Cover Page for Protocol

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16.1.1 Protocol and protocol amendments

List of contents

Protocol

Protocol title: Efficacy and safety of co-administration of cagrilintide s.c. 2.4 mg and semaglutide s.c. 2.4 mg once weekly in subjects with type 2 diabetes

Substance name: cagrilintide, semaglutide

IND Number: 155796

Universal Trial Number: U1111-1266-2931

Trial phase: 2

In the following, Novo Nordisk A/S and its affiliates will be stated as "Novo Nordisk".

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1 Protocol summary

1.1 Synopsis

Rationale:

Weight loss is recommended for type 2 diabetes (T2D) management, as it reduces fat accumulation in liver and pancreas, leading to improved insulin secretion and insulin sensitivity. Weight loss in patients with T2D with overweight or obesity is associated with a decrease in HbA_{1c}. Combined administration of the long-acting amylin analogue cagrilintide and the glucagon-like peptide-1 (GLP-1) receptor agonist semaglutide was investigated in a phase 1 trial (NN9838-4395) and associated with a substantial weight loss compared to semaglutide alone in individuals with overweight and obesity without T2D. Treatment with semaglutide is well-established in T2D to secure good glycaemic control and is approved worldwide under this indication. One short-acting amylin agonist is currently approved for treatment of type 1 diabetes (T1D) and T2D. A combination of a long-acting amylin agonist and semaglutide could lead to not only substantial weight loss but potentially also an improved glycaemic control in subjects with T2D. Consequently, it is relevant to investigate whether a greater improvement in glycaemic control as measured by a decrease in HbA_{1c} is observed after combined administration of cagrilintide and semaglutide compared to semaglutide or cagrilintide alone.

Objectives and endpoints:

Primary objectives

To compare the effect of co-administered semaglutide and cagrilintide versus semaglutide in subjects with T2D inadequately controlled on metformin with or without SGLT2 inhibitor on:

- change from baseline (week 0) to week 32 in HbA_{1c} (%-point)

Secondary objectives

To compare the effect of co-administered semaglutide and cagrilintide versus semaglutide in subjects with T2D inadequately controlled on metformin with or without SGLT2 inhibitor on:

- other parameters for glycaemic control
- body weight

To compare the effect of co-administered semaglutide and cagrilintide versus cagrilintide in subjects with T2D inadequately controlled on metformin with or without SGLT2 inhibitor on:

- HbA_{1c}
- other parameters for glycaemic control
- body weight

To compare the effect of co-administered semaglutide and cagrilintide, semaglutide and cagrilintide in subjects with T2D inadequately controlled on metformin with or without SGLT2 inhibitor on:

- safety and tolerability
- hypoglycaemia

Primary endpoint

Endpoint title	Time frame	Unit
Change in HbA_{1c}	From baseline (week 0) to week 32	%-point

Primary estimand

The primary estimand addresses the main question of interest: What is the effect of co-administered semaglutide and cagrilintide versus semaglutide on HbA_{1c} (%-points) from baseline to week 32 in subjects with T2D inadequately controlled on metformin with or without SGLT2 inhibitor, had all subjects remained on trial treatment without use of rescue medication (anti-diabetic). A hypothetical strategy is applied for both intercurrent event of premature treatment discontinuation and initiation of rescue medication. The population level summary is difference in means.

The primary estimand estimates the achievable treatment effect without the confounding of treatment discontinuation and initiation of rescue intervention. This approach is considered relevant for evaluating a mechanistic effect.

Overall design:

This is a 32-week, randomised, double-blind, active-controlled, three-arm, parallel group, multicentre clinical trial. The trial will compare the efficacy and safety of co-administration of cagrilintide subcutaneus (s.c.) 2.4 mg and semaglutide s.c. 2.4 mg versus semaglutide s.c. 2.4 mg monotherapy and versus cagrilintide s.c. 2.4 mg monotherapy in subjects with T2D.

Subjects will be randomised to 1 of the 3 treatment arms in a ratio of 1:1:1.
Randomisation will be stratified according to the SGLT2 inhibitor treatment (Yes/No).

Key inclusion criteria:

- Female of non-childbearing potential or male
- Age above or equal to 18 years at the time of signing informed consent
- Body mass index (BMI) $\geq$ 27.0 kg/m^2
- Diagnosed with type 2 diabetes mellitus $\geq$ 180 days before screening
- HbA_{1c} of 7.5-10.0% (58-86 mmol/mol) (both inclusive) as assessed by central laboratory at screening
- Stable daily dose(s) $\geq$ 90 days before screening of the following antidiabetic drug(s) or combination regimen(s) at maximum tolerated or effective dose as judged by the investigator: metformin with or without SGLT2 inhibitor

Key exclusion criteria:

- Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria within 90 days before screening. However, short term insulin treatment for a maximum of 14 days and prior insulin treatment for gestational diabetes are allowed
- Renal impairment with estimated Glomerular Filtration Rate (eGFR) < 60 ml/min/1.73m^2 by central laboratory at screening
- Uncontrolled and potentially unstable diabetic retinopathy or maculopathy. Verified by a fundus examination performed within 90 days before screening or in the period between

screening and randomisation. Pharmacological pupil-dilation is a requirement unless using a digital fundus photography camera specified for non-dilated examination

Number of subjects:

Approximately 90 subjects will be randomly assigned to trial product.

Treatment groups and duration:

The trial includes a minimum 10-day screening period to assess the subject's eligibility, a 32-week treatment period and a 5-week follow up period. The 32-week treatment period consists of a 16-week dose escalation period and a 16-week maintenance period. The planned total trial duration for the individual subject is approximately 39 weeks.

The following trial products will be supplied by Novo Nordisk A/S for the duration of the trial:

- Semaglutide B 3.0 mg/mL PDS290 pre-filled pen-injector and semaglutide placebo, solution for injection, 3 mL PDS290 pre-filled pen-injector
- Cagrilintide A 10 mg/mL and cagrilintide placebo, solution for injection, 3 mL under-filled cartridge, 1 ml solution for injection to be used with NovoPen Echo®

Data monitoring committee:

Not applicable for this study.

1.2 Flowchart

	Screening	Randomisation	Dose escalation period								Maintenance period					End of treatment	End of trial
Visit/Phone	V1	V2	P3	V4	P5	V6	P7	V8	P9	V10	V11	V12	P13	V14	V15	V16	V17
Timing of Visit (Weeks)	-2	0	2	4	6	8	10	12	14	16	18	20	24	28	30	32	37
Visit Window (Days)	+4	±0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	0 to +5
Informed Consent and Demography[a] (10.1.3)	X																
Eligibility Criteria (5.1 and 5.2)	X	X															
Medical History/Concomitant Illness (8.2)	X																
Childbearing Potential[b] (10.4)	X																
Tobacco Use (5.3.2)	X																
Randomisation		X															
Concomitant Medication (6.5)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test[c] (10.4)	X	X		X		X		X		X		X	X	X		X	X
Hand out home pregnancy tests[c] (10.4)		X										X				X	
Body Weight (8.1.1)	X	X		X		X		X		X		X		X		X	
Height (8.1.1)	X																
Physical Examination (8.2.1)	X															X	
Eye Examination (8.2.4)	X															X	
Vital Signs (8.2.2)	X	X		X		X		X		X		X		X		X	
Electrocardiogram (ECG) (8.2.3)		X										X				X	
Attend Visit Fasting (5.3.1)		X		X		X		X				X				X	
Laboratory Assessments (10.2)	X	X		X		X		X				X		X		X	X
Pharmacokinetics (PK) samples (8.5)				X		X						X				X	
Continuous glucose monitoring (CGM) fitted to subject (8.1.2)	X										X				X		
CGM removed/returned from subject (8.1.2)		X										X				X	
Adverse Event incl. hypoglycaemic episodes (8.3 and 10.3)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	Screening	Randomisation	Dose escalation period								Maintenance period					End of treatment	End of trial
Visit/Phone	V1	V2	P3	V4	P5	V6	P7	V8	P9	V10	V11	V12	P13	V14	V15	V16	V17
Timing of Visit (Weeks)	-2	0	2	4	6	8	10	12	14	16	18	20	24	28	30	32	37
Visit Window (Days)	+4	±0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	0 to +5
Hand Out ID Card	X																
Hand Out and Instruct in Diaries		X		X		X		X		X		X		X			
Hand Out Direction for Use (6.1)		X															
Hand Out and Instruct in BG-meter (10.7)		X															
Training in Trial Product, Pen-handling		X		X		X		X		X		X					
Hand Out Dose Reminder Card		X		X		X		X		X		X					
Dispensing Visit		X		X		X		X		X		X		X			

[a] Demography consists of date of birth, sex, ethnicity, and race (according to local regulation).

