject's ability to conduct normal life functions (eg 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 dyscrasiasis or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

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

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

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

12.1.2 Non-serious adverse event

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

12.1.3 Medication errors

Medication errors concerning trial products are defined as:

- Administration of wrong drug. Note: Use of wrong DUN is not considered a medication error.
- Wrong route of administration, such as intramuscular instead of subcutaneous.
- Administration of an overdose with the intention to cause harm (eg 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 extend 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 8.4.2.

12.1.4 Adverse events requiring additional data collection

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

In this trial the following AEs require the completion of specific event forms in the eCRF, see Table 12–1

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

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

For details about specific event form, see appendix B

12.1.5 Technical complaint

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 (eg discoloration, particles or contamination)
- The packaging material including labelling

- Problems related to devices (eg to the injection mechanism, dose setting mechanism, push button or interface between the pen and the needle)

12.2 Reporting of adverse events

All events meeting the definition of an AE must be collected and reported. This includes events from the first trial-related activity after the subject has signed the informed consent until the end of the post-treatment follow-up period (see section 2). 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, either observed by the investigator or subject, must be reported by the investigator and evaluated. All AEs must be recorded by the Investigator on an AE form. The investigator should report the diagnosis, if available. If no diagnosis is available, the investigator should record each sign and symptom as individual AEs using separate AE forms.

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

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

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

Timelines for initial reporting of AEs:

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

- **SAEs**: The AE form **within 24 hours** and the safety information form **within 5 calendar** days of the investigator's first knowledge of the SAE.

- **SAEs requiring reporting on a specific event form :** In addition to above, the specific eventI form **within 14 calendar days** of the investigator's first knowledge of the AE.

- **Events for adjudication**: The event adjudication form must be completed **within 14 calendar days of investigator's first knowledge of the AE, see section 12.7.2.** The investigator should provide the medical documentation within 4 weeks of event identification according to instructions in the event adjudication site manual.

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

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

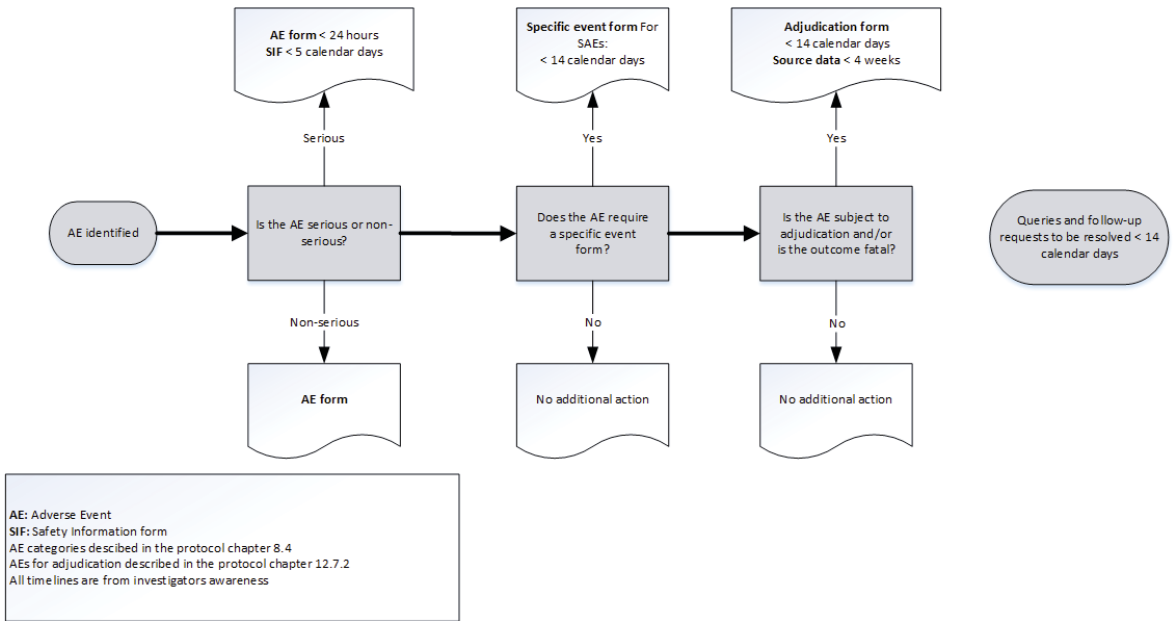


Figure 12–1 Reporting of AEs

Novo Nordisk assessment of AE expectedness:

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

- Semaglutide: NN9535 IB[27] (subcutaneous administration), Type 2 diabetes, current version and any updates thereto
- Sitagliptin (Januvia®): EU Summary of Product Characteristics (SmPC)[56] current version.

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

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

Novo Nordisk products used as concomitant medication

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

12.3 Follow-up of adverse events

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

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

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

  The SAE follow-up information should only include new (eg 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 and on any of the following products:

- Semaglutide 1.34 mg/mL solution for injection, 1.5 mL pre-filled PDS290 pen-injector
- Semaglutide placebo, solution for injection, 1.5 mL pre-filled PDS290 pen-injector
- Sitagliptin (Januvia®) 100 mg, tablet
- Sitagliptin placebo, tablet
- Needles for pre-filled pen systems

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

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

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

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

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

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

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

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

12.4.2 Collection, storage and shipment of technical complaint samples

The investigator must collect the technical complaint sample and notify the monitor **within 5 calendar days** of obtaining the sample at trial site. The monitor must coordinate the shipment to Customer Complaint Center, Novo Nordisk (the address is provided in Attachment I) and ensure that the sample is sent as soon as possible. A print or copy of the technical complaint form must be sent with 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

12.5.1 Pregnancies in female subjects

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

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

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

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

1. **Reporting of pregnancy information**
   Information about the pregnancy and pregnancy outcome/health of the newborn infant(s) has to be reported on maternal form 1A and 1B, respectively.

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

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

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

<u>Forms and timelines for reporting AEs:</u>
Non-serious AEs:

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

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

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

12.6 Precautions and/or overdose

Semaglutide

Events of nausea, vomiting and headache have been reported in connection with accidental administration of up to 4.0 mg semaglutide. No symptoms of hypoglycaemia have been reported in connection with overdose of semaglutide. In the event of overdose, appropriate supportive treatment should be initiated according to the subject's clinical signs and symptoms.

For other precautions, please see section 3.5.1.

Sitagliptin

During controlled clinical trials in healthy subjects, single doses of up to 800 mg sitagliptin were generally well tolerated. Minimal increases in QTc, not considered to be clinically relevant, were observed in one study at a dose of 800 mg sitagliptin. There is no experience with doses above 800 mg in clinical studies. In Phase I multiple-dose studies, there were no dose-related clinical adverse reactions observed with sitagliptin with doses of up to 600 mg per day for periods of up to 10 days and 400 mg per day for periods of up to 28 days.

In the event of an overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring (including obtaining an electrocardiogram), and institute supportive therapy if required. Sitagliptin is modestly dialysable. In clinical studies, approximately 13.5 % of the dose was removed over a 3- to 4-hour hemodialysis session. Prolonged hemodialysis may be considered if clinically appropriate. It is not known if sitagliptin is dialysable by peritoneal dialysis.

For other precautions, please see section 3.5.5.

12.7 Committees related to safety

12.7.1 Novo Nordisk safety committee

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

12.7.2 Event adjudication committee

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

The EAC is composed of permanent members covering required medical specialities. EAC members must disclose potential conflicts of interest and must be independent of Novo Nordisk. The events are reviewed by the EAC in a blinded manner. The EAC will have no authorisations to impact trial conduct, trial protocol or amendments.

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

The events outlined in section 12.1.4 have been selected for adjudication in order to obtain an external independent validation of the diagnosis. In addition, cardiovascular events are being adjudicated according to Standardized Definitions[57].

The EAC will review copies in English (translated if necessary) of medical documentation received in the adjudication package (for example X-ray, ECGs, ultrasound images, discharge summaries, pathology reports, and death certificates). The investigator must provide medical documentation as soon as possible, when receiving a request from Novo Nordisk or the event adjudication vendor.

The AEs for adjudication are listed in Table 12–2.

Table 12–2 Adverse events for adjudication

Events	Description	Adjudication outcome
Death*	• All-cause death	• Cardiovascular death (including undetermined cause of death) • Non-Cardiovascular death
Acute Coronary Syndrome	Acute Coronary Syndrome conditions include: • ST-elevation acute myocardial infarction (STEMI) • Non-ST elevation acute myocardial infarction (NSTEMI) • Silent MI • Unstable angina pectoris (UAP) requiring hospitalisation	• Acute myocardial infarction (STEMI or NSTEMI), silent MI • Unstable angina pectoris requiring hospitalisation
Cerebrovascular events	• Episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of haemorrhage or infarction • Transient Ischaemic Attack (TIA) is defined as a transient episode (< 24 hours) of focal neurological dysfunction caused by brain, spinal cord, or retinal ischaemia, without acute infarction	• Ischaemic stroke • Haemorrhagic stroke • Undetermined stroke • TIA
Heart failure requiring hospitalisation	• Hospitalisation with a primary diagnosis of heart failure (new episode or worsening of existing heart failure)	• Heart failure requiring hospitalisation
Acute pancreatitis	The diagnosis of acute pancreatitis requires two of the following three features: • Abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back) • Serum lipase activity (and/or amylase activity) at least three times greater than the upper limit of normal • Characteristic findings of acute pancreatitis on imaging	Acute pancreatitis • Mild • Moderate severe • Severe
Malignant neoplasm	Malignant neoplasms are defined as: • Neoplasms in which abnormal cells divide without control and can invade nearby tissues and/or spread to other parts of the body through the blood and lymph systems • Thyroid neoplasms are excluded in this event category	• Malignant neoplasm
Thyroid disease, if malignant thyroid neoplasm or C-cell hyperplasia	• Malignant thyroid neoplasms are defined as thyroid neoplasms in which abnormal cells divide without control and can invade nearby tissues and/or spread to other parts of the body	• Malignant thyroid neoplasm • C-cell hyperplasia

	through the blood and lymph systems • C-cell hyperplasia, defined as hyperplasia of the parafollicular C-cells of the thyroid gland	

*Death is not a separate event, but an outcome

There are different processes for capturing events for adjudication:

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

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

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

13 Case report forms

Novo Nordisk will provide a system for the electronic case report forms (eCRF). This system and support services to the system will be supplied by a vendor.

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 (eg is not applicable), indicate this according to the data entry instructions.

The following will be provided as paper CRFs:

- Pregnancy forms

In addition paper AE forms and safety information forms will be provided. These must be used when access to the eCRF is revoked.

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

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

13.2 Case report form flow

13.2.1 Electronic case report form flow

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

At the end of trial the investigator must ensure that all remaining data have been entered into the eCRF no later than 3 days after the last subject’s last visit 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 investigator site after the trial database is released and access to update the trial data on the EDC application has been removed. This data will be retained by the site.

When the final CTR is available the data will be archived by Novo Nordisk.

13.2.2 Paper case report form flow

The pregnancy forms are paper based CRFs.

Also, the SIF, technical complaint form, and AE form will be provided in paper but are only to be used if for any reason the eCRF is unavailable.

The investigator must ensure that data are recorded in these forms as soon as possible and ensure that Novo Nordisk receives these forms within the required timeline (see section 12).

Corrections to the data in the 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 were crossed out. Each correction must be initialled, dated and explained (if necessary) by the investigator or the investigator's authorised staff.

14 Monitoring procedures

During the course of the trial, the monitor will visit the trial site to ensure that the protocol is adhered to, that all issues have been recorded, to perform source data verification and to monitor drug accountability. The first monitoring visit will be performed as soon as possible after FPFV or FSFV and no later than 4 weeks after. The monitoring visit intervals will depend on the outcome of the remote monitoring of the CRFs, 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 intervals between monitoring visits can be shorter. Factors to be considered in this determination may include objective, endpoints, purpose, design, complexity, blinding, number of subjects and expected recruitment rate.

The monitor must be given direct access to 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 (eg by telephone).

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

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. Considering the electronic source data environment, it is accepted that the earliest practically retainable record should be considered as the location of the source data. Therefore transcription to the diary from the blood glucose meter is considered the source document for BG values.

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 diaries and PROs are considered as source data and must not be removed from the trial site.