[b] Only for female subjects.

[c] Only postmenopausal female subjects who have stopped menstruating within the last 5 years. A pregnancy test should be performed every 4 weeks and at the End of trial (5 weeks after end of treatment) (refer to Appendix 2, Section 10.2 and Appendix 4, 10.4).

2 Introduction

Diabetes mellitus is a metabolic disorder characterised by the presence of hyperglycaemia due to defective insulin secretion, insulin action or both. Chronic hyperglycaemia of diabetes mellitus is associated with significant long-term complications, particularly damage, dysfunction and failure of various tissues – especially the kidney, eye and nerves.[1] Diabetes is generally classified according to aetiological factors, where T1D and T2D constitute the vast majority of cases. In the International Diabetes Federation's Diabetes Atlas (2019), the estimated worldwide diabetes prevalence was 463 million, with a prediction that by 2045, the number of people with diabetes will have increased to 700 million.[2]

The purpose of the present trial is to investigate the efficacy and safety of the combination of the GLP-1 receptor agonist (GLP-1 RA), semaglutide and amylin analogue, cagrilintide (international nonproprietary name), both administered once weekly.

GLP-1 is an incretin hormone released from intestinal L-cells with a glucose-dependent stimulatory effect on insulin and inhibitory effect on glucagon secretion from the pancreatic islets.[3] GLP-1 is a physiological regulator of appetite and GLP-1 receptors are present in several areas of the brain involved in appetite regulation.[4] Treatment with GLP-1 receptor agonists lowers body weight and reduces HbA_{1c}.[4] Semaglutide s.c. is a once-weekly GLP-1 receptor agonist approved for the treatment of adults with T2D at doses of 0.5 and 1.0 mg (Ozempic®). Once-weekly semaglutide s.c. has recently been submitted for regulatory review at dose of 2.0 mg for additional glycaemic control for adults with T2D, and at dose of 2.4 mg for weight management in adults.

Endogenous amylin is a neuroendocrine peptide hormone that is co-secreted with insulin from pancreatic beta-cells in response to food intake. Studies indicate that endogenous amylin is involved in the central regulation of food intake and body weight.[5] Pramlintide (Symlin®) is a short-acting amylin analogue which was approved in 2005 in the United States (US) as a mealtime adjunct treatment to insulin in patients with T1D and T2D to control blood glucose.[6] Pramlintide has been shown to slow gastric emptying and to suppress post-prandial glucagon release.[7] Cagrilintide is a long-acting amylin analogue with agonistic effects on amylin receptors. The weight loss potential of cagrilintide has been investigated in a phase 2 trial and the combination with semaglutide has been investigated in a phase 1 trial. The results collectively indicated that the combination has the potential to offer substantially greater weight loss than either monotherapy.

2.1 Trial rationale

Weight loss is recommended in clinical practice guidelines for T2D management,[8, 9] as it reduces fat accumulation in liver and pancreas, leading to improved insulin secretion and insulin sensitivity.[10] Weight loss in patients with T2D with overweight or obesity is associated with a decrease in HbA_{1c}.[11]

Based on the weight-lowering effect of combining cagrilintide and semaglutide, the established effect of semaglutide on glycaemic control as well as the potential involvement of amylin agonists in glucose metabolism, it is relevant to investigate whether a greater improvement in glycaemic control as measured by a decrease in HbA_{1c} is observed after combined administration of cagrilintide and semaglutide compared to semaglutide or cagrilintide alone.

2.2 Background

Semaglutide

Semaglutide s.c. is a once-weekly GLP-1 receptor agonist approved for the treatment of adults with T2D at doses of 0.5 and 1.0 mg (Ozempic®). Once-weekly semaglutide s.c. has recently been submitted for regulatory review at dose of 2.0 mg for additional glycaemic control for adults with T2D, and at dose of 2.4 mg for weight management. Semaglutide has a half-life of approximately 160 hours, making it suitable for once-weekly dosing.[12]

In the phase 3 development programme for semaglutide s.c. 0.5 and 1.0 mg (the SUSTAIN programme), semaglutide provided superior long-term glycaemic control and body weight reduction as compared to commonly used marketed products across the spectrum of patients with T2D, ranging from treatment-naïve to insulin-treated. The safety profile of semaglutide is well-documented based on data from the nonclinical and clinical development programmes, and is consistent with the safety profile of other drugs within the GLP-1 RA drug class.[13, 14]

The SUSTAIN FORTE trial (NN9535-4506) included 961 people with T2D. In the trial, people treated with semaglutide 2.0 mg achieved a superior reduction in HbA_{1c} compared to semaglutide 1.0 mg. Both doses of semaglutide appeared to have safe and well-tolerated profiles. The most common adverse events were gastrointestinal, the vast majority were mild to moderate and diminished over time and were consistent with the GLP-1 receptor agonist class. Compared to semaglutide 1.0 mg, the gastrointestinal adverse events were similar for semaglutide 2.0 mg.[15]

A global phase 3a clinical development programme with semaglutide s.c. 2.4 mg once weekly has been completed in people with overweight or obesity (STEP programme). The largest trial (NN9536-4373; STEP1) included 1,961 adults with obesity or overweight with comorbidities. Subjects treated with semaglutide s.c. 2.4 mg once weekly achieved significantly greater weight loss (14.9%) after 68 weeks compared to placebo (2.4%), both in conjunction with lifestyle intervention.[16] In a trial with 1,210 adults with BMI ≥27 kg/m^2 and T2D (NN9536-4374; STEP 2) a significantly greater weight loss was achieved with semaglutide s.c. 2.4 mg once weekly (9.6%) vs. semaglutide s.c. 1.0 mg (7.0%) and vs. placebo (3.4%); all in conjunction with lifestyle intervention.[17] The safety profile of semaglutide s.c. 2.4 mg once weekly was consistent with that seen previously with semaglutide once weekly in type 2 diabetes,[18] and with the established profile of the GLP-1 receptor agonist class.[19, 20] The most common adverse events among people treated with semaglutide 2.4 mg once weekly were gastrointestinal events.[16, 17]

A comprehensive review of results from the nonclinical and clinical studies of semaglutide s.c. 2.4 mg once weekly can be found in the current edition of the investigator's brochure (IB)[21] and any updates hereof.

Cagrilintide

Cagrilintide is a long-acting amylin agonist under investigation for the treatment of subjects with overweight and obesity, as well as subjects with T2D. The half-life of cagrilintide is approximately 180 hours indicative of a pharmacokinetics (PK) profile suitable for a once-weekly dosing regimen.

A phase 2 dose-finding trial has been completed for cagrilintide (NN9838-4433). The 26-week blinded phase 2 monotherapy trial with cagrilintide s.c. investigated safety, tolerability and efficacy for weight management in 706 adults with obesity or overweight with at least one weight-related comorbidity. The subjects were randomised equally to once-weekly treatment with five different doses of cagrilintide s.c. (0.3 mg, 0.6 mg, 1.2 mg, 2.4 mg, 4.5 mg), placebo once weekly or liraglutide 3.0 mg once daily, in conjunction with lifestyle intervention. Based on the primary endpoint, the weight loss observed for all cagrilintide doses was significantly greater than for placebo. From a baseline weight of approximately 100 kg, treatment with 2.4 mg and 4.5 mg s.c. cagrilintide resulted in a weight loss of 9.7% and 10.8% at week 26, respectively, compared to a weight loss of 3.0% with placebo. Cagrilintide had a safe and well-tolerated profile with the most frequently reported adverse events being gastrointestinal (non-serious and mild to moderate in severity) and injection site reactions (all non-serious and mild to moderate in severity).

A comprehensive review of results from the nonclinical and clinical studies of cagrilintide can be found in the current edition of the IB[22] and any updates hereof.

Combination trial

Results are available from a multiple-ascending dose trial investigating the safety, tolerability and PK properties of 6 cagrilintide doses (0.16 mg up to 4.5 mg per week) administered in combination with the same semaglutide dose (2.4 mg per week) as separate s.c. injections (NN9838-4395). A 20-week treatment period was applied including a 16-week dose-escalation period followed by 4 weeks at the target dose. The results demonstrated that cagrilintide was well-tolerated in combination with semaglutide 2.4 mg with the most frequent adverse events related to gastrointestinal intolerance and injection site reactions. No new safety concerns were identified for the combination compared to the safety profile of the mono-components. After 20 weeks of treatment, subjects receiving 2.4 mg cagrilintide in combination with 2.4 mg semaglutide lost an average of 17.1% of body weight while a weight loss of 9.8% was observed for semaglutide 2.4 mg monotherapy. Hence, an additional weight loss was observed when combining 2.4 mg cagrilintide and 2.4 mg semaglutide treatment.

A comprehensive review of results from the nonclinical and clinical studies of cagrilintide in combination with semaglutide can be found in the current edition of the cagrilintide IB[22] and any updates hereof.

2.3 Benefit-risk assessment

Main benefits and risks are described in the below sections. More detailed information about the known and expected benefits and risks and reasonably expected adverse events of cagrilintide or semaglutide may be found in the IBs[21, 22] and any updates thereof.

2.3.1 Risk assessment

Table 2-1 Risk assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Trial treatment		
Gastrointestinal (GI) adverse event (AE) cagrilintide, semaglutide	GI AEs such as nausea, vomiting and diarrhoea have been identified for both cagrilintide and semaglutide. The frequency of GI AEs appears to be dose-dependent and affected by dose escalation schedules (see IBs[21, 22]) In general, these reactions were mild or moderate in severity. In subjects treated with GLP-1 RAs, nausea, vomiting and diarrhoea may lead to significant dehydration. This should be considered when treating subjects with impaired renal function as it may cause a deterioration of renal function.	Clinical studies with cagrilintide and with semaglutide have shown that a low starting dose and gradual dose escalation mitigates the risk of developing GI symptoms. Subjects with GI symptoms are recommended to drink plenty of fluids to avoid volume depletion.
Cholelithiasis semaglutide	Events of cholelithiasis were the most frequently reported gallbladder events in the STEP clinical development programme for semaglutide s.c. 2.4 mg for weight management. In the phase 3a studies cholelithiasis was reported in 1.6% and led to cholecystitis in 0.6% of patients treated with semaglutide 2.4 mg. The increased risk of cholelithiasis with semaglutide s.c. 2.4 mg appeared to be at least partly explained by the larger weight loss.	Subjects should be informed of the characteristic symptoms of cholelithiasis. If cholelithiasis is suspected, appropriate clinical follow-up is to be initiated at the investigator's discretion.
Injection site reactions cagrilintide, semaglutide	Injection site reactions are always a risk with injectable protein molecules incl. peptides. Injection site reactions such as rash, erythema and pruritis were observed in the phase 2 trial (NN9838-4433) more frequently with cagrilintide compared to placebo. Injection site reactions such as pain, bruising and haematoma were reported by similar proportions of subjects with semaglutide 2.4 mg and placebo in the STEP clinical development programme. Few events led to permanent treatment discontinuation	As for all injectables, rotation of injection site is recommended. Injection site reactions will be monitored, and additional information collected on event specific form in the eCRF (see Appendix 3, Section 10.3).
Hypersensitivity cagrilintide, semaglutide	As is the case with all protein-based pharmaceuticals, subjects treated with cagrilintide and semaglutide are at risk of developing immunogenic and allergic reactions[22], including serious adverse reactions such as angioedema and anaphylactic reactions.	As a precaution, subjects with known or suspected hypersensitivity to cagrilintide, semaglutide or related products will not be enrolled in the trial (see Section 5.2). In addition, subjects will be instructed to contact the site staff as soon as possible for further guidance if suspicion of a systemic hypersensitivity reaction to the trial product occurs (see Section 8.3.7).

Activation of the Renin-Angiotensin-Aldosteron System cagrilintide	Treatment with cagrilintide has been associated with increased mean levels of aldosterone and renin, within normal range. No stimulatory effect on blood pressure, heart rate or changes in electrolytes has been observed.[21]	Plasma renin activity, aldosterone levels, electrolytes and blood pressure will be monitored (Appendix 2, Section 10.2).
Development of anti-cagrilintide antibodies cagrilintide	Cagrilintide has a high homology to native amylin. In the phase 2 trial (NN9838-4433), up to 73% of subjects developed anti-cagrilintide antibodies in a dose-dependent manner. An increased risk of injection site reactions was observed in subjects with antibodies.	No mitigating actions are implemented. Sampling for investigation of presence of antibodies (anti-cagrilintide IgE and anti-semaglutide IgE) will be performed in case of systemic hypersensitivity reactions (see Section 8.3.7).
Acute pancreatitis semaglutide	Acute pancreatitis has been observed with the use of GLP-1 RAs.[21, 22] The frequency of adjudication-confirmed acute pancreatitis reported in STEP clinical development programme was 0.2% for semaglutide 2.4 mg and <0.1% for placebo, respectively. Overall, semaglutide was not associated with an increased risk of acute pancreatitis vs comparator.	Subjects with a history of chronic or recent acute pancreatitis will not be enrolled (see Section 5.2). Subjects should be informed of the characteristic symptoms of acute pancreatitis and if pancreatitis is suspected, trial product should be discontinued. If confirmed, trial product should not be restarted in accordance with Section 7.
MTC (based on non-clinical data) semaglutide	Thyroid C-cell tumours have been observed in carcinogenicity studies of semaglutide in rodents, but not in monkeys. The rodent C-cell tumours are caused by a non-genotoxic, specific GLP-1 receptor-mediated mechanism to which rodents are particularly sensitive. The GLP-1 receptor is not expressed in the normal human thyroid, and therefore the clinical relevance of the findings is considered to be low.[22]	Subjects with a family or personal history of multiple endocrine neoplasia type 2 (MEN2) or medullary thyroid cancer will be excluded from the trial (see Section 5.2).
Neoplasms (malignant and non-malignant) semaglutide	Patients with overweight or obesity as well as patients with T2D, have an increased risk of certain types of cancer. There is no evidence from clinical studies that GLP-1-based therapies increase the risk of neoplasms. No imbalance was observed in the semaglutide 2.4 mg for weight management phase 3a trials with regards to the proportions of subjects with neoplasms (malignant and non-malignant). However, in the semaglutide s.c. as well as oral semaglutide phase 3a studies for T2D, the proportion of subjects with neoplasms (malignant and non-malignant) were slightly higher with semaglutide than with comparator. The number of subjects exposed to semaglutide s.c. or oral semaglutide for a longer period is considered insufficient for a thorough assessment of the risk of neoplasms.	Subjects with a history of malignant neoplasms within the past 5 years prior to screening will not be enrolled in this trial. Basal and squamous cell skin cancer and any carcinoma in-situ is allowed (see Section 5.2).

Pancreatic cancer semaglutide	Patients with T2D have an increased risk of certain types of cancer such as pancreatic cancer. There is currently no support from nonclinical studies, clinical studies or post-marketing data that GLP-1 RA-based therapies increase the risk of pancreatic cancer. However, pancreatic cancer has been classified as a potential class risk for all marketed GLP-1 RAs by regulatory agencies.[22]	Subjects with a history of malignant neoplasms within the past 5 years prior to screening will be excluded from the trial (see Section 5.2).
Teratogenicity cagrilintide	Craniofacial malformations were observed in rodents after exposure to cagrilintide during pregnancy. This was not observed in the rabbit or dog. Additional studies suggest that the development of these adverse effects is caused by a species-specific mechanism in rodents. There are no data from the use of cagrilintide in pregnant women. For further information, please see current edition of the IB, section 'Reproductive and development toxicity.[21]	Only females of non-childbearing potential (refer to section 5.1 and definition in Appendix 4) are eligible for this trial. The trial products must be discontinued if pregnancy occurs (see Section 7.1).
Hypoglycaemia cagrilintide, semaglutide	There is a low risk of hypoglycaemic episodes when semaglutide or cagrilintide is used as monotherapy. Subjects treated with semaglutide or cagrilintide in combination with sulfonylurea or insulin may have an increased risk of hypoglycaemia.	This risk of hypoglycaemia is considered very low in this trial since subjects on sulfonylurea or insulin are excluded. However, sulfonylurea or insulin may be used as rescue therapy. The risk of hypoglycaemia can be lowered by reducing the dose of sulfonylurea or insulin.
Diabetic retinopathy complications semaglutide	In a 2-year clinical trial with s.c. semaglutide (NN9535-3744) involving 3,297 subjects with T2D, high CV risk, long duration of diabetes and poorly controlled blood glucose, EAC-confirmed events of diabetic retinopathy complications occurred in more subjects treated with s.c. semaglutide (3.0%) compared to placebo (1.8%). The absolute risk increase for diabetic retinopathy complications was larger among subjects with a history of diabetic retinopathy at baseline. In the subjects who did not have a documented history of diabetic retinopathy the number of events were similar for s.c. semaglutide and placebo. In the other clinical trials up to 1 year involving 4,807 subjects with T2D, AEs related to diabetic retinopathy were reported in similar proportions of subjects treated with s.c. semaglutide (1.7%) and comparators (2.0%).	As a precaution, subjects with a history of uncontrolled and potentially unstable diabetic retinopathy or maculopathy will be excluded from the trial, and eye examination will be performed according to flowchart (Section 1.2). Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy, but other mechanisms cannot be excluded. Long-term glycaemic control decreases the risk of diabetic retinopathy. These subjects should be monitored closely and treated according to clinical guidelines.
Trial procedures		
Risk of COVID-19 infection in relation to participation in trial	Subjects may be exposed to the risk of COVID-19 transmission and infection in relation to site visits if an outbreak is ongoing in the given country	To minimise the risk as much as possible, local guidelines must be followed.