The monitor will ensure that the CRFs are completed on an on-going basis within the agreed timelines.

The monitor must ensure that all required eCRF forms for screening failures are completed, (e.g. screening failure form and the case book sign of (affirmation statement) is electronically signed by the investigator).

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

When data has been source verified and all queries have been resolved the case book must be signed by the investigator in the eCRF.

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

15 Data management

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

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 from the laboratory performing the analyses. 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 identification number. Appropriate measures such as encryption or leaving out certain identifiers will be enforced to protect the identity of subjects in all presentations and publications as required by local, regional and national requirements.

16 Computerised systems

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

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

17 Statistical considerations

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

Results from the statistical analysis will generally be presented by two-sided confidence intervals with a confidence level of 95% and associated p-value. Superiority will be formulated and tested as one-sided hypotheses at a 2.5% significance level. Non-inferiority between two treatments will be evaluated by comparing the upper limit of the associated two-sided 95% confidence interval for the difference with the pre-defined non-inferiority margin.

When grouping or analysing data by country, subjects from Hong Kong and Taiwan will be grouped with Chinese subjects if not otherwise specified.

Handling of missing data

In the case of missing data no general imputation will be performed for the analyses, unless otherwise specified. If an assessment has been made both at screening and randomisation, the value from the randomisation visit will be used as the baseline value. If the value measured at the randomisation visit is missing and the assessment also has been made at screening, then the screening value will be used as the baseline value.

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

The primary analysis model will be the mixed model for repeated measurements (MMRM), see section 17.3 for further details. One of the assumptions behind (MMRM) is that the missing data mechanism is missing at random (MAR). This means that given the observed data, the mechanism generating missing values is independent of the unobserved data that is the missing data. The MMRM and the negative binomial model both rely on the MAR assumption for generating unbiased estimates of treatment differences.

Based on previous semaglutide trials in subjects with type 2 diabetes, the treatment discontinuation rate from randomised treatment and trial withdrawal is expected to be about 20%. The treatments in this trial should be effective, given the historical documentation, and this should minimise treatment discontinuation due to ineffective therapy. The main reasons for treatment discontinuation are expected to be AEs, ineffective therapy and non-eligibility (subjects randomised although not fulfilling inclusion/exclusion criteria). Treatment discontination due to non-eligibility can be regarded as missing completely at random (MCAR), i.e. it does not depend on the observed or missing data values. This category of missing data is not expected to introduce bias in the estimated treatment differences. Treatment discontinuation due to lack of efficacy is expected to be reflected in the observed data obtained prior to the discontinuation from randomised treatment, and the

corresponding missing data can therefore be assumed as MAR to some extent. Missing data due to AEs is expected to be similar between groups except for, potentially, a slightly higher incidence in the semaglutide treatment group due to gastrointestinal side effects. Together with potential withdrawals from trial due to the own will of the subject, the MAR assumption may be less adequate for this category of drop-outs.

Several different sensitivity analyses will be used to investigate whether the results from the MMRM approach are robust towards deviations from the assumption of MAR.

17.1 Sample size calculation

The primary objective is to compare the effect of two dose levels of semaglutide once-weekly treatment (0.5 mg or 1.0 mg) with sitagliptin 100 mg on the primary endpoint, change from baseline in HbA_{1c} after 30 weeks of treatment. In the calculations determining the sample size it is presumed that in the analysis the two sitagliptin/semaglutide placebo groups will be pooled assuming no correlation between endpoints and placebo volume.

In total 1050 subjects will be randomised in a 2:2:1:1 manner. Assuming 20% of subjects discontinuing randomised treatment, and further taking the assumption that these subjects are excluded from the per protocol (PP) analysis set, 280 subjects in each group are expected to be included in the PP analysis set.

The sample size calculation is based on demonstrating HbA_{1c} non-inferiority for semaglutide 0.5 mg vs. sitagliptin 100 mg and HbA_{1c} non-inferiority for semaglutide 1.0 mg vs. sitagliptin 100 mg.

The two hypothesis tests are assumed to be independent and for each of the hypothesis the power calculation is based on a t-statistic under the assumption of a one-sided test of size 2.5%. Using a non-inferiority margin of 0.3%, and assuming a true HbA_{1c} difference (semaglutide minus sitagliptin) of 0% and a standard deviation (SD) of 1.1%, a total of 280 subjects per group in the PP analysis set will give 90% marginal power to conclude HbA_{1c} non-inferiority for the comparison of a semaglutide dose vs. sitagliptin 100 mg.

Assuming the same HbA_{1c} effect for the two dose levels of semaglutide, the overall power to demonstrate HbA_{1c} non-inferiority for the two dose levels of semaglutide vs. sitagliptin will be at least 80%.

For change in body weight, the power calculation is based on the assumptions of a true difference of -1.5 kg and a SD of 4.0 kg. In addition, 50% efficacy retention is assumed for the anticipated 20% of subjects discontinuing randomised treatment giving an expected treatment difference of -1.35 kg, which is the number used in the power calculation. With the above assumptions, a total of 350 subjects per group in the full analysis set (FAS) will give more than 99% marginal power to

conclude superiority in body weight for the comparison of a semaglutide dose vs. sitagliptin 100 mg.

17.2 Definition of analysis sets

The following analysis sets are defined in accordance with the ICH-E9 guideline[58] .

Full Analysis Set (FAS): includes all randomised subjects. Subjects in the FAS will contribute to the evaluation "as randomised".

Per Protocol (PP) Analysis Set:

Includes all subjects in the FAS who fulfil the following criteria:

- have not violated any inclusion criteria
- have not fulfilled any exclusion criteria
- have a non-missing HbA_{1c} measurement at screening and /or randomisation
- have at least 23 weeks actual treatment weeks of expose
- have at least one non-missing HbA_{1c} measurement after 23 actual weeks of expoures

Subjects in the PP Analysis Set will contribute to the analysis "as treated".

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".

Before data are locked for statistical analysis, a review of all data will take place. Any decision to exclude a subject or single observations from the statistical analysis is the joint responsibility of the members of the internal 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 must be documented and signed by those responsible before database lock. The subjects and observations excluded from analysis sets, and the reason for this, will be described in the CTR.

Data selections and observation periods

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

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

Definition of the observation periods:

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

- The last direct subject-site contact, which is scheduled to take place 5 weeks after planned last dose of trial product at a follow-up visit
- Withdrawal for subjects who withdraw their informed consent
- The last subject-investigator contact as defined by the investigator for subjects who are lost to follow-up
- Death for subjects who dies before any of the above

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

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

- the follow-up visit (V10)
- the follow-up prematurely discontinuation visit (V10A)
- the last date on trial product + 42 days
- the end-date for the in-trial observation period

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

For efficacy and other safety assessments (laboratory assessments, physical examination and vital signs) the observation period ends at the last date on trial product + 7 days in accordance with trial

flow chart and assessment times. This ascertainment window corresponds to the dosing interval and will be used to avoid attenuation of a potential treatment effect on endpoints for which the effect is reversible shortly after treatment discontinuation. Hence, for those assessments this period reflects the period in which subjects are treated.

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

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

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

For subjects who have no post-baseline scheduled assessments available in the on-treatment without rescue period, the baseline value will be carried forward to the first scheduled visit for the associated endpoint to ensure that all randomised subjects will contribute to the statistical analysis.

Data points collected outside an observation period will be treated as missing in the analysis. Baseline data will always be included in an observation period. For adjudicated events, the onset date will be the EAC adjudicated onset date.

17.3 Primary endpoint

The primary endpoint is change from baseline in HbA_{1c} after 30 weeks of treatment. In the analysis the two sitagliptin/semaglutide placebo groups will be pooled assuming no correlation between HbA_{1c} change after 30 weeks and placebo volume.

The primary endpoint will be based on FAS using data from the 'on-treatment without rescue medication' observation period in a Mixed Model for Repeated Measures (MMRM). A restricted maximum likelihood (REML) will be used. The model will include all post baseline HbA_{1c} measurements collected at scheduled visits up to and including week 30 data as dependent variables. The independent effects included in the model will be treatment and country as fixed effects and baseline response as covariate, all nested within visit. An unstructured covariance matrix will be employed for measurements within the same subjects, assuming that measurements across subjects are independent. Regarding missing data this analysis approach relies on the assumption that data are missing at random (MAR). From this mode, the two by dose level estimated treatment

differences between s.c.semaglutide versus sitagliptin at week 30 will be presented together with associated two-sided 95% confidence intervals and unadjusted two sided p-values (nominal alpha=0.05) for testing non-inferiority and superiority. In order to preserve the overall type 1 error the conclusion of non-inferiority and superiority with treatment of each semaglutide dose versus sitagliptin after 30 weeks will be evaluated hierarchically according to the sequence below, and starting with the first. In this testing sequence it is necessary to fulfil the test criteria, which is to reject the corresponding null hypothesis in order to go to the next step. If the corresponding null hypothesis is not rejected, the testing will stop and no further conclusions will be drawn.

The following ordering in the statistical test sequence will be used:

1. Non-inferiority in change in HbA_{1c} for semaglutide 1.0 mg vs. sitagliptin
2. Non-inferiority in change in HbA_{1c} for semaglutide 0.5 mg vs. sitagliptin
3. Superiority in change in HbA_{1c} for semaglutide 1.0 mg vs. sitagliptin
4. Superiority in change in body weight for semaglutide 1.0 mg vs. sitagliptin
5. Superiority in change in body weight for semaglutide 0.5 mg vs. sitagliptin
6. Superiority in change in HbA_{1c} for semaglutide 0.5 mg vs. sitagliptin

Non-inferiority will be concluded if the upper limit of the two-sided 95% confidence interval for the estimated difference in HbA_{1c} between semaglutide and sitagliptin is less than 0.3%. Superiority for either change in HbA_{1c} or change in body weight will be claimed if the upper limit of the two-sided 95% confidence interval for the estimated difference is below 0% or 0 kg respectively.

When establishing non-inferiority the analysis will be based on the full analysis set (FAS) and supplemented by an analysis with the per protocol population using the data from the 'on treatment without rescue medication' observation period as supportive evidence. The FAS population will be used in the analysis when concluding superiority.

Sensitivity analysis

To investigate the sensitivity of the main results, complimentary and separate analyses for primary endpoint and the confirmatory secondary endpoint will be performed, using the FAS only, except for HbA_{1c}, where the PP analysis set will be used in a sensitivity analysis regarding the non-inferiority evaluation. These analyses will investigate the sensitivity of the results due to the impact of missing values.

The primary analysis regarding non-inferiority of the primary endpoint change in HbA_{1c} after 30 weeks will also be performed separately based on the data in the PP analysis set only.

The primary endpoint and the secondary confirmatory endpoint will be evaluated in the following sensitivity analyses:

- An analysis of covariance (ANCOVA) model will be analysed with imputation of missing values according to the last observation carried forward (LOCF) method. based on the FAS using the data from the 'on-treatment without rescue medication' observation period. The model will include terms for treatment, country, and the corresponding baseline value as a covariate. The response variable will be the last available value obtained within the 30 weeks period of the trial
- The MMRM will be analysed based on all data from the 'in-trial' observation period The MMRM will be analysed based on data only from subjects that completed the trial without receiving rescue treatment.

A pattern mixture model based on the FAS using the 'on-treatment without rescue medication' observation period approach mimicking an ITT scenario where withdrawn subjects are assumed to be switched to a treatment inferior to the control treatment after treatment discontinuation will be performed for evaluation of non-inferiority for the primary endpoint change in HbA_{1c} at 30 weeks.

- In the first step 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 treatment group separately and 500 copies of the dataset will be generated.
- In the second step, for each of the 500 copies of the dataset, an analysis of variance model with the same factors as the primary model, and baseline HbA_{1c} and HbA_{1c} at 4 weeks (V3) as covariate is fitted to the change in HbA_{1c} from baseline to 8 weeks (V5) for the sitagliptin group only. The estimated parameters, and their variance, from this model are used to impute missing value at 8 weeks for subjects in all treatment groups, based on country and HbA_{1c} at baseline and 4 weeks.
- In the third step, for each of the 500 copies of the dataset, missing HbA1c values at 12 weeks (V6) are imputed in the same way as for 8 weeks. Now the imputation are based on

an analysis of variance model with the same factors and the HbA1c values at baseline, 4 weeks and 8 weeks as covariates, fitted to the control group.