Other		
Fertility and lactation	Studies in animals have shown reproductive toxicity (see Teratogenicity above). The effect of semaglutide and cagrilintide on fertility in humans is unknown. Therefore, semaglutide and cagrilintide should not be used during pregnancy. In lactating rats, semaglutide was excreted in milk. It is unknown if cagrilintide is excreted in milk. A risk to a breast-fed child cannot be excluded. Cagrilintide and semaglutide should not be used during breast-feeding.	Only females of non-childbearing potential (refer to section 5.1 and definition in Appendix 4, Section 10.4) are eligible for this trial. Female subjects who are pregnant, breast feeding or intend to become pregnant are excluded (Section 5.2)

2.3.2 Benefit assessment

Semaglutide s.c. 2.4 mg once weekly has demonstrated clinically relevant improvements in glycaemic control and body weight in subjects with T2D.[17] Cagrilintide 2.4 mg has demonstrated clinically significant weight loss in patients without T2D (see Section 2.2).Weight loss in overweight and obese patients with T2D is associated with a decrease in HbA_{1c}.[11] Additional weight loss was observed when combining cagrilintide 2.4 mg with semaglutide 2.4 mg (see Section 2.2). Consequently, it is expected that treatment with either cagrilintide 2.4 mg or semaglutide 2.4 mg or a combination will provide additional glycaemic and body weight control in subjects with T2D. All subjects are therefore expected to be treated with a more efficacious regimen compared to the treatment they receive at trial entry.

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

Safety and efficacy will be monitored regularly, and acceptable glycaemic control will always be reinforced during the trial.

2.3.3 Overall benefit-risk conclusion

Considering the measures taken to minimise risk to subjects participating in this trial, the potential risks identified in association with either co-administration of cagrilintide and semaglutide or administration of each component alone are justified by the anticipated benefits that may be afforded to subjects with T2D.

3 Objectives and endpoints

3.1 Primary, secondary and exploratory objective(s) and estimand(s)

3.1.1 Primary objectives

To compare the effect of co-administered semaglutide and cagrilintide versus semaglutide in subjects with T2D inadequately controlled on metformin with or without SGLT2 inhibitor on:

- change from baseline (week 0) to week 32 in HbA_{1c} (%-point)

3.1.2 Secondary objectives

To compare the effect of co-administered semaglutide and cagrilintide versus semaglutide in subjects with T2D inadequately controlled on metformin with or without SGLT2 inhibitor on:

- other parameters for glycaemic control
- body weight

To compare the effect of co-administered semaglutide and cagrilintide versus cagrilintide in subjects with T2D inadequately controlled on metformin with or without SGLT2 inhibitor on:

- HbA_{1c}
- other parameters for glycaemic control
- body weight

To compare the effect of co-administered semaglutide and cagrilintide, semaglutide and cagrilintide in subjects with T2D inadequately controlled on metformin with or without SGLT2 inhibitor on:

- safety and tolerability
- hypoglycaemia

3.1.3 Estimands

A primary and an additional estimand is defined for the primary objective. Two intercurrent events are identified: treatment discontinuation and initiation of anti-diabetic rescue intervention. The attributes for the estimands are summarised in Table 3-1.

Primary estimand

The primary estimand addresses the main question of interest: What is the effect of co-administered semaglutide and cagrilintide versus semaglutide on change in HbA_{1c} (%-points) from baseline to week 32 in subjects with T2D inadequately controlled on metformin with or without SGLT2 inhibitor, had all subjects remained on trial treatment without use of rescue medication (anti-diabetic). A hypothetical strategy is applied for both intercurrent event of premature treatment discontinuation and initiation of rescue medication. The population level summary is difference in means.

The primary estimand estimates the achievable treatment effect without the confounding of treatment discontinuation and initiation of rescue intervention. This approach is considered relevant for evaluating a mechanistic effect.

Additional estimand for the primary objective

The additional estimand addresses a different question of interest: What is the effect of co-administered semaglutide and cagrilintide versus semaglutide on HbA_{1c} (%-points) from baseline to week 32 in subjects with T2D inadequately controlled with metformin with or without SGLT2 inhibitor, regardless of premature treatment discontinuation or initiation of rescue medication (anti-diabetic).

For the additional estimand, the treatment policy strategy is applied for both the intercurrent event of initiation of premature treatment discontinuation or rescue medication. The population-level summary is difference in means. Results based on the additional estimand are expected to mirror the

clinical practice scenario because the estimand considers both the efficacy and tolerability of treatments.

Table 3-1 Attributes for the estimands

Estimand category	Treatment condition	Variable/ Endpoint	Population of interest	Intercurrent event strategy	Population-level summary measure
Primary	The effect of co-administered semaglutide and cagrilintide versus semaglutide on HbA_{1c}, both as add-on to metformin with or without SGLT2 inhibitor and without rescue medication	Change in HbA_{1c} (%-point) from baseline to week 32	Subjects with T2D inadequately controlled on metformin with or without SGLT2 inhibitor	Hypothetical strategy for • Initiation of any rescue medication • Treatment discontinuation	Difference in means
Additional	The effect of co-administered semaglutide and cagrilintide versus semaglutide on HbA_{1c}, both as add-on to metformin with or without SGLT2 inhibitor			Treatment policy strategy for • Initiation of any rescue medication • Treatment discontinuation	

3.2 Primary, secondary and exploratory endpoint(s)

3.2.1 Primary endpoint

Endpoint title	Time frame	Unit
Change in HbA_{1c}	From baseline (week 0) to week 32	%-point

3.2.2 Secondary endpoints

3.2.2.1 Confirmatory secondary endpoints

Not applicable for this trial.

3.2.2.2 Supportive secondary endpoints

Endpoint title	Time frame	Unit
Change in fasting plasma glucose (FPG)	From baseline (week 0) to week 32	mmol/L and mg/dL
CGM: Change in mean glucose	From baseline (week 0) to week 32	mmol/L and mg/dL
CGM: Time above range (TAR) >10.0 mmol/L (>180 mg/dL)	At week 32	% of readings
CGM: Time in range (TIR) 3.9–10.0 mmol/L (70–180 mg/dL)	At week 32	% of readings
Change in body weight	From baseline (week 0) to week 32	%
Change in body weight	From baseline (week 0) to week 32	Kg
Number of treatment emergent adverse events (TEAEs)	From baseline (week 0) to week 37	Count
Number of clinically significant hypoglycaemic episodes (level 2) (<3.0mmol/L (54mg/dL), confirmed by BG meter) or severe hypoglycaemic episodes (level 3)	From baseline (week 0) to week 37	Count of episodes

4 Trial design

4.1 Overall design

This is a 32-week, randomised, double-blind, active-controlled, three-arm, parallel group, multicentre clinical trial. The trial will compare the efficacy and safety of co-administration of cagrilintide s.c. 2.4 mg once weekly and semaglutide s.c. 2.4 mg once weekly versus semaglutide s.c. 2.4 mg once weekly monotherapy versus cagrilintide s.c. 2.4 mg once weekly monotherapy in subjects with T2D.

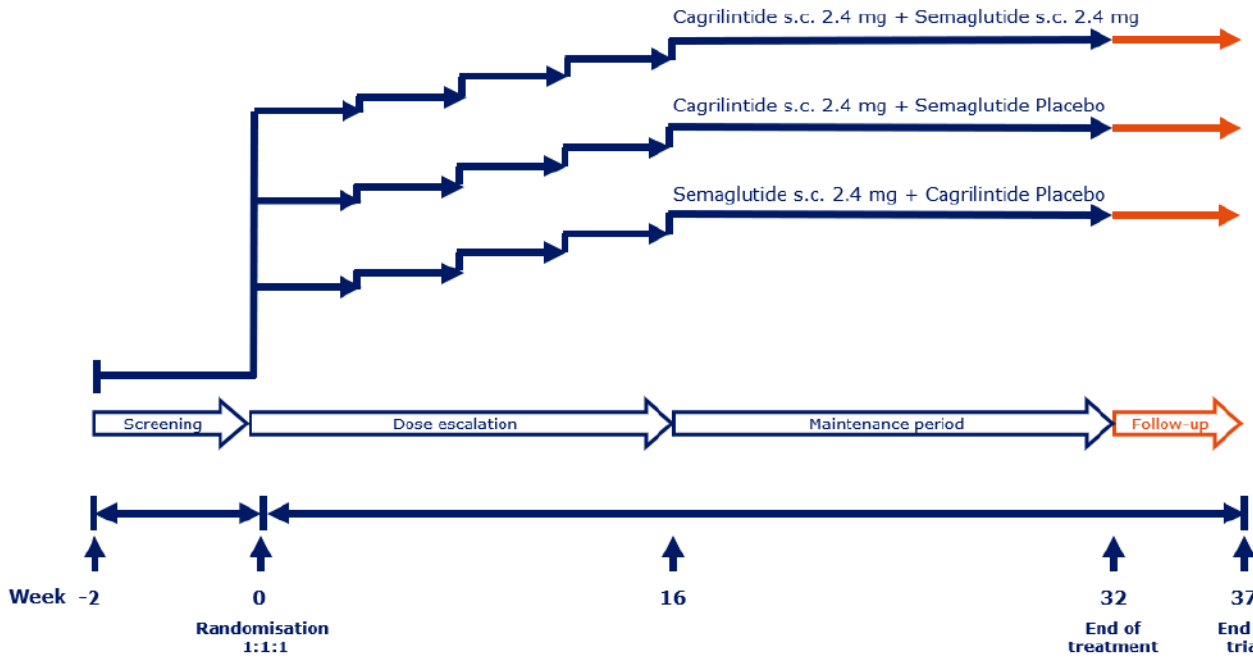
Approximately 90 eligible subjects will be randomised to 1 of the 3 treatment arms in a ratio of 1:1:1. Randomisation will be stratified according to the SGLT2 inhibitor treatment (Yes/No).

The trial includes a minimum 10-day screening period to assess subject eligibility, a 32-week treatment period and a 5-week follow up period. The 32-week treatment period consists of a 16-week dose escalation period and a 16-week maintenance period. The planned total trial duration for the individual subject is approximately 39 weeks.

To evaluate the effect on glycaemic control, subjects will have CGM profiles collected, as specified in the flowchart (see Section 1.2). This will include CGM profiling during the 10-day screening period representing baseline CGM evaluation. The CGM will be blinded for both subjects and investigators and not used for dose adjustments.

The trial design is illustrated in Figure 4-1.

Figure 4-1 Schematic diagram of the trial design



4.2 Scientific rationale for trial design

A randomised, double-blinded trial design has been chosen to increase the validity of the trial and to avoid bias. Cagrilintide s.c. 2.4 mg once weekly and semaglutide s.c. 2.4 mg once weekly are

chosen as active comparators. The primary objective is to compare the effect of co-administration of cagrilintide s.c. 2.4 mg once weekly and semaglutide s.c. 2.4 mg once weekly versus semaglutide s.c. 2.4 mg once weekly on glycaemic control. Both efficacy and safety of co-administration of cagrilintide s.c. 2.4 mg once weekly and semaglutide s.c. 2.4 mg once weekly compared to each individual component will be investigated. Semaglutide is known to have a glucose lowering effect and is approved for treatment of T2D in lower doses than investigated in this trial. No clinical data on the effect of treatment with cagrilintide on glycaemic control in subjects with T2D are currently available and therefore a cagrilintide s.c. 2.4 mg once weekly treatment arm has been included in this trial.

The planned treatment duration is 32 weeks. The treatment duration includes a 16-week dose escalation period and a 16-week maintenance period. The dose of trial product will be escalated every 4 weeks to mitigate the risks of gastrointestinal side effects. The total treatment duration of 32 weeks is expected to ensure adequate time for comparing the effect on HbA_{1c} in accordance with the primary objective of the trial. A 10-day screening period is included to ensure eligibility of subjects and to collect CGM profiles before the initiation of treatment with trial products. Furthermore, a 10-day CGM data collection will be conducted after the dose escalation period and at the end of the maintenance period. A follow-up visit is planned to collect data on safety 5 weeks after end of treatment to account for the long half-life of trial products.

The randomisation ratio is 1:1:1 to ensure a balanced comparison between groups. To avoid a pronounced difference in SGLT2 inhibitor use between the treatment arms at baseline, randomisation will be stratified according to the SGLT2 inhibitor treatment (Yes/No).

The relatively homogeneous trial population of subjects with T2D who are in inadequate glycaemic control using metformin with or without SGLT2 inhibitor have been chosen to limit the variability. Including subjects with HbA_{1c} of 7.5%-10.0% allows for an evaluation of glucose parameters. Only subjects with BMI $\geq$ 27.0 kg/m^2 are included to mitigate the need for reduction in dose in case the co-administration of cagrilintide and semaglutide leads to pronounced weight reduction in subjects with T2D.

4.3 Justification for dose

Semaglutide s.c. has been approved for treatment of T2D in the doses of 0.5 mg and 1.0 mg and a dose of 2.0 mg is currently under regulatory review. Within the weight management indication, a global phase 3a clinical development programme with semaglutide s.c. 2.4 mg once weekly is under regulatory review. One of the trials completed within the phase 3a weight management programme (NN9536-4374) included 1210 subjects with overweight or obesity and T2D. Semaglutide s.c. 2.4 mg once weekly appeared to have a safe and well tolerated profile in line with what has previously been observed for semaglutide[23].

Based on the results from clinical trials (see Section 2.1) a cagrilintide dose of 2.4 mg administered in combination with semaglutide s.c. 2.4 mg is considered to provide maximum effect on body weight while ensuring safety and tolerability. The once weekly combination of cagrilintide 2.4 mg and semaglutide 2.4 mg is being investigated within the indication of weight management. Since weight loss is associated with improvements in glycaemic parameters (see Section 2.1) doses of

2.4 mg for both cagrilintide and semaglutide will be used to investigate whether cagrilintide adds to the glucose lowering effect of semaglutide in subjects with T2D.

Escalation of the cagrilintide and semaglutide doses will be done every 4 weeks, until the maintenance dose is reached after 16 weeks, in order to mitigate the well-known gastrointestinal side effects observed with both cagrilintide and semaglutide treatments.

4.4 End of trial definition

A subject is considered to have completed the trial if he/she has completed all phases of the trial including the last visit shown in the flowchart.

The end of the trial is defined as the date of the last visit of the last subject in the trial.