- This stepwise procedure is then repeated sequentially over the available planned visits, adding one visit in each step until the last planned visit at 30 weeks (V9).
- For each withdrawn subject in the investigational treatment group, a value of 0.3% (the non-inferiority limit) is added to the change in HbA_{1c} at 30 weeks.
- For each of the complete data sets, the change from baseline to week 30 is analysed using an analysis of variance model with the same set of factors and the baseline HbA_{1c} value as a covariate.
- The estimates and standard deviations for the 500 data sets are pooled to one estimate and associated standard deviation using Rubin's rule (page 255-257)[59] From these pooled estimates the confidence interval for the treatment differences and the associated p-value are calculated.

A pattern mixture model approach mimicking an ITT scenario where withdrawn subjects are assumed to be switched to the control treatment after treatment discontinuation will be performed separately for the evaluation of superiority in the primary endpoint change in HbA_{1c} and change in body weight at 30 weeks. The same types of approach as used for the non-inferiority assessment in change in HbA_{1c} will be employed, see above. However, the step where 0.3%, the non-inferiority limit, is added to the change in HbA_{1c} at 30 weeks will not be performed in this sensitivity analysis.

Chinese/Korean subgroup analyses

Subgroup analyses for the primary endpoint and the confirmatory secondary endpoint will be performed by country with the aim to assess the treatment effect in China and Korea. They will be performed in a combined model using all data similar to the main analysis of the respective parameter but with an interaction between treatment and country. In addition the safety in China and Korea will be assessed.

17.4 Secondary endpoints

The planned secondary endpoints used to support the primary objective will be analysed as outlined in this section.

17.4.1 Confirmatory secondary endpoints

Weight loss

A confirmatory secondary variable is change in body weight after 30 weeks of treatment. This variable will be analysed in the same type of model as the primary endpoint although with baseline body weight as covariate.

17.4.2 Supportive secondary endpoints

17.4.2.1 Efficacy endpoints

All efficacy endpoints in this section will be summarised and evaluated using the FAS.

Continuous variables

Change from baseline to week 30 in:

- FPG
- Insulin
- C-peptide
- glucagon
- pro-insulin
- pro-insulin/insulin ratio
- HOMA-B
- HOMA-IR
- fasting blood lipids (total cholesterol, LDL-cholesterol, VLDL-cholesterol, HDL-cholesterol, triglycerides and free fatty acids)
- BMI
- waist circumference
- systolic and diastolic blood pressure
- hsCRP

will all be analysed based on the same data and type of model as the primary endpoint, but with the associated baseline value as a covariate.

Except for FPG, BMI, waist circumference, and blood pressure the values of the variables will be log transformed subject to analysis.

Beta-cell function

Beta-cell function (fasting HOMA-B and fasting HOMA-IR) will be calculated based on fasting insulin and FPG. The calculation will be done at the same time points as for fasting insulin and FPG samples (section 2).

The calculation of the fasting HOMA endpoints will be done as follows:
Fasting HOMA-B (%) = 20 x fasting insulin [µU/ml]/(FPG[mmol/l]-3.5)
Fasting HOMA-IR (%) = fasting insulin [µU/ml] x FPG [mmol/l]/22.5

PRO outcomes

The PRO outcome endpoints:

- PRO questionnaire outcome DTSQs (individual items and treatment satisfaction score (6 of the 8 items summed)), and
- PRO questionnaire outcome SF-36v2™ short Form health survey: Total scores (physical component and mental component) and scores from the 8 domains will be analysed separately using the ANCOVA model based on the data from the on-treatment without rescue medication observation period. Factors in the model will be treatment and country. The baseline value of the corresponding endpoint will be used as covariate in the analysis model.

7-point profile

Subjects will be asked to perform SMPG measurements see section 8.5.1.5.

The endpoints from the 7-point profiles that will be analysed at week 30 are:

- Mean of the 7-point profile, defined as the area under the profile, calculated using the trapezoidal method, divided by the measurement time
- Mean increment over all meals

The mean of the 7-point profile and the mean of the post prandial increments at week 30 will be analysed separately with the same data and type of methods as primary endpoint but with the corresponding baseline assessment as a covariate.

Response in HbA_{1c} and/or weight loss after 30 weeks

The secondary variables related to fixed response in HbA_{1c} and/or weight loss at 30 weeks will be:

- Responder in HbA_{1c} after 30 weeks of treatment (yes/no) defined as HbA_{1c} <7.0% (<53 mmol/mol) – ADA target
- Responder in HbA_{1c} after 30 weeks of treatment (yes/no) defined as HbA_{1c} ≤6.5% (48 mmol/mol) – AACE target
- Weight loss ≥5%
- Weight loss ≥10%
- HbA_{1c} <7.0% (53 mmol/mol) without severe or confirmed symptomatic hypoglycaemia (plasma glucose ≤3.1 mmol/L) and no weight gain

All these variables will be analysed based on the 'on-treatment without rescue medication' observation period separately in the same type of logistic regression model. The model will include factors for treatment and country. For the two responder in HbA_{1c} endpoints, baseline HbA_{1c} will be included in the model as a covariate, whereas for the weight responder endpoint (≥5% and ≥10%

weight loss), baseline weight will be included instead. For the composite endpoint (cf. last bullet), both baseline HbA_{1c} and baseline weight will be included.

Missing response data at 30 weeks will be imputed from respectively the MMRM used for the primary analysis of HbA_{1c} and the confirmatory secondary endpoint change in body weight at 30 weeks. The results will be described by the odds ratio and the associated 95% confidence interval for the odds ratio.

17.4.2.2 Safety endpoints

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

- Number of treatment emergent AEs during 30 weeks of treatment
- Number of treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes during 30 weeks of treatment
- Severe or BG confirmed symptomatic hypoglycaemic episodes during 30 weeks of treatment (yes/no)

Change in safety endpoints assessed from baseline to 30 weeks of treatment and/or follow up:

- Haematology
- Biochemistry
- Calcitonin
- Urinalysis
- UACR
- Pulse
- ECG evaluation
- Physical examination evaluation
- Eye examination

Occurrence of semaglutide antibodies during 35 weeks of study duration (yes/no):

- Anti-semaglutide antibodies
    - Anti-semaglutide antibodies with in vitro neutralising effect
    - Anti-semaglutide antibodies cross reacting with endogenous GLP-1
        - Cross reacting antibodies with in vitro neutralising effect to endogenous GLP-1

Anti-semaglutide antibody level during and after 30 weeks of treatment

All safety endpoints will be summarised and evaluated by descriptive statistics using the SAS.

Adverse events

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

- Number of treatment emergent adverse events (TEAEs)

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

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

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

Pulse

Pulse will be analysed separately using an analysis similar to the primary analysis of the primary endpoint. However this analysis will be based on FAS using the data from the on-treatment observation period but with the pulse value at baseline as a covariate.

Laboratory assessments

Amylase and lipase will be analysed separately with the same type of methods as for pulse with the corresponding baseline assessment as a covariate. The values will be log transformed in the analysis.

Calcitonin

Calcitonin will be displayed in terms of the number of subjects (N), the percentage of subjects (%) and the event rate per 1000 years of exposure (R). The following criteria are defined for tabulations:

Persistent (all post baseline measurements)

- From <upper normal limit (UNL) to persistently ≥UNL
- From <UNL to persistently ≥1.5 UNL
- From <UNL to persistently ≥20 ng/L
- From <UNL to persistently ≥50 ng/L

- From <20 ng/L to persistently ≥20 ng/L
- From <50 ng/L to persistently ≥50 ng/L

Incidental (at least one post baseline measurements)

- From <UNL to ≥UNL
- From <UNL to ≥1.5 UNL
- From <UNL to ≥20 ng/L
- From <UNL to ≥50 ng/L
- From <20 ng/L to ≥20 ng/L
- From <50 ng/L to ≥50 ng/L

Summaries tables of calcitonin continuous measurements, will include number and percentage of observations < and ≥ LLOQ, minimum, Q25, median, Q75 and maximum. Summaries will be presented for all subjects and by gender.

Classification of Hypoglycaemia

Treatment emergent: hypoglycaemic episodes will be defined as treatment emergent if the onset of the episode occurs within the on-treatment observation period (see definition of observation periods in Section 17.2.

Nocturnal hypoglycaemic episodes: are episodes with time of onset between 00:01 and 05:59 both inclusive.

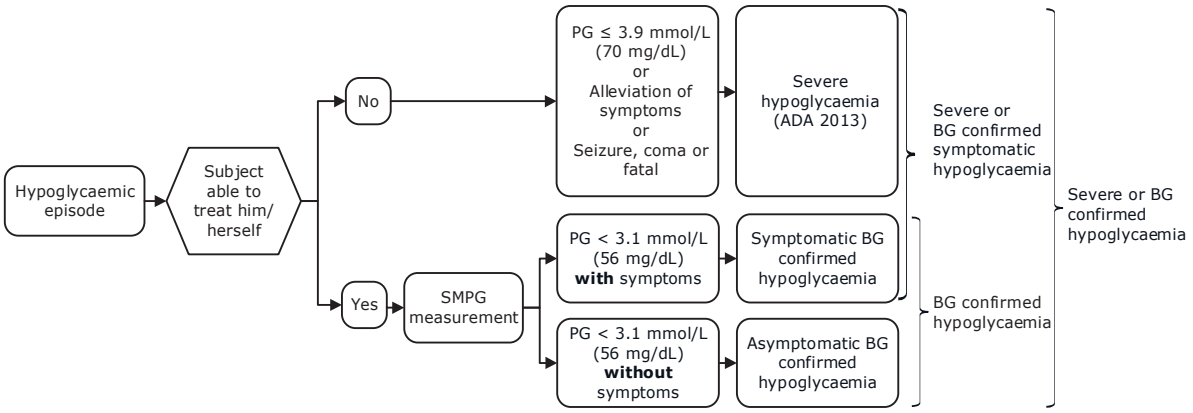
Hypoglycaemic episodes are classified according to the Novo Nordisk classification of hypoglycaemia and the ADA classification of hypoglycaemia (see Figure 17–2).

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)[60]. Therefore, Novo Nordisk has included hypoglycaemia with plasma glucose levels below this cut-off point of hypoglycaemia.

In this trial Novo Nordisk use the following classification in addition to the ADA classification (see Figure 17–1):

- Severe or BG confirmed symptomatic hypoglycaemia: An episode that is severe according to the ADA classification[51] or BG confirmed by a plasma glucose value <3.1 mmol/L (56 mg/dL) with symptoms consistent with hypoglycaemia.



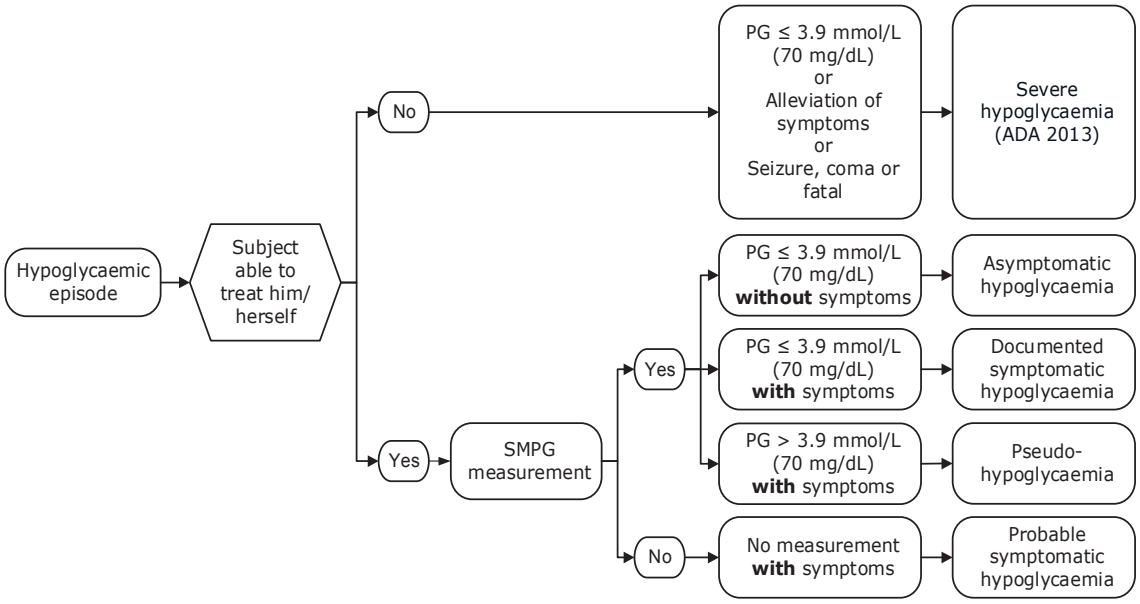
Note: Glucose measurements are performed with capillary blood calibrated to plasma equivalent glucose values

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

Figure 17–1 Novo Nordisk classification of hypoglycaemia

ADA classification of hypoglycaemia[51]

- Severe hypoglycaemia: An episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take of other corrective actions. Plasma glucose concentration 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 17–2 ADA classification of hypoglycaemia

Number of severe or BG confirmed symptomatic hypoglycaemic episodes

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 episodes 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.