5 Trial population

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion criteria

Subjects are eligible to be included in the trial only if all of the following criteria apply:

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. Female of non-childbearing potential (see definition in Appendix 4, Section 10.4) or male
3. Age above or equal to 18 years at the time of signing informed consent
4. BMI $\geq$ 27.0 kg/m^2
5. Diagnosed with type 2 diabetes mellitus $\geq$ 180 days before screening
6. HbA_{1c} of 7.5-10.0% (58-86 mmol/mol) (both inclusive) as assessed by central laboratory at screening
7. Stable daily dose(s) $\geq$ 90 days before screening of the following antidiabetic drug(s) or combination regimen(s) at maximum tolerated or effective dose as judged by the investigator: metformin with or without SGLT2 inhibitor
8. Able and willing to adhere to the protocol including wearing provisioned continuous glucose monitoring (CGM) device based on the Investigator's judgement

5.2 Exclusion criteria

Subjects are excluded from the trial if any of the following criteria apply:

1. Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria within 90 days before screening. However, short term insulin treatment for a maximum of 14 days and prior insulin treatment for gestational diabetes are allowed
2. Previous or planned (during the trial period) obesity treatment with surgery or a weight loss device. However, the following are allowed: (1) liposuction and/or abdominoplasty, if performed > 1 year before screening, (2) lap banding, if the band has been removed > 1 year before screening, (3) intragastric balloon, if the balloon has been removed > 1 year before screening or (4) duodenal-jenunal bypass sleeve, if the sleeve has been removed > 1 year before screening

3. Anticipated initiation or change in concomitant medications (for more than 14 consecutive days) known to affect weight or glucose metabolism (e.g. treatment with orlistat, thyroid hormones, or corticosteroids)
4. Presence or history of chronic pancreatitis[a]
5. Presence or history of acute pancreatitis within 180 days before screening[a]
6. Myocardial infarction, stroke, hospitalization for unstable angina pectoris or transient ischaemic attack within 180 days before screening
7. Chronic heart failure classified as being in New York Heart Association (NYHA) Class IV at screening
8. Planned coronary, carotid or peripheral artery revascularisation
9. Personal or first-degree relative(s) history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma[a]
10. Renal impairment with estimated Glomerular Filtration Rate (eGFR) < 60 ml/min/1.73m^2 by central laboratory at screening
11. Impaired liver function, defined as Alanine Aminotransferase (ALT) ≥ 2.5 times or Bilirubin >1.5 times upper normal limit (UNL) by central laboratory at screening
12. History or presence of a disease, causing impaired calcium homeostasis as judged by the investigator
13. Uncontrolled and potentially unstable diabetic retinopathy or maculopathy. Verified by a fundus examination performed within 90 days before screening or in the period between screening and randomisation. Pharmacological pupil-dilation is a requirement unless using a digital fundus photography camera specified for non-dilated examination
14. Any episodes[a] of diabetic ketoacidosis within 90 days before screening
15. Recurrent severe hypoglycaemic episodes within the last year as judged by the Investigator
16. Inadequately treated blood pressure defined as Systolic ≥180 mmHg or diastolic ≥110 mmHg at screening
17. Presence or history of malignant neoplasm (other than basal or squamous cell skin cancer, in-situ carcinomas of the cervix, or in situ prostate cancer) within 5 years before screening
18. Surgery scheduled for the duration of the trial, expect for minor surgical procedures, in the opinion of the Investigator
19. Use of any medication with unknown or unspecified content within 90 days before screening.
20. Known or suspected hypersensitivity to trial product(s) or related products
21. Previous participation in this trial. Participation is defined as signed informed consent
22. Female who is pregnant, breast-feeding or intends to become pregnant or is of childbearing potential
23. Participation in any clinical trial of an approved or non-approved investigational medicinal product within 90 days before screening
24. Any disorder, which in the investigator's opinion might jeopardise subject's safety or compliance with the protocol

a: As declared by the subject or in the medical records

5.3 Lifestyle considerations

To ensure alignment regarding performance of assessments across subjects and trial sites, the below restrictions apply.

5.3.1 Meals and dietary restrictions

Subjects must attend the visits fasting according to the flowchart (Section 1.2).

Fasting is defined as at least 8 hours before the visit, without food or liquids, except for water. Trial product and any medication which should be taken with or after a meal should be withheld on the day of the visit until blood samples have been obtained.

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. Procedures requiring subject to fast include blood sampling of FPG.

5.3.2 Caffeine, alcohol and tobacco

Subject should avoid caffeine and smoking at least 30 minutes prior to measuring the blood pressure.
Tobacco use is defined as smoking at least one cigarette or equivalent daily.

5.4 Screen failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are not eligible for participation according to inclusion/exclusion criteria. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet requirements from regulatory authorities. Minimal information includes informed consent date, demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

A screen failure session must be made in the interactive web response system (IWRS).

Individuals who do not meet the criteria for participation in this trial may not be rescreened. If the subject has failed one of the inclusion criteria or fulfilled one of the exclusion criteria related to laboratory parameters, re-sampling is not allowed. However, in case of technical issues (e.g. haemolysed or lost), re-sampling is allowed for the affected parameters.

5.5 Run-in criteria and/or randomisation criteria

Not applicable for this trial.

6 Treatments

6.1 Treatments administered

Investigational medicinal products (IMP)

All trial products listed in Table 6-1 are considered investigational medicinal products (IMP).

Table 6-1 Investigational medicinal product provided by Novo Nordisk A/S

Trial product name	Cagrilintide (NNC0174-0833 A) 10 mg/mL	Semaglutide B 3.0 mg/mL	Cagrilintide (NNC0174-0833 A) Placebo	Semaglutide Placebo
Dosage form	Solution for injection	Solution for injection	Solution for injection	Solution for injection

Route of administration	Subcutaneous	Subcutaneous	Subcutaneous	Subcutaneous
Dosing instructions	Once weekly	Once weekly	Once weekly	Once weekly
Delivery device	3 mL under-filled cartridge, 1 ml solution for injection to be used with NovoPen Echo®[a]	PDS290 pre-filled pen-injector (containing 3 mL solution for injection)	3 mL under-filled cartridge, 1 ml solution for injection to be used with NovoPen Echo®[a]	PDS290 pre-filled pen-injector (containing 3 mL solution for injection)
Other information	N/A	N/A	N/A	N/A

[a]NovoPen Echo® durable device used outside of intended use

Directions for use

- The investigator must document that directions for use (DFU) are given to the subject verbally and in writing at the first dispensing visit.
- First dose of trial products must be injected at site by the subject guided by trained site staff or injected by trained site staff.
- Subjects will be instructed to inject trial products once weekly on the same day of the week (to the extent possible) throughout the trial at home.
- Injections may be administered at any time of day, irrespective of timing of meals.
- Injections must be administered s.c. in the abdomen, thigh or upper arm.
- Injection of cagrilintide/cagrilintide placebo should be performed as the first injection. Injection of semaglutide/semaglutide placebo should be performed immediately after completion of the injection of cagrilintide/cagrilintide placebo.
- Injection of cagrilintide/cagrilintide placebo must always be in the right side of the abdomen thigh, or upper arm. Injection site can be changed between the abdomen, thigh and upper arm.
- Injection of semaglutide/semaglutide placebo must always be in the left side of the abdomen, thigh or upper arm. Injection site can be changed between the abdomen, thigh and upper arm.
- To prevent pen mix-up and medication errors, The Pen Differentiation Guide must be used during training of subjects and handed out to subjects.

Dose escalation

- Dose escalation of trial products should take place during the first 16 weeks after randomisation as described in Table 6-2.
- All subjects should aim at reaching the maintenance dose of trial products.

Table 6-2 Dose escalation and maintenance

Trial product name		Cagrilintide (NNC0174-0833 A) 10 mg/mL or placebo		Semaglutide B 3.0 mg/mL or placebo	
Device		NovoPen Echo®[a]		PDS290 pre-filled pen-injector	
Dose	**Duration**	Dose	Value shown in dose counter	Dose	Value shown in dose counter

Dosage escalation step 1	4 weeks	0.25mg	2½	0.24 mg	8
Dosage escalation step 2	4 weeks	0.5 mg	5	0.5 mg	17
Dosage escalation step 3	4 weeks	1.0 mg	10	1.0 mg	34
Dosage escalation step 4	4 weeks	1.7 mg	17	1.7 mg	57
Maintenance dose	16 weeks	2.4 mg	24	2.4 mg	80

[a]NovoPen Echo® durable device used outside of intended use

Missed doses

In case of missed doses, the investigator should follow the guidance in Table 6-3.

Table 6-3 Missed doses

Missed dose situation:	Recommended action:
When to administer the next dose	
If a single dose of trial product is missed and the time to the next scheduled dose is at least 2 days (48 hours)	Administer missed dose of trial product as soon as possible. A missed dose should not affect the scheduled dosing day the following weeks
If a single dose of trial product is missed and the time to the next scheduled dose is less than 2 days (48 hours)	Do not administer the missed dose of trial product. Administer the next scheduled dose on the scheduled dosing day
If 2 or more doses of trial product are missed	Trial product should be administered as soon as possible, and the day of treatment will be the dosing day going forward.
What dose to administer	
If time since last dose is less than 3 weeks (21 days)	Administer the same dose of trial product as the latest dose.
If time since last dose is at least 3 weeks but less than 4 weeks	Restart treatment one dose step lower than the latest dose
If time since last dose is at least 4 weeks but less than 5 weeks	Restart treatment two dose steps lower than the latest dose
If time since last dose is at least 5 weeks	Restart treatment starting at the lowest dose

- In case of questions related to re-initiation of trial products, the investigator should consult Novo Nordisk
- It is recommended that the investigator consults Novo Nordisk in case of persistent deviations from the planned escalation and maintenance regimen

Auxiliary supplies

Auxiliary supplies will be provided in accordance with the trial materials manual (TMM) and Table 6-4.

Table 6-4 Auxiliary supplies

Auxiliary supply	Details
Needles	Only needles provided and approved by Novo Nordisk must be used for administration of trial product.
Blood glucose (BG) meter	Subjects must be instructed in how to use the BG meter as specified in Appendix 7, Section 10.7. Please refer to the manufacturer's guide.
Continuous glucose monitoring (CGM)	Subjects must be instructed in handling of the CGM as specified in the flowchart , Section 1.2. Please refer to the CGM Subject Guide provided.
Direction for use (DFU)	DFU for PDS290 pre-filled pen-injector and NovoPen Echo® Not included in the dispensing unit and to be handed out separately

The BG meter provided by Novo Nordisk should be used if the subject experiences a hypoglycaemic episode, see Appendix 7 (Section 10.7).

Training in the pen-injector and durable device is the responsibility of the investigator or a delegate and must be repeated during the trial at regular intervals, as specified in the flowchart (see Section 1.2) in order to ensure correct use of the pen-injector.

6.1.1 Medical devices

Information about the PDS290 pre-filled pen-injector for semaglutide/placebo and NovoPen Echo® durable device for cagrilintide/placebo can be found in the DFU.

6.2 Preparation/handling/storage/accountability

Only subjects randomised to treatment may use trial product and only delegated site staff may supply trial product.

- Each site will be supplied with sufficient trial products for the trial on an ongoing basis. Trial products will be distributed to the sites according to screening and randomisation.
- The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all trial products received, and that any discrepancies are reported and resolved before use of the trial products.
- All trial products must be stored in a secure, controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and delegated site staff.
- The investigator must inform Novo Nordisk immediately if any trial product has been stored outside specified conditions. The trial product must not be dispensed to any subject before it has been evaluated and approved for further use by Novo Nordisk. Additional details regarding handling of temperature deviations can be found in the trial materials manual (TMM).
- The investigator or designee is responsible for drug accountability and record maintenance (i.e. receipt, accountability and final disposition records).
- The investigator or designee must instruct the subject in what to return at next visit.

- Drug accountability should be performed at pen level.
- Destruction of trial products can be performed on an ongoing basis and will be done according to local procedures after accountability is finalised by the site and reconciled by the monitor.
- All returned, un-used, expired or damaged trial products (for technical complaint samples, see Section 10.5) must be stored separately from non-allocated trial products. No temperature monitoring is required.
- Non-allocated trial products including expired or damaged products must be accounted as unused, at the latest at closure of the site.

6.2.1 Shipment of trial product to subject's home

If permitted by local regulations, the investigator may offer to send trial products and auxiliaries from the trial site or pharmacy to the subject's home by courier service.

The process for sending trial product from the trial site or pharmacy to a subject's home is described in the "Trial site/pharmacy instruction for shipment of trial product to subjects' homes" document. This document contains detailed instructions for preparing packaging and setting up the pick-up of trial products, handover of trial products from the trial site or pharmacy staff to the courier, required temperature monitoring of trial products, delivery to and receipt of trial producst by the subject. The process for returning trial product to the trial site or pharmacy by courier is also described in this document.

Investigators, trial site staff and subjects who will be involved in shipment of trial product to the subject's home will be adequately trained in this process.

6.3 Measures to minimise bias: Randomisation and blinding

All subjects will be centrally screened and randomised using an IWRS and assigned to the next available treatment according to randomisation schedule. Trial products will be dispensed/allocated at the trial visits summarised in the flowchart.

Randomisation will be stratified according to treatment with SGLT2 inhibitor at screening (yes/no).

At screening, each subject will be assigned a unique 6-digit Subjects ID, which will remain the same throughout the trial. Each site is assigned a 3-digit number and Subject IDs start with the site number.

The IWRS is used for blind-breaking. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a subjects' treatment is warranted. Subject safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact Novo Nordisk prior to unblinding a subjects' treatment unless this could delay emergency treatment of the subject. If a subject's treatment is unblinded, Novo Nordisk (Global Safety department) must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the medical records. The person breaking the blind must print the "code break confirmation" notification generated by the IWRS, sign and date the document. If IWRS is not accessible at the time of blind break, the IWRS helpdesk should be contacted. Contact details are

listed in Attachment I. Treatment with trial product can be resumed if there are no safety concerns at the discretion of the investigator.

During the entire trial conduct, subjects, investigators and Novo Nordisk will be blinded to individual treatment assignments. For special considerations in relation to the interim analysis please see Section 9.5.

6.4 Treatment compliance

Drug treatment compliance

Throughout the trial, the investigator will remind the subjects to follow the trial procedures and requirements to encourage subject compliance.

When subjects self-administer trial products at home, compliance with trial products administration will be assessed and the assessment will be documented in medical records at each visit where information is available. If any suspicion of non-compliance arises, the site must enter a dialogue with the subject, re-emphasizing the importance of compliance and uncover barriers to compliance. This dialogue must be documented. Compliance will be assessed by cross checking the following sources and comparing these to the expected use:

- Review of dosing diary
- Questioning of subjects

6.5 Concomitant medication

Any medication (including over the counter or prescription medicines, vitamins, and/or herbal supplements) or vaccine other than the trial products that the subject is receiving at the time of the first visit or receives during the trial must be recorded along with:

- Trade name or generic name
- Indication
- Dates of administration including start and stop dates
- Doses and frequency (only applicable for anti-diabetic medication)

Approved COVID-19 vaccines that the subject received within 6 months prior to screening should be recorded in the eCRF at the screening visit (V1).

During the trial subjects should not initiate any anti-obesity treatment (e.g. medication). If such treatment is initiated, the subject should be instructed to stop the anti-obesity treatment.

After randomisation subjects should continue their pre-trial oral metformin and SGLT2 inhibitor background medication throughout the entire trial. The background metformin and SGLT2 inhibitor should be maintained at the stable, pre-trial dose and at the same frequency during the entire treatment period unless glycaemic rescue treatment is needed (as described in Section 7.1.2) or adjustment is required due to safety concerns.

In addition, the background medication:

- is considered non-investigational medicinal product (NIMP)

- will not be provided by Novo Nordisk unless required by local law and should be purchased or otherwise delivered to subjects in accordance with local health plans
- Should be used in accordance with standard of care or local label in the country

Investigators can switch oral anti-diabetic (OAD) treatment within the same drug class, e.g. in case specific drugs become unavailable. Changes in concomitant medication, including switch of OAD treatment within the same drug class must be recorded at each visit/phone contact. If a change is due to an AE, then this must be reported according to Section 8.3.

6.5.1 Rescue medication

Glycaemic rescue medication, i.e. intensification of background oral anti-diabetic (OAD) medication and/or initiation of new anti-diabetic medication, should be implemented at the discretion of the investigator in case of persistent hyperglycaemia. Please see Section 7.1.2.

Rescue medication should be selected according to the ADA/EASD guideline[24, 25] (excluding GLP-1 RAs, dipeptidyl peptidase-4 (DPP-4) inhibitors and amylin analogues).

Subjects that are started on rescue medication should continue to follow the protocol-specified visit schedule and stay on randomised treatment unless the investigator judge that it jeopardises subject's safety.

Rescue medication (intensification of existing background medication and/or initiation of new medication) and any changes to this should be documented in medical records and reported on the concomitant medication form in the eCRF.

Rescue medication will not be supplied by Novo Nordisk.