The number of severe or BG confirmed symptomatic hypoglycaemic episodes during 30 weeks treatment 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, country as fixed factors and baseline HbA_{1c} as covariate. The SAS will be used for the analysis.

Number of nocturnal hypoglycaemic episodes

The number of nocturnal (00:01-05:59 am) severe or BG confirmed symptomatic hypoglycaemic episodes during 30 weeks of treatment will be analysed separately in the same type of model as the number of severe or BG confirmed symptomatic hypoglycaemic episodes during 30 weeks treatment.

Severe or BG confirmed symptomatic hypoglycaemic 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 with treatment, country as fixed factors and baseline HbA_{1c} as covariate.

Nocturnal severe or BG confirmed symptomatic hypoglycaemic episodes (yes/no)

The binary endpoint indicating whether a subject has no treatment emergent nocturnal (00:01-05:59 am) severe or BG confirmed symptomatic hypoglycaemic episodes or at least one will be analysed using the same type model as severe or BG confirmed symptomatic hypoglycaemic episodes during 30 weeks treatment.

17.5 Health economics and/or patient reported outcomes

The PRO questionnaires, SF-36v2^{TM} and DTSQs, will be used to evaluate the objective regarding Quality of Life, see section 17.4.2.1for the details of the corresponding statistical analysis.

18 Ethics

The trial will be conducted in compliance with ICH GCP[1] and applicable regulatory requirements, and in accordance with the Declaration of Helsinki[2].

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 treatment. Subjects will be treated within a regimen anticipated to be better than or equal to the treatment they receive at the time of entry into the trial. Subjects will have to spend some extra time, as additional assessments and visits to the clinic are required. It is the responsibility of the investigator to ensure the best possible care according to the principles outlined in Diabetes Care 2013 Standards of Medical Care in Diabetes[61], or any updates thereof.

It is concluded that the potential benefits from participating in the trial outweigh the potential risks. The safety profile of semaglutide generated from the clinical and nonclinical development programme has not revealed any safety issues that would prohibit administration of once weekly doses of 0.5 mg or 1.0 mg semaglutide in accordance with the planned clinical trial. It is concluded that the risk to the subjects in this trial is low and acceptable in view of the benefits a long-acting GLP-1 analogue would provide to people with type 2 diabetes (please see 3.5)

The trial products may be associated with AEs, but relevant precautions have been implemented in the design and planned conduct of the trial in order to minimise the risks and inconveniences of participation in the trial. These precautions include thorough information regarding the correct administration of the trial products and gradual dose adjustment. Furthermore, subjects are fully informed about possible AEs and inconveniences and will be instructed to contact the investigator in case of any concerns regarding the trial participation.

When treatment with trial products ends, the subject and investigator will decide on the best available treatment.

18.1 Informed consent

In seeking and documenting informed consent, the investigator must comply with applicable regulatory requirement(s) and adhere to ICH GCP[1] and the requirements in the Declaration of Helsinki[2].

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

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

18.2 Data handling

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

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

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

18.3 Information to subject during trial

The site will be offered a communication package to the subject during the conduct of the trial. The package content is issued by Novo Nordisk. The communication package will contain the letters intended for distribution to the subjects. The letters will be translated and adjusted to local requirements and distributed to the subject by discretion of the investigator. The subject may receive a “welcome to the trial letter” and a “thank for your participation letter” at the end of the trial. Further the subject may receive trial letters during the trial period.

All information to the subjects will be submitted to the health authorities and IECs/IRBs for approval according to local regulations.

18.4 Premature termination of the trial and/or trial site

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

If a 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 IRBs/IECs and provide a detailed written explanation. The relevant regulatory authorities must be informed.

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

19 Protocol compliance

Deviations from the protocol should be avoided.

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

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

Documentation on protocol deviations must be kept in the investigator's trial file and Novo Nordisk trial master file.

20 Audits and inspections

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

21 Critical documents

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

- Regulatory approval and/or acknowledgement of notification as required
- Approval/favourable opinion from IRBs/IECs clearly identifying the documents reviewed as follows: protocol, any protocol amendments, subject information/informed consent form, any other written information to be provided to the subject and subject recruitment materials
- List of IRB/IEC members and/or constitution
- Curricula vitae of investigator and sub-investigator(s) (current, dated and signed - must include documented GCP training or a certificate)
- Signed receipt of Investigator's Brochure and local label for comparator
- Signed and dated agreement on the final protocol
- Signed and dated agreement on protocol amendment, if applicable
- Financial agreement(s)
- Source document agreement
- Central laboratory certification and normal ranges
- Insurance statement, if applicable
- Signed and dated Investigator Agreement
- Financial disclosure form from investigator and sub-investigator(s)

Novo Nordisk will analyse and report data from all sites together.

By signing the protocol, each investigator agrees to comply fully with ICH GCP[1], applicable regulatory requirements and the Declaration of Helsinki[2].

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

22 Responsibilities

All staff Novo Nordisk, site, Central Laboratories, CRO etc. must conduct the trial in compliance with ICH GCP[1], applicable regulatory requirements, and in accordance with the Declaration of Helsinki[2].

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

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

The investigator is responsible for filing essential documents (ie those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced) in the investigator's trial file. The documents should be kept in a secure locked facility, so no unauthorized persons can get access to the data. The subject identification code list must be kept securely and separate from the personal 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 (eg 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 Novo Nordisk for regulatory purposes and 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.

One principal investigator will be appointed 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[62].

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.

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 principal 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[62] (sometimes referred to as the Vancouver Criteria).

At the end of the trial, one or more publications (abstracts, posters, manuscripts) will be prepared for submission to scientific congresses and peer-reviewed journals in collaboration between Novo Nordisk and investigator(s) appointed by Novo Nordisk. These investigator(s) must meet the ICMJE authorship criteria to be named authors on publications.

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 for publication of such primary policy 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 and human biospecimens

24.1 Retention of clinical trial documentation

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

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

The investigator must be able to access his/her trial documents without involving Novo Nordisk in any way. Site-specific CRFs and other subject data (in an electronic readable format or as paper copies or prints) will be provided to the investigator before access is revoked to the systems and/or electronic devices supplied by Novo Nordisk. These data must be retained by the trial site. If the Novo Nordisk provided data (eg 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 as long as the product is on the market plus 20 years.

The files from the investigator site/institution must be retained for 15 years after the completion of the trial, or longer if required by local regulations. The deletion process must ensure confidentiality of data and must be done in accordance with local regulatory requirements.

24.2 Retention of human biospecimens

Antibody samples may be stored until market authorisation in case Health Authorities requests further characterisation of the antibody response.

(For Brazil: the laboratory samples for BR subjects will be destroyed at the latest at the completion of the CTR, including samples for anti-semaglutide antibody analysis. No sample will be stored after the completion of CTR).

None of the data will be identified by name. Antibody samples and thyroid tissue will be identified only by a subject number, a visit number and a trial identification number. The trial staff is responsible for maintaining a code list which links to the subject number. The code list must be kept for at least 15 years. The code list may be reviewed by Novo Nordisk staff including auditors or representatives from regulatory authorities, but no copies will be made of this list.

25 Institutional Review Boards/Independent Ethics Committees and regulatory authorities

IRB/IEC:

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

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

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

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

The investigator must maintain an accurate and complete record of all submissions made to the IRB/IEC. The records must be filed in the investigator's trial 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 local laws/acts/guidelines.

27 References

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Appendix A

NN9535-4114

Medical events of special interest

	Event **Appendix A**	Definition	Rationale	EAC
1	Medication errors concerning trial products	1) Administration of wrong drug or use of wrong device 2) Wrong route of administration, such as intramuscular instead of subcutaneous 3) Administration of a high dose with the intention to cause harm, e.g. suicide attempt 4) Accidental administration of a lower or higher dose than intended. That is a dose of semaglutide 10% lower or higher than 1.0 mg week (± 24h) or of sitagliptin that is lower or higher than 100 mg/day; however the administered dose must deviate from the intended dose to an extend where clinical consequences for the trial subject were likely to happen as judged by the investigator, although not necessarily did happen.	Standard MESI in all Novo Nordisk clinical trials. Medication errors are captured to collect information which may be used to improve the design, name or packaging of the product and/or information which may have an impact on product labelling (for example information about substantial overdoses).	No
2	Fatal events (if not covered by another MESI)	All cause death: 1) Cardiovascular death, 2) Non-cardiovascular death, 3) Undetermined cause of death[2,3]	A FDA guidance document[1] requests that sponsors demonstrate the cardiovascular safety profile of any new therapy for type 2 diabetes in order to ensure, that the new therapy does not increase the cardiovascular risk to an unacceptable extent.	All events will be adjudicated

3	Acute coronary syndrome[3]: • Myocardial Infarction • Hospitalisation for unstable angina	All types of myocardial infarction (MI) must be reported: • Spontaneous MI (including re-infarction and MI associated with stent thrombosis) • Percutaneous coronary intervention (PCI) related MI • Coronary artery bypass graft surgery (CABG) related MI • Silent MI[2] All events with symptoms of myocardial ischemia requiring hospitalization must be reported.	Requested in FDA guidance document[1]	All events will be adjudicated
4	Cerebrovascular event (stroke or transient ischemic attack)	Stroke (Ischemic, haemorrhagic, undetermined) Stroke is defined as an acute episode of neurological dysfunction caused by focal or global brain, spinal cord, or retinal vascular injury[2,3]. Transient Ischemic Attack Transient ischemic attack (TIA) is defined as a transient (<24 hours) episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction[2,3].	Requested in FDA guidance document[1]	All events will be adjudicated
5	Coronary Revascularisation Procedure	Coronary Revascularisation Procedure (Coronary Artery Bypass Graft surgery (CABG), Percutaneous Coronary Intervention (PCI)): A coronary revascularisation procedure is a catheter-based or open surgical procedure designed to improve myocardial blood flow[2,3].	Requested in FDA guidance document[1]	All events will be adjudicated

6	Peripheral Arterial Revascularisation Procedure	Peripheral Arterial Revascularisation Procedure (lower extremity, renal, mesenteric, iliac, subclavian, aortic etc.): A peripheral arterial revascularisation procedure is a catheter-based or open surgical procedure designed to improve peripheral arterial blood flow. This procedure may include thrombectomy, embolectomy, atherectomy, dissection repair, angioplasty, and stent placement. Pre-planned procedures of peripheral revascularisation should not be reported as MESI.	Requested in FDA guidance document[1]	No
7	Heart failure requiring hospital admission	Clinical manifestations of new episode or worsening of existing heart failure[2,3].	Requested in FDA guidance document[1]	All events will be adjudicated
8	Neoplasm (excluding thyroid neoplasm)	All types of neoplasms must be reported including: • Malign neoplasm • In situ neoplasm • Benign neoplasm • Neoplasms of uncertain or unknown behaviour For operational reasons thyroid neoplasm will be reported as per thyroid disease MESI.	Neoplasm is an event Novo Nordisk follows closely for GLP-1 analogues due to non-clinical findings in rats and mice treated with GLP-1 receptor agonists.	All events will be adjudicated
9	Thyroid disease (including thyroid neoplasm)	All disorders of thyroid gland must be reported. For operational reasons thyroid neoplasm will be reported as per thyroid disease MESI	Thyroid C-cell carcino-genicity has been reported in rats and mice treated with GLP-1 receptor agonists in non-clinical studies	Only adjudicated if thyroid neoplasm or resulting in thyroidectomy

10	Pancreatitis or clinical symptoms leading to suspicion of pancreatitis	Two of following diagnostic criteria fulfilling the diagnosis of acute pancreatitis: 1) Severe acute abdominal pain 2) elevated blood levels of pancreatic enzymes (lipase, amylase) > 3xUNR 3) characteristic imaging finding (ultrasound, CT, MRI) Chronic pancreatitis will be defined by characteristic imaging finding (ultrasound, CT, MRI) with abnormal pancreatic function tests or characteristic histological findings	Treatment with GLP-1 receptor agonists has been associated with acute pancreatitis and Novo Nordisk therefore monitors these events closely	All events will be adjudicated
11	Immunogenicity events (allergic reactions, immune complex disease, and anti-semaglutide antibody formation)	All events suspected to involve an immune reaction to trial product must be reported: Events to be reported can be defined according to the below: **A) Immediate hypersensitivity reactions.** Typically occurring within minutes after administration of the antigen. Clinical symptoms include (but are not limited to): • Urticaria • Angioedema • Allergic rhinitis • Exacerbation of pre-existing, or de novo development of, allergic asthma • Systemic anaphylactic reaction	All protein based drugs have a risk of hypersensitivity reactions	No

		B) Delayed hypersensitivity reactions Typically occurring 48 to 72 hours after exposure to the antigen and manifested by various types of skin reactions with or without pruritus **C) Immune complex disease** Either de novo development or exacerbation of pre-existing immune complex disease. Most frequent clinical syndromes include: • Lupus erythematosus • Vasculitis syndromes • Non-viral hepatitis • Pneumonitis • Arthritis • Glomerulonephritis **D) Anti-semaglutide antibody formation** Hypersensitivity reactions very rarely occur at the first administration of antigen and will always reoccur if exposed again. Hypersensitivity reactions can be present at the injection site, but are not equivalent to local irritative injection site reactions caused by trauma.		

1. Guidance for Industry. Diabetes Mellitus – Evaluating cardiovascular Risk in new Antidiabetic Therapies to Treat Type 2 Diabetes. FDA, Center for Drug Evaluation and Research (CDER). December 2008. Clinical/medical or any updates hereof.

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Appendix A

Monitoring of Calcitonin

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.

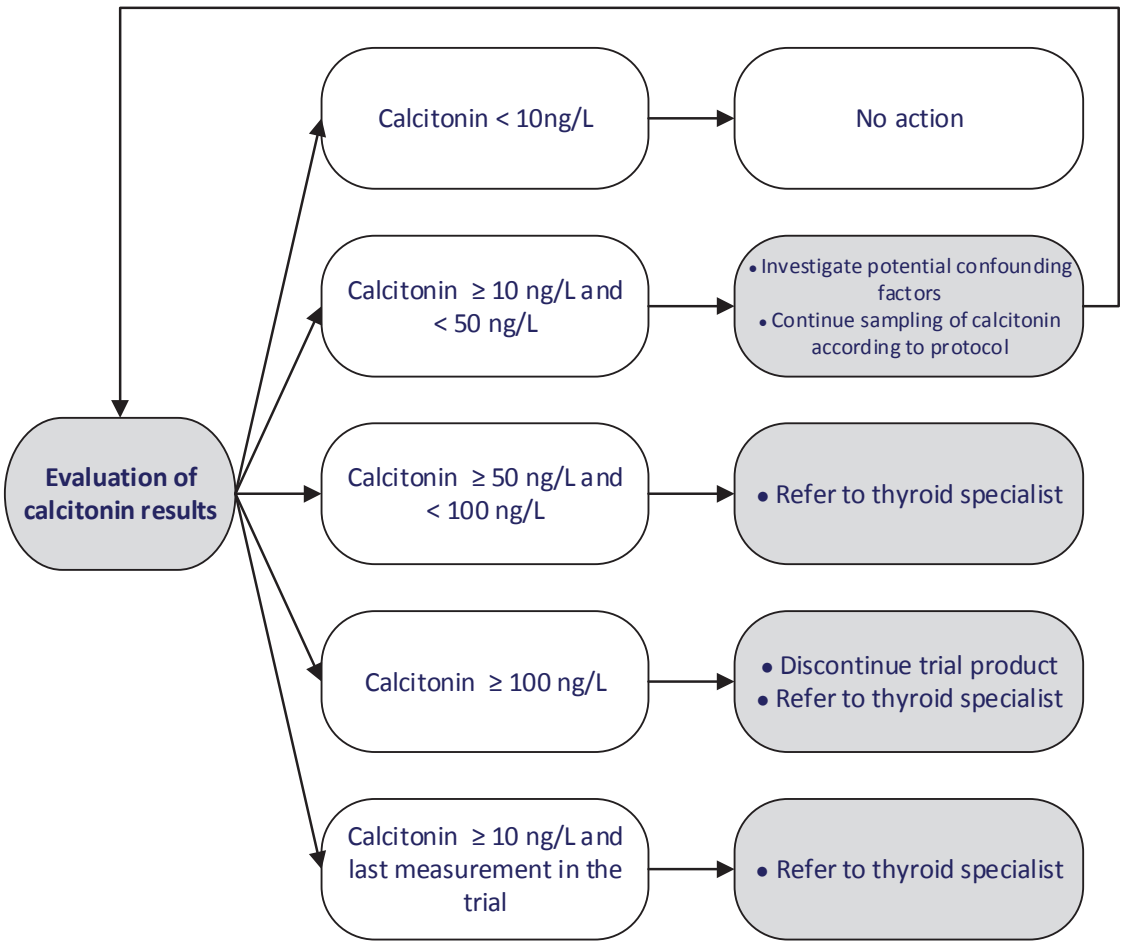

Figure 1 Flow of calcitonin monitoring

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 (see protocol Section 6.5 premature discontinuation of trial

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

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

Diagnostic evaluation should include:

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

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

2.2 Calcitonin ≥ 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].

3 References

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

2. Scheuba C, Kaserer K, A m, drosten R. Sporadic hypercalcitoninemia: clinica and therapeutic consequences. Endocrine Related Cancer. 2009;16(1):243-53.

3. Verga U, Ferrero S, Vicentini L, Brambilla T, Cirello V, Muzza M, et al. Histopathological and molecular studies in patients with goiter and hypercalcitoninemia: reactive or neoplastic C-cell hyperplasia? Endocr Relat Cancer. 2007;14(2):393-403.

Appendix A

Monitoring of Calcitonin

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3 References **7**

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.

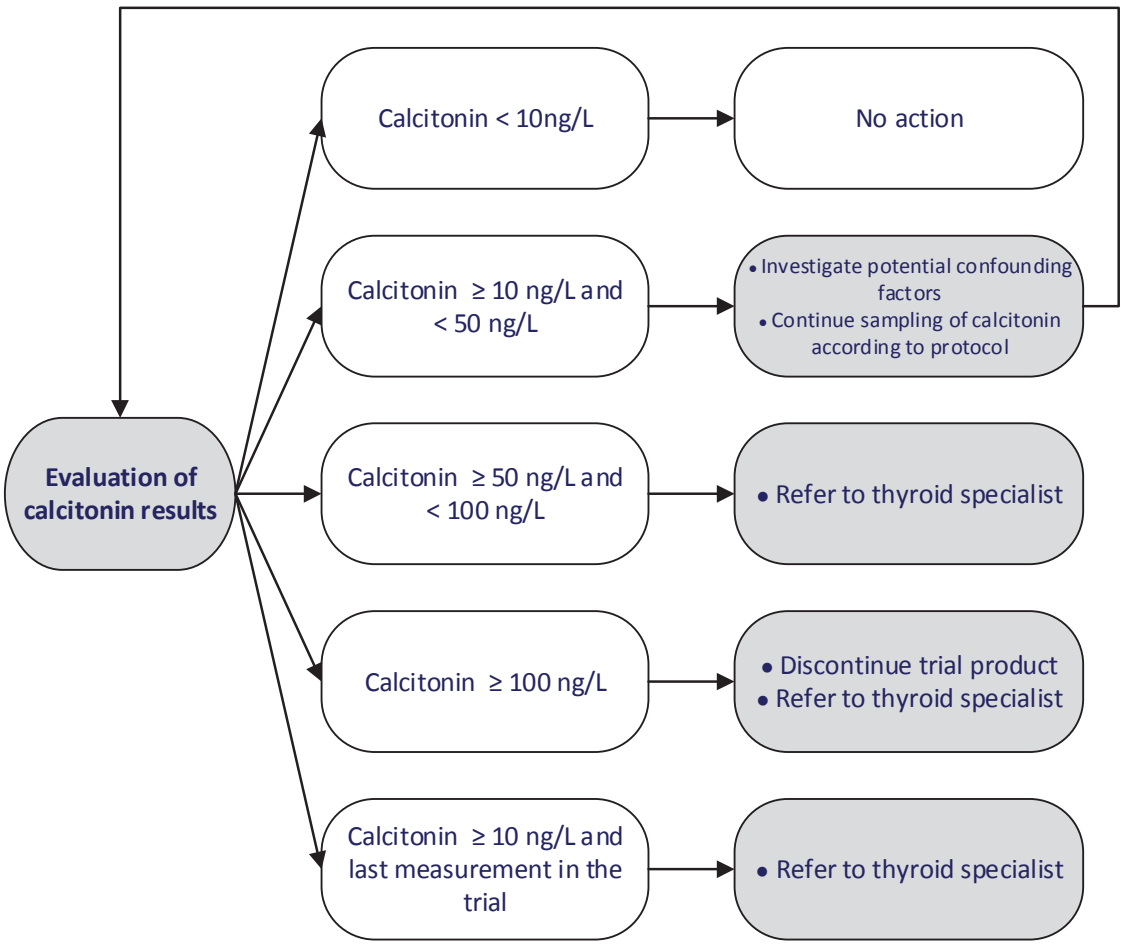

Figure 1 Flow of calcitonin monitoring

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 (see protocol Section 6.5 premature discontinuation of trial

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

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

Diagnostic evaluation should include:

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

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

2.2 Calcitonin ≥ 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].

3 References

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

2. Scheuba C, Kaserer K, A m, drosten R. Sporadic hypercalcitoninemia: clinica and therapeutic consequences. Endocrine Related Cancer. 2009;16(1):243-53.

3. Verga U, Ferrero S, Vicentini L, Brambilla T, Cirello V, Muzza M, et al. Histopathological and molecular studies in patients with goiter and hypercalcitoninemia: reactive or neoplastic C-cell hyperplasia? Endocr Relat Cancer. 2007;14(2):393-403.

Appendix B

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Monitoring of Calcitonin

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3 References **6**

1 Background

Semaglutide treatment is associated with thyroid C-cell changes in rodents but not in the non-human primate. The proliferative C-cell changes in rodents are a known effect following GLP-1 receptor activation by GLP-1 receptor agonists and 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 a 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 can become challenging.

There are several known confounding factors affecting calcitonin levels, namely renal dysfunction, smoking, autoimmune thyroiditis and several drug classes (eg proton pump inhibitors, beta-blockers, H2-blockers and glucocorticoids). Physiology of C-cell activation in various clinical conditions and in different patient populations (ie 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 and C-cell abnormalities - evaluation and follow-up

Subjects with a personal or family history of medullar thyroid cancer (MTC) or multiple endocrine neoplasia syndrome type 2 (MEN 2) or with a screening calcitonin ≥50 ng/L will be excluded from the NN9535-4114 trial.

A blood sample will be drawn at pre-specified trial visits for measurement of calcitonin. In case a subject has an calcitonin value ≥10 ng/L the algorithm outlined below (see Section 2.1 to 2.4) should be followed. The algorithm applies for all calcitonin values including screening values.

All calcitonin values ≥20 ng/L will be submitted to an independent Calcitonin Monitoring Committee (CMC) of thyroid experts, together with relevant supplementary data, ie subject's demographics, diabetes history, concomitant medical history, concomitant medications, smoking status as well as information about relevant adverse events reported during the trial.

The CMC will provide recommendations to the investigators with regards to further investigation and treatment of the individual subject. The CMC will be blinded to trial treatment.