6.6 Dose modification

Consider delaying dose escalation or reducing the dose during dose escalation if:

- The current dose is not tolerated by the subject. This should only be allowed if the subject would otherwise discontinue trial products completely and only if considered safe to continue on any trial products dose, as per investigator's discretion

Consider reducing the maintenance dose if:

- The maintenance dose is not tolerated by the subject. The subject may stay at a lower dose level but only if the subject would otherwise discontinue trial products completely and only if considered safe to continue on any trial products dose, as per investigator's discretion.
- The subject achieves a BMI of <22.5 kg/m^2 and continues losing weight, per investigator's discretion

Dose modifications must be applied to both trial products. In case of deviations from the planned dose escalation regimen, it is recommended that the subject makes at least one attempt to re-escalate to the maintenance dose, as per the investigator's discretion. It is recommended that the investigator consults Novo Nordisk in case of persistent deviations from the planned escalation regimen.

6.7 Treatment after end of trial

When discontinuing trial products at the 'end-of-treatment' visit, the subject should be transferred to a suitable marketed product at the discretion of the investigator. Considering the long half-life of semaglutide and cagrilintide and to avoid over-exposure to GLP-1 RAs and interference with safety data collection, initiating GLP-1RA, DPP-4i or amylin analogues should be avoided between the end-of-treatment visit (V16) and the end-of-trial visit (V17).

7 Discontinuation of trial treatment and subject discontinuation/withdrawal

Treatment of a subject may be discontinued at any time during the trial at the discretion of the investigator for safety, behavioural, compliance or administrative reasons.

7.1 Discontinuation of trial treatment

Trial products may be discontinued at any time during the trial at the discretion of the subject or at the discretion of the investigator for safety, behavioural, compliance or administrative reasons.

The trial products must be discontinued, if any of the following applies for the subject:
1. Safety concern as judged by the investigator
2. Suspicion of acute pancreatitis
3. Pregnancy
4. Simultaneous use of an approved or non-approved investigational medicinal product in another clinical trial

Subjects meeting discontinuation of treatment criteria no. 1, 2 or 3 can resume trial products if the criteria is no longer met.

For discontinuation of treatment criterion no. 2:
If acute pancreatitis is suspected, appropriate actions should be initiated, including local measurement of amylase and lipase see Appendix 3 (Section 10.3).

Subjects can resume trial products if the Atlanta criterion[26] is not fulfilled and thus the suspicion of acute pancreatitis is not confirmed. Trial products may be resumed for subjects with a gallstone-induced pancreatitis in case of cholecystectomy.

The primary reason for discontinuation of trial products must be specified in the subject's medical records and the end-of-treatment form in the eCRF, and final drug accountability must be performed. A 'treatment status session' must be made in the IWRS to discontinue trial products.

If a subject has discontinued trial products, efforts must be made to have subjects attend and complete all remaining scheduled visit procedures. All efforts should be made to have the subject attend at least visit V12, the 'end of treatment' visit (V16) and the 'end of trial' visit (V17). If the subjects do not wish to attend the scheduled clinic visits, efforts should be made to have the remaining clinic visits converted to phone call visits. If a subject is unwilling to attend the remaining visits, information about the attempts to follow up with the subject must be documented in the subject's medical records.

The 'end of trial' visit (V17) is scheduled approximately 5 weeks after end of treatment to ensure the safety of the subject. If the subject has discontinued trial products >5 weeks prior to the 'end of treatment' visit (V16), and the requirements for the follow-up period prior to the 'end of trial' visit (V17) are fulfilled, then the 'end of trial' visit (V17) can be omitted.

7.1.1 Temporary discontinuation of trial treatment

If a subject has discontinued trial products due to temporary safety concern not related to trial products and can resume treatment, the subject should follow the guide for missed doses Table 6-3. Similarly, a subject who discontinues trial products on their own initiative should be encouraged to resume trial products (Section 6.1). A 'treatment status session' must be made in the IWRS when a subject pauses treatment or resumes treatment.

In case of suspicion of acute pancreatitis, the trial products must promptly be discontinued; however, 'treatment status session' should not be made in IWRS before diagnosis of acute pancreatitis is confirmed. If acute pancreatitis is confirmed, treatment with trial products must not be restarted, and a 'treatment status session' should be made in IWRS.

7.1.2 Rescue criteria

If any of the FPG values exceed the limits outlined below and no intercurrent cause of the hyperglycaemia can be identified, the subject should be offered rescue medication, see Section 6.5.1).

Rescue medication should be offered if FPG values exceeds:

- 15.0 mmol/L (270 mg/dL) from randomisation to end of week 8
- 13.3 mmol/L (240 mg/dL) from week 9 to end of week 20
- 11.1 mmol/L (200 mg/dL) from week 21 to end of treatment

A confirmatory FPG should be obtained by the central laboratory. If the confirmatory FPG exceeds the values described above, the subject should be offered rescue medication at the discretion of the investigator and in accordance with the ADA/EASD guideline[24, 27] (excluding GLP-1 RAs, DPP-4 inhibitors and amylin analogues). Rescue medication should be prescribed as add-on to randomised treatment and subjects should continue to follow the protocol-specified visit schedule.

7.2 Subject withdrawal from the trial

A subject may withdraw consent at any time at his/her own request

If a subject withdraws consent, the investigator must ask the subject if he/she is willing, as soon as possible, to have assessment performed according to 'end of treatment' visit (V16). See the flowchart (Section 1.2) for data to be collected.

Final drug accountability must be performed even if the subject is not able to come to the site. A 'treatment status session' must be made in the IWRS.

If the subject withdraws consent, Novo Nordisk may retain and continue to use any data collected before such a withdrawal of consent.

If a subject withdraws from the trial, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the medical record.

Although a subject is not obliged to give his/her reason(s) for withdrawing, 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 withdrawal must be specified in the end of trial form in the eCRF.

7.2.1 Replacement of subjects

Subjects who discontinue trial products or withdraw from trial will not be replaced.

7.3 Lost to follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the site.

The following actions must be taken if a subject fails to return to the site for a required visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the trial.
- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, at least three telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical records.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the trial with a primary reason of `lost to follow-up'.

8 Trial assessments and procedures

The following sections describe the assessments and procedures, while their timing is summarised in the flowchart.

- Informed consent must be obtained before any trial related activity, see Section 10.1.3.
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all inclusion criteria and none of the exclusion criteria.
- The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reason for screen failure, as applicable.
- At screening, subjects will be provided with a card stating that they are participating in a trial and giving contact details of relevant site staff that can be contacted in case of emergency.
- Adherence to the trial design requirements, including those specified in the flowchart, is essential and required for trial conduct.
- Assessments should be carried out according to the clinic's standard of practice unless otherwise specified in the current section. Efforts should be made to limit the bias between assessments. The suggested order of the assessments:
    - Blood samples
    - Body measurements (see Section 8.1.1)

- Vital signs (see Section 8.2.2)
- ECG

- Diaries will include the following in relation to the visit they support:
  - Reminders:
    - to attend visit fasting (see flowchart in Section 1.2)
    - to return trial products at next site visit
    - to return diary at next site visit
    - to remind only to use each cagrilintide cartridge two times
  - Instruction on how to use the diary
  - Information to be collected:
    - dose, date and site of injection of trial products
    - dose, date, site and time of last 2 doses prior to PK samples
    - hypoglycaemic events (according to Appendix 6, Section 10.6)
    - health issues
- Review of diaries, ECG, laboratory reports and eye examinations must be documented either on the documents or in the subject's medical records. If clarification of entries or discrepancies in the diaries is needed, the subject must be questioned, and a conclusion made in the subject's medical records. Care must be taken not to bias the subject.
- Results of pregnancy testing must be documented in the subject's medical records.
- Repeat samples may be taken for technical issues and unscheduled samples or assessments may be taken for safety reasons. Please refer to Appendix 2, Section 10.2 for further details on laboratory samples.

8.1 Efficacy assessments

Planned time points for all efficacy assessments are provided in the flowchart (Section 1.2) and Appendix 2, Table 10-1.

8.1.1 Body measurements

- **Body weight** should be measured without shoes, on an empty bladder and only wearing light clothing and recorded in the eCRF in kilograms [kg] or pounds [lb], with precision of 1/10 unit (e.g. 75.3 kg /166.0 lb). The body weight should be assessed on the same calibrated weighing scale throughout the trial. The calibration standard should preferably be once yearly or reflect the country requirements, unless the manufacturer certifies that calibration of the weighing scale is valid for the lifetime of the scale.
- **Height** is measured without shoes in centimetres or inches (one decimal). BMI will be calculated in the eCRF from screening data.

8.1.2 Continuous glucose monitoring

Subjects will be equipped with a CGM device at the site visits