The summary for the rationale for the use of specific calcitonin values to trigger medical evaluation is provided in section 2.1 to 2.4.

2.1 Calcitonin values ≥100 ng/L

The value will be submitted to the CMC and the subject should be discontinued from trial product. If the value is a screening value the subject cannot be randomised and the subject must be referred to a thyroid specialist.

These values were found in 0.15% of the population published by Costante et al1 and in one subject (on active comparator) in the liraglutide development program. For a calcitonin value of ≥100 ng/L, the subject should be assumed to have significant C-cell disease and a high likelihood of having medullary carcinoma of the thyroid. Diagnostic evaluation should consist of thyroid ultrasound, fine needle aspiration of any nodules >1 cm and potentially surgery with neck dissection. Family history of MTC or MEN 2 should be evoked and a RET proto-oncogene analysis should be performed.

2.2 Calcitonin values ≥50 and <100 ng/L

The value will be submitted to the CMC and the investigator will receive guidance from the CMC with regards to continuation of trial product. If the value is a screening value the subject cannot be randomised and the subject should be referred to a thyroid specialist.

These values were found in 0.18% of a population with thyroid nodular disease published by Costante et al.1 Diagnostic evaluation will likely include ultrasound examination and if available

and if there is no contraindication, subjects should undergo a pentagastrin stimulation test (Europe). Subjects with positive pentagastrin stimulation tests will be considered to undergo surgery. In the US where pentagastrin is not available, thyroid ultrasound and fine needle aspiration biopsy may add important clinical information informing the need for surgery.

2.3 Calcitonin values ≥20 and <50 ng/L

The value will be submitted to the CMC. If the subject is a screen failure the subject should be referred to a thyroid specialist for further evaluation.

These values are expected to be found in up to 1% of subjects. Based on data from Costante et al[1], the predictive value calcitonin levels ≥20 and <50 ng/L clinically significant C-cell disease begins to fall. However, up to 25% of these subjects had a positive pentagastrin stimulation test. The likelihood of having a medullary carcinoma >1 cm with calcitonin in this range is extremely low.

2.4 Calcitonin values ≥10 and <20 ng/L

Confounding factors should be evaluated. If drugs potentially affecting calcitonin can be discontinued safely, calcitonin measurement can be repeated after a washout period. Gastrin levels return to the normal range by ~ 10 days after stopping proton-pump inhibitors (PPIs).[2] No further actions are needed during the trial if the next calcitonin values remain below 20 ng/L.

If the subject is a screening failure or if the value is the last one taken in the trial, the subject should preferably be referred to a thyroid specialist for further evaluation.

These values may be found in ~ 2.5 to 4% of the trial population. Costante et al[1] had 216 patients in this category. One out of 216 patients had a subsequent basal (unstimulated) calcitonin of 33 ng/L, and had C-cell hyperplasia at surgery, a lesion of unknown clinical significance. Two other studies used a cutoff of CT > 10 ng/L to screen for C-cell disease, but they do not provide sufficient information on patients with basal CT >10 and <20 ng/L to allow conclusions.[3,4]

3 References

1 Costante G, Meringolo D, Durante C, Bianchi D, Nocera M, Tumino S et al. Predictive value of serum calcitonin levels for preoperative diagnosis of medullary thyroid carcinoma in a cohort of 5817 consecutive patients with thyroid nodules. J Clin Endocrinol Metab 2007; 92(2):450-455.

2 Klinkenberg-Knol EC, Jansen JB, Lamers CB, Nelis F, Meuwissen SG. Temporary cessation of long-term maintenance treatment with omeprazole in patients with H2-receptor-antagonist-resistant reflux oesophagitis. Effects on symptoms, endoscopy, serum gastrin, and gastric acid output. Scand J Gastroenterol 1990; 25(11):1144-1150.

3 Scheuba C, Kaserer K, moritz A, drosten R. Sporadic hypercalcitoninemia: clinica and therapeutic consequences. Endocrine Related Cancer 2009; 16(1):243-253.

4 Verga U, Ferrero S, Vicentini L, Brambilla T, Cirello V, Muzza M et al. Histopathological and molecular studies in patients with goiter and hypercalcitoninemia: reactive or neoplastic C-cell hyperplasia? Endocr Relat Cancer 2007; 14(2):393-403.

Appendix B

Adverse events requiring additional data collection

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1 Adverse events requiring additional data collection

For the following AEs, additional data collection is required and specific event forms must be completed in addition to the AE form. In case any of these events fulfil the criteria for an SAE, please report accordingly, see Section 12.1.1.

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

Additional information on a specific form is also required for hypoglycaemic episode and medication errors. The hypoglycaemia form is described in protocol section 8.4.4 and medication errors are described in protocol section 12.1.3 and 8.4.2

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

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

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

1.2 Cerebrovascular event (stroke or TIA)

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

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

1.3 Heart failure requiring hospitalisation

If an event of heart failure requiring hospitalisation (admission to an in-patient unit or a visit to an emergency department that results in at least a 24 hour stay) is applicable for reporting the following additional information must be reported, if available:

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

1.4 Hypersensitivity reactions

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

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

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

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

To assist in the diagnostic evaluation it is recommended to draw a blood sample for measurement of tryptase (total and/or mature tryptase, local assessment) within 3 hours of onset of the

hypersensitivity reaction, and if this is achieved, a tryptase sample should also be drawn 2 weeks after the event.

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

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

1.5 Neoplasm

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

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

1.6 Pancreatitis

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

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

Assessments in case of suspicion of acute pancreatitis

Most patients with acute pancreatitis experience severe abdominal pain that is located generally in the epigastrium and radiates to the back. The onset of the pain may be swift, reaching maximum

intensity within 30 min, is frequently unbearable, and characteristically persists for more than 24 hours without relief[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 must be performed, including local 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.

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

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

1.7 Renal event

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

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

Risk or confounding factors identified including exposure to nephrotoxic agents

1.8 Thyroid disease

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

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

1.9 Hepatic event

- ALT or AST > 5 × 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 must be reported if available:

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

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

*Please note that risk of liver injury defined as ALT or AST > 3 × UNL and total bilirubin > 2 × UNL, where no alternative aetiology exits (Hy's law), should also be reported as a SAE (important medical event, according to section 12.1.1).

1.10 Diabetic retinopathy

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

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

1.11 Laboratory outlier

As a minimum but not limiting to the specified cut-offs for the following laboratory parameters a value above or below are considered to be clinically significant[4] and should be reported as a laboratory outlier by completing both an AE and a laboratory outlier form.

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

If a laboratory outlier is observed, the following additional information must be reported, if available:

- Signs and symptoms associated with the event
- Risk factors
- Relevant laboratory test results
- Treatment for the event
- Possible cause(s) of the event

Furthermore, repeated laboratory assessments should be obtained at the central laboratory until the value is within the normal range or back to baseline values.

2 References

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

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Adverse events requiring additional data collection

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- Cardiac stress testing
- Angiography
- Use of thrombolytic drugs
- Revascularisation procedures

1.2 Cerebrovascular event (stroke or TIA)

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

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

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- Treatment given for the condition
- Risk factors identified
- Family history of thyroid disease

1.9 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 must be reported if available:

- Signs and symptoms associated with the event
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- Relevant laboratory test results
- Diagnostic imaging performed
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1.10 Diabetic retinopathy

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

- Signs and symptoms associated with the event
- Results of the eye examination
- Treatment for and complications of the event
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1.11 Laboratory outlier

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- Thrombocyte count: < 25000/mm^3 or 25x10^9/L
- Total calcium (serum corrected): <1.5 mmol/L or > 3.4 mmol/L
- Potassium:< 2.5 mmol/L or > 7 mmol/L
- Sodium: < 120 mmol/L or > 160 mmol/L
- Creatine Kinase (CK) > 10x ULN

If a laboratory outlier is observed, the following additional information must be reported, if available:

- Signs and symptoms associated with the event
- Risk factors
- Relevant laboratory test results
- Treatment for the event
- Possible cause(s) of the event

Furthermore, repeated laboratory assessments should be obtained at the central laboratory until the value is within the normal range or back to baseline values.

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3. Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, et al. Classification of acute pancreatitis-2012: revision of the Atlanta classification and definitions by international consensus. Gut. 2013;62(1):102-11.
4. National Cancer Institute. Common Terminology Criteria for Adverse Events v4.03 (NIH publication # 09-7473). http://evsncinihgov/ftp1/CTCAE/CTCAE_403_2010-06-14_QuickReference_5x7pdf. 2010.

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
to Protocol, final version 1.0
dated 14 April 2014

Trial ID:NN9535-4114

SUSTAIN – CHINA MRCT

Efficacy and safety of semaglutide once-weekly versus sitagliptin once daily as add-on to metformin in subjects with type 2 diabetes

Trial phase: 3a

Applicable to *all countries*

Amendment originator:

[redacted]

Semagutide Diabetes & Diabetes Outcomes

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1 Introduction including rationale for the protocol amendment

The CFDA approval of the final protocol version 1.0, dated 14 April 2014 were approved on 28 September 2016. Since the preparation of the trial protocol in 2014, new information regarding the trial products is known and also some of the Novo Nordisk standards and processes have evolved and updated, which are the primary reasons for preparing the amendment and updating the protocol. Secondly, this is in accordance with the feed-back received from CFDA, refer to below text copied from the approval letter, optimisation of the protocol is allowed:

"Before the clinical trial, clinical research organization should further refine and optimize the protocol, pay attention to the exposed and potential safety risk of the product, and make a risk management plan."

While amending the protocol, special attention has been on patient safety and reporting, data quality and GCP compliance. This means, that minor refinements have been made throughout the protocol with the purpose of improving data quality and clarifying issues, where applicable.

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 Minor editorial changes throughout the protocol due to new naming standards and/or changes in the protocol template

Rationale: Since the approval of this protocol the protocol template has been extensively updated included improved explanation of several procedures. Accordingly throughout the protocol changes have been made in order to incorporate some of these changes

2.2 Flow chart updates (section 2)

Rationale: flow chart has been updated to align to the CDISC terminology. Clarification on the completion of end of trial and end of treatment forms in eCRF. Eye examination has been updated to also taken at end of treatment visit(s) V9 and V9A in line with FDA recommendations. Training in trial product and pen handling has been amended to coincide with dose escalation. Fasting definition has been updated to project standard definition.

2.3 Background information and rationale for the trial (section 3)

Rationale: Since the protocol was written in 2014, a phase 3a program on semaglutide s.c. has been completed and update information has been included into this section. Sitigliptin has also had some updated information since the protocol was written.

2.4 Supportive secondary endpoints (section 4.2.2.2)

Rationale: Eye examination added as supportive secondary safety endpoint

2.5 Trial design figure (section 5, Figure 5-1)

Rationale: the figure has been re-drawn for better clarity regarding the dose escalations and for easier understanding regarding the trial.

2.6 Inclusion criteria (section 6.2)

Rationale: Inclusion criteria updated to have Korean specific requirement regarding age.

2.7 Exclusion criteria (section 6.3)

Rationale: Exclusion criteria 14 updated to include dilated fundoscopy/fundus photography performed within the past 90 days.

2.8 Discontinuation of trial product (section 6.5.1)

Rationale: Include discontinuation criteria regarding calcitonin, safety concern and simultaneous participation in other clinical trials.

2.9 Milestones (section 7)

Rationale: Updated to be in line with new planned dates.

2.10 Methods and assessments (section 8)

Rationale: In this section the following have been updated:

- Screening visit (section 8.1.1) updated to remove the requirement for subjects to demonstrate ability and willingness to self-inject with a semaglutide placebo test pen as test pens for human use is not used in the rest of the SUSTAIN project.

- Diabetes history and diabetes complication (section 8.2.2) updated to reflect the correct form in the standard templates in the eCRF.

- Concomitant medication (section 8.2.4) updated to reflect the correct form in the standard templates in the eCRF.

- Childbearing potential (section 8.2.6) updated in relation to childbearing potential added.
- Medication error (section 8.4.2) updated to current classification.
- Adverse events requiring additional data collection (section 8.4.3) updated from old terminology (MESI).
- Hypoglycemic episodes (section 8.4.4) updated to current classification.
- Eye examination (section 8.4.6) section updated to current project standards and moved to assessment for safety (section 8.4) due to the fact that eye examination will now be performed at EOT and has been added as a safety endpoint
- Calcitonin (section 8.5.2.4) CMC no longer required.
- Pregnancy test (section 8.5.2.5) updated with better description.
- In case of specific safety issues (section 8.8) section has been deleted as the description is already contained in appendix B and central pathologist for thyroidectomy is no longer used

2.11 Trial Supplies (section 9)

Rationale: semaglutide placebo test pen has been removed as subjects will no longer demonstrate ability and willingness to self-inject with a semaglutide placebo test pen as test pens for human use is not used in the rest of the SUSTAIN project.

2.12 Interactive voice/web response system (section 10)

Rationale: detail regarding using barcode scanner is added.

2.13 Adverse events and technical complaints and pregnancies (section 12)

Rationale: In this section the following have been updated:

- Serious adverse event (section 12.1.1) definitions that always must be added as SAEs added (including Hy's law).
- Medications errors (section 12.1.3) updated to current standards.
- Adverse events requiring additional data collection (section 12.1.4) section updated from older terminology and diabetic retinopathy, laboratory outlier and hepatic event added according to current project standards.
- Events adjudication committee (section 12.7.2) updated to current project definitions.

- Calcitonin monitoring committee (section 12.7.3) deleted as no longer required.

2.14 Statistical considerations (section 17)

Rationale: In this section the following have been updated

- Definitions of treatment discontinuation and withdrawal from trial have been clarified and specified according to current project standards.

- FAS and SAS (section 17.2) updated to current project definitions according to current project standards.

- The concept of observation periods has been introduced to further clarify data selections for all analyses. The observation periods specified include: an in-trial, an on-treatment, and an on-treatment without rescue medication observation period (section 17.2), all in line with current project standards.

- Specified observation periods added to clarify the data foundation for analyses (section 17.3) according to current project definitions.

- Number of imputations in the multiple imputation analysis has been increased from 100 to 500 according to current project decision. This has been done based on experience obtained from the completed phase 3a trials to further reduce the sample variation in analysis results.

- Due to that patient-reported outcomes (PRO) only will be assessed at baseline and at end-of-trial the analyses model for the PRO outcomes has been changed from a MMRM to an ANCOVA. In contrary, due to that the SMPG 7-point profile also will be assessed at an intermediate trial visit the analysis has been changed from an ANCOVA to a MMRM (section 17.4.2.2). Both changes are in accordance with current project standards.

- Evaluation of safety endpoints (section 17.4.2.2) have been clarified in context of the specified observation periods and, hence, aligned with the current project standards.

- Eye examination (section 17.4.2.2) added to align with section 4 and the additional safety assessment included.

- The definition of treatment emergent adverse events and hypoglycaemic episodes has been clarified in context of the on-treatment observation period and, hence, aligned with the current project definitions (section 17.4.2.2).

- Novo Nordisk classification of hypoglycaemia (section 17.4.2.2, Figure 17-1) figure describing Novo Nordisk classification of hypoglycaemia has been added.

2.15 References (section 27)

Rationale: References updated according to the update of the protocol.

3 Changes to the SI/IC

3.1 Introduction section

Rationale:
New country allocation has been approved by GTA since protocol was approved in 2014.
Impact:
The trial is planned to include a total of approximately 1050 subjects in *5*~~6~~ countries.

3.2 Purpose of the trial

Rationale:
Clinical trials investigating efficacy have been completed since protocol was approved in 2014.
Impact:
Some clinical trials have already been completed to investigate the *efficacy and* safety of semaglutide so far.

3.3 Procedures if you participate in the trial

Physical examination:

Rationale:
To align with the CDISC terminology.
Impact:
You will be asked some general questions about your health, medical conditions, ~~smoking habits~~ *tobacco use* and your current medication (other medication than the trial products) and previous diabetes treatment.

Rationale:
Section was updated to be in alignment with Semaglutide project standards on eye examination.
Impact:
You will also go through a general examination of your body, have a heart examination (electrocardiogram) and an eye examination (fundus photography or *dilated* fundoscopy) performed.

Fasting visits:

Rationale:
To align with the fasting requirement for the other SUSTAIN protocols
Impact:
Fasting is defined as having consumed only water *within the last 6 hours prior to the visit* ~~since midnight~~. Trial products and any other *anti-diabetic* medication ~~which should be taken with or after~~

~~a meal~~ should be withheld on the day of the visit until blood sampling has~~ve~~ been taken. *Other medication should be taken as prescribed.*

Body measurements:

Rationale:
Wrong visit number
Impact:
Height will be measured only once at visit ~~1~~*2*, weight and waist circumference will be measured from visit 2 and forward.

Blood samples:

Rationale:
Amount of blood drawn was not defined in the protocol approved in 2014.
Impact:
You will have blood samples drawn from the arm and approximately ~~xxx~~*130* ml blood will be drawn in total for all visits.

Pregnancy test:

Rationale:
To align with the phrasing in other SUSTAIN protocols
Impact:
If you are female of childbearing ~~age~~ *potential* the blood sample will also include a pregnancy test.

Urine samples:

Rationale:
Deletion of typo and aligning wording to other SUSTAIN protocols
Impact:
The urine will be used to access your kidney function. You will receive material to collect the first morning ~~your~~ urine at home and bring it to the clinic. During the trial urine pregnancy tests must be performed at home if you are female of childbearing ~~age~~ *potential* and a menstrual period is missed or as required by local law.

Eye examination:

Rationale:
Eye examination added as supportive secondary safety endpoint and will be performed at EOT.

Impact:
An eye examination called fundosphotography or *dilated* fundoscopy should be performed. If you have a recent ~~fundoscopy or fundosphotography~~ *eye examination* performed within 90 days prior to visit 2 this will be acceptable if the results are available for evaluation at visit 2.

An eye examination will also be performed at your end of treatment visit.

Self measured plasma blood sugar (named SMPG 7 point profile):

Rationale:
Wrong listing of visit numbers.
Impact:
You will also be asked to measure your own blood sugar values seven times (see Diaries below) prior to visit 2, *visit 7 and visit 9* and record the values in a diary.

Diaries:

Rationale:
To be aligned with update of protocol and diaries.
Impact:

- Date, time *and* dose ~~and site~~ of first dose of ~~injection~~ trial product*s (injection and tablet)*
- ~~Date, time and dose of first tablet~~

3.4 Overview of the procedures

Rationale:
To align with updates of protocol and CDISC terminology.
Impact:

Trial Periods			Treatment period						End of Treat-ment	Follow Up	End of Treatment premature disconti-nuation	Follow Up premature disconti-nuation
Visit (V) or Phone (P) number	V 1	V 2	V 3	P 4	V 5	V 6	V 7	V 8	V9	V10	V9A	V10A
Weeks in relation to visit 2	-2	0	4	6	8	12	16	23	30	35		
Fasting visits		x	x		x	x	x	x	x	x	x	x
Informed consent	x											
Dispense trial identity card	x											
Physical examination	x								x		x	
Randomisation		x										
Medical History	x											
~~Diagnosis of diabetes and treatment history~~ *Diabetes history and diabetes complication*	x											

Trial Periods			Treatment period						End of Treat-ment	Follow Up	End of Treatment premature disconti-nuation	Follow Up premature disconti-nuation
Visit (V) or Phone (P) number	V 1	V 2	V 3	P 4	V 5	V 6	V 7	V 8	V9	V10	V9A	V10A
Concomitant medication	x	x	x	x	x	x	x	x	x	x	x	x
~~Smoking habits~~ *Tobacco use*	x											
Body measurements		x	x		x	x	x	x	x		x	
Vital signs	x	x	x		x	x	x	x	x		x	
ECG		x							x	x	x	x
Blood samples	x	x	x		x	x	x	x	x	x	x	x
Pregnancy test	x	x	x		x	x	x	x	x	x	x	x
Urinalysis		x					x		x		x	
Eye examination		x							*x*		*x*	
SMPG 7 point profile		x					x		x		x	
Adverse events		x	x	x	x	x	x	x	x	x	x	x
2 questionnaires		x							x		x	
Supply & instruction in BG meter use	x											
Training in trial product and pen handling		x	*x*		x		~~x~~					
Receive trial products		x			x		x					
Return trial products					x		x		x		*x*	
Receive diary and instruction for use	x	x	x		x	x	x	x	x	x	x	x

3.5 Premature discontinuation of trial product

Rationale:
To clarify the term discontinuation.

Impact:
In addition to those visits *you are encouraged to* ~~it is important that you~~ attend the scheduled visits ~~approximately 30 and 35 weeks after first dose of trial product~~.

3.6 Stop participating in the trial

Rationale:
Text was deleted, as it was misleading.

Impact:
If for any reason you decide to stop your participation in the trial (see section 1.8), you will need to inform the trial staff who will encourage you to come in for the end of treatment visit as soon as possible and the follow-up visit 5 weeks later for safety evaluation~~., and also encourage you to continue with the scheduled vists.~~

3.7 In case of thyroid surgery during the trial

Rationale:
It has been agreed not to collect information on thyroid surgery during the trial.
Impact:
~~If for any reason you are scheduled to have an operation to remove your thyroid gland or part of it during the trial, you need to inform your trial doctor well in advance. You will be asked to consent to another subject information form to allow for additional safety assessment to be made.~~
~~Samples of the removed thyroid tissue will be investigated. Such tissue samples are routinely made after operations of the thyroid gland of the hospital where the operation is performed. The tissue samples will allow specialists at your hospital to examine the thyroid cells under the microscope in order to determine the exact diagnosis. The tissue samples will be sent to another expert for a second opinion. When the tissue samples have been examined they will be sent back to the hospital where you had your operation. Your trial doctor will be informed about the findings of both the hospital specialist and the expert and you will be able to discuss the results with him/her.~~

3.8 Information about the treatment procedure

Rationale:
Test pens will not be provided.
Impact:
~~If you do not have experience with injecting medicine yourself, you will have the option to try this at the trial clinic with a test pen containing semaglutide placebo.~~

3.9 Information about the Risks/Benefits

Rationale:
To align with the newest MMST for Semaglutide, which has been updated to version 11.0.
Impact:
The entire section on Semaglutide was re-written in alignment with the MMST.
The entire section on Sitagliptin was re-written according to newest safety text provided by Global Safety representative.

3.10 Confidential information

Rationale:
To meet local requirements to obtain export license of samples out of the country.
Impact:
In order to standardise the sample analysis used in this trial, some samples including yours, will be shipped to a special laboratory outside of your country. This is to ensure the comparability of results from subjects at all investigational sites involved in the trial.

3.11 Short summary

Rationale:
Text has been changed, as it was misleading.
Impact:
Your ~~discontinuation~~ *withdrawal* will not affect the standard of care that you receive.

3.12 Informed Consent form

Rationale:
To allow a legally acceptable/authorised representative to consent for the subject.
To ensure subject related information can be obtained from other sources than trial doctor.
Impact:

- I *or my legally acceptable/authorised representative* will receive a copy of this subject information/informed consent form signed and dated to bring home.
- *I accept that the trial doctor may obtain trial relevant information from other sources, for example my primary physician (family doctor).*

3.13 Signature page

Rationale:
To allow a legally acceptable/authorised representative to consent for the subject.
Impact:
Impartial Witness and/or legal representative, if applicable:

Date: _____ *Signature:* _____

Name (print): _____

3.14 Signature page to allow your trial doctor to contact your family doctor at end of trial

Rationale:
This part was moved to the Informed Consent Form.
Impact:
The entire section has been deleted.

4 Changes to SI/IC for male partner

4.1 Information about adverse effects on the developing offspring during pregnancy in animal studies

Rationale:
Safety text on Semaglutide has been updated
Impact:
In animal studies, semaglutide caused reduced food intake and less weight gain during pregnancy. In rats, bone and blood vessel abnormalities were observed in the offspring at doses below a normal human dose. In rabbits and monkeys, a possible link between an excessive weight loss of the pregnant animal and observations of early pregnancy loss and foetal abnormalities could not be excluded. The potential risk for an unborn human child is unknown and therefore pregnancy should be avoided when taking semaglutide.
~~The effect of semaglutide on fertility and foetal development has been investigated in rats and monkeys. In both species exposure to semaglutide caused reduction of the amount of food eaten and weight gained by the mother during pregnancy. The monkey studies gave no reason to suspect an effect of semaglutide on foetal development in monkeys, but there was a possible link between the mother's loss of body weight and an increased risk for early pregnancy loss. In rats, bone and major blood vessel abnormalities were observed in the offspring at doses below a normal human dose. The potential risk to humans is unknown and therefore pregnancy should be avoided when taking semaglutide.~~

4.2 Informed consent form

Rationale:
To allow a legally acceptable/authorised representative to consent for the subject.
Impact:

- I *or my legally acceptable/authorised representative* will receive a copy of this subject information/informed consent form signed and dated

Protocol Amendment

no 2
to Protocol, final version 2.0
dated 28 October 2016

Trial ID:NN9535-4114

SUSTAIN – CHINA MRCT

Efficacy and safety of semaglutide once-weekly versus sitagliptin once daily as add-on to metformin in subjects with type 2 diabetes

Trial phase: 3a

Applicable to all countries

Amendment originator:

[redacted]

Semaglutide Diabetes & Diabetes Outcomes

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1 Introduction including rationale for the protocol amendment

Protocol amendment and protocol version 2.0 were finalised on 28 October 2016. On 31 October GTA finalised reallocation of 60 subjects from China to Hong Kong and Taiwan. The subjects will be grouped together with Chinese subjects in the stratification and analysis. The protocol amendment has been created to specify this information in the protocol.

Additionally, minor refinements have been made and insurance text in SI/IC has been updated.

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 Milestones (section 7)

Rationale:
Timelines updated to include visit windows.

Impact:
Planned date for last patient last visit (LPLV): *19*~~05~~-Nov-2018

2.2 Biochemistry (section 8.5.2.2)

Rationale:
Added to specify that GFR, estimated (per MDRD formula), should be calculated in this trial.
Added to be in alignment with exclusion criteria 11.

Impact:
- Creatinine*, including eGFR (per MDRD formula)*

2.3 Randomisation procedure and breaking of blinded codes (section 11)

Rationale:
To clarify that the subjects allocated to Taiwan and Hong Kong will be grouped together with the Chinese subjects in the stratification, to support the regulatory submission to Chinese HA (CFDA).

Impact:

Randomisation will be stratified by country. *When grouping or analysing data by country, subjects from Hong Kong and Taiwan will be grouped with Chinese subjects if not otherwise specified.*

2.4 Statistical considerations (section 17)

Rationale:
To clarify that the subjects allocated to Taiwan and Hong Kong will be grouped together with the Chinese subjects, to support the regulatory submission to Chinese HA (CFDA).

Impact:
Non-inferiority between two treatments will be evaluated by comparing the upper limit of the associated two-sided 95% confidence interval for the difference with the pre-defined non-inferiority margin.

When grouping or analysing data by country, subjects from Hong Kong and Taiwan will be grouped with Chinese subjects if not otherwise specified.

2.5 Primary analysis (section 17.3)

Rationale:
To clarify that the subgroup analysis will be focused on Chinese and Korean subjects to support NDA submission in China and Korea.

Impact:

Chinese/Korean subgroup analyses

~~A number of s~~Subgroup analyses *for the primary endpoint and the confirmatory secondary endpoint* ~~by country~~ will be performed *by country* with the aim to assess the treatment effect in ~~the individual countries including~~ China and Korea. They will be performed in a combined model using all data similar to the main analysis of the respective parameter but with an interaction between treatment and country. *In addition the safety in China and Korea will be assessed.*

3 Changes to the SI/IC

3.1 Financial Issues (section 4)

Rationale:

To include newest SOP template text on liability and insurance, as this was not sufficiently described.

Impact:

~~**Product liability**~~

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

~~If you feel something has gone wrong during the course of this trial, please contact the trial doctor or study nurse staff in the first instance.~~

What if something goes wrong?

If you suffer any injury as a direct result of the administration of the Novo Nordisk trial product under investigation or trial procedures to which you would not have been exposed if you had not participated in this trial, Novo Nordisk will ensure that you receive necessary medical care for such injuries in accordance with local laws. Novo Nordisk assumes liability as sponsor in accordance with the applicable laws and guidelines in the countries where the trial is conducted, unless others have shown negligence. Novo Nordisk has appropriate insurance coverage in place to cover its liability as defined above. If you have any questions or believe that you may have suffered an injury as a result of your participation in the trial or administration of the trial product, you should promptly inform your trial doctor. Some countries have other mandatory 'Compensation for injury' clauses approved by Global Legal that can replace this paragraph without PRC approval.

Protocol Amendment

no 3

to Protocol, version 3
dated 09 December 2016

Trial ID: NN9535-4114

SUSTAIN – CHINA MRCT

Efficacy and safety of semaglutide once-weekly versus sitagliptin once-daily as add-on to metformin in subjects with type 2 diabetes

Trial phase: 3a

Applicable to all countries

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1 Introduction including rationale for the protocol amendment

The sample size calculations for this trial were performed before the results for the phase 3a programme were available and estimated based on limited evidence (phase 2 global data). The semaglutide phase 3a results showed significant reductions in HbA_{1c} and body weight versus all comparators that were larger than assumed, why a reconsideration of the sample size in this trial seems appropriate. The aim is to ensure a sample size that is sufficient to show efficacy for region China (China, Hong Kong and Taiwan). The number of subjects in trial NN9535-4114 can be reduced without compromising the efficacy and safety evaluation
Re-estimating the sample size in this trial is acceptable as it is based on blinded data, thus the integrity of the trial will be maintained.
Reducing the sample size is also considered relevant from an ethical standpoint, and the trial integrity will not be compromised. The number of planned randomised subjects is suggested to be reduced from a total of 1050 subjects to 858 subjects. This mainly affects region China, where the number of planned randomised subjects will be reduced from 792 to 600.

Additionally, minor refinements have been made.

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 Type of trial (section 5.1)

Rationale:

Planned number of subjects to be screened and randomised has decreased in accordance to the new statistical considerations in section 17.

Impact:

A planned total of ~~1050~~ *858* subjects will be randomised whereof approximately ~~792~~ *600* subjects will be from *region* China *(China mainland, Hong Kong and Taiwan).* Randomisation will be stratified by country.

2.2 Number of subjects (section 6.1)

Rationale:

Planned number of subjects to be screened and randomised has decreased in accordance to the new sample size calculations in section 17.

Impact:

Planned number of subjects to be screened (i.e. documented informed consent): Up to ~~1750~~ *1420*

Planned number of subjects to be randomised: ~~1050~~ *858*

Planned number of subjects to complete the trial: ~~840~~ *686*

Planned number of Chinese subjects to be randomised: ~~792~~ *600*

Expected number of Chinese subjects to complete the trial: ~~636~~ *450*

2.3 Milestones (section 7)

Rationale:

Dates have changed in line with the speed of recruitment.

Impact:

Planned duration of recruitment period (i.e. FPFV– LPFV): ~~26~~ *56 weeks*

End of trial is defined as last patient last visit.

Planned date for first patient first visit (FPFV): *28-Aug-2017*

Planned date for last patient first visit (LPFV): ~~26 Feb 2018~~ *27-Aug-2018*

Planned date for last patient last visit (LPLV): ~~19 Nov 2018~~ *20-May-2019*

2.4 Hypoglycaemic episodes (section 8.4.4)

Rationale:

A typographical error was made when a > sign was missed.

Impact:

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 according to the instructions below and section 8.6.2 throughout the trial from V1 to V10/10A.

2.5 Sample size calculation (section 17.1)

Rationale:

The sample size calculations for trial NN9535-4114 were performed before the results for the phase 3a programme were available and estimated based on limited evidence (phase 2 global data). The semaglutide phase 3a results showed significant reductions in HbA_{1c} and body weight versus all comparators that were larger than assumed, why a reconsideration of the sample size in trial NN9535-4114 seems appropriate.

Impact:

The primary objective is to compare the effect of two dose levels of semaglutide once-weekly treatment (0.5 mg or 1.0 mg) with sitagliptin 100 mg on the primary endpoint, change from baseline in HbA_{1c} after 30 weeks of treatment. In the *power* calculations *below* ~~determining the sample size~~ it is presumed that in the analysis the two sitagliptin/semaglutide placebo groups will be pooled assuming no correlation between endpoints and placebo volume.

At the time of finalising the first version of the protocol, the regulatory guidance in China was to have 300 subjects in region China treated with semaglutide. To ensure an adequate and robust evaluation of safety and efficacy in the subjects from China 300 subjects completing treatment with semaglutide is used. In the following, subjects from Hong Kong and Taiwan will be grouped with the Chinese subjects and referred to as region China. Assuming a treatment discontinuation rate of 25% in this region and considering the 2:2:1:1 randomisation, this means that 600 subjects need to be randomised in region China. Trial NN9535-4114 is a multi-regional clinical trial, and 258 subjects are planned to be randomised outside region China as has already been approved by local authorities for these countries. For some countries the allocated subject number is required to support local NDA submissions. In total, 858 subjects are planned to be randomised ~~In total 1050 subjects will be randomised~~ in a 2:2:1:1 manner. Assuming *that* 20% of *all randomised* subjects ~~discontinuing~~ *discontinue* randomised treatment, and further taking the assumption that these subjects are excluded from the per protocol (PP) analysis set, ~~280~~ *228* subjects in each group are expected to be included in the PP analysis set.

~~The sample size calculation is based on demonstrating HbA_{1c} non-inferiority for semaglutide 0.5 mg vs. sitagliptin 100 mg and HbA_{1c} non-inferiority for semaglutide 1.0 mg vs. sitagliptin 100 mg.~~

In total six confirmatory hypotheses are to be tested (see section 17.3). The ~~two~~ *six* hypothesis tests are assumed to be independent and for each of the hypotheses the power calculation is based on a t-statistic under the assumption of a one-sided test of size 2.5%.

Using a non-inferiority margin of 0.3%-*point*, ~~and assuming a true HbA_{1c} difference (semaglutide minus sitagliptin) of 0% and~~ a standard deviation (SD) of 1.1%-*point and* a total of ~~280~~ *228* subjects per group in the PP analysis set will give 90% marginal power to conclude HbA_{1c} non-inferiority for the comparison of a semaglutide dose vs. sitagliptin 100 mg *if the true HbA_{1c} treatment difference (semaglutide minus sitagliptin) is as low as -0.03 %-point. Thereby,* ~~Assuming the same HbA_{1c} effect for the two dose levels of semaglutide,~~ the overall power to demonstrate HbA_{1c} non-inferiority for the two dose levels of semaglutide vs. sitagliptin will be at least 80%, *even if the true treatment difference for the low dose comparison is as low as -0.03 %-point. With 286 subjects per group in the full analysis set (FAS), a marginal power of at least 90% for demonstrating HbA_{1c} superiority, for any dose of the two dose level comparisons, is obtained if the true treatment difference is as low as -0.30%-point.*

For change in body weight, using a SD of 4 kg and 286 subjects per group, a marginal power of at least 90% for demonstrating superiority for the comparison of a semaglutide dose vs. sitagliptin 100 mg is obtained if the true treatment difference is as low as -1.09 kg body weight.

~~For change in body weight, the power calculation is based on the assumptions of a true difference of -1.5 kg and a SD of 4.0 kg. In addition, 50% efficacy retention is assumed for the anticipated 20% of subjects discontinuing randomised treatment giving an expected treatment difference of -1.35 kg, which is the number used in the power calculation. With the above assumptions, a total of 350 subjects per group in the full analysis set (FAS) will give more than 99% marginal power to conclude superiority in body weight for the comparison of a semaglutide dose vs. sitagliptin 100 mg.~~

In SUSTAIN 2, the mother trial of NN9535-4114, semaglutide showed marked and significant reductions in HbA_{1c} and body weight vs sitagliptin at week 56. The change over time in HbA_{1c} and body weight in SUSTAIN 2 showed marked reductions in both endpoints already at week 30 which supports that the above mentioned true treatment differences for trial NN9535-4114.

2.6 Retention of human biospecimens (section 24.2)

Rationale: A typographical error was made when "thyroid tissue" was not removed from the previous version of the protocol.

Impact:

None of the data will be identified by name. Antibody samples ~~and thyroid tissue~~ will be identified only by a subject number, a visit number and a trial identification number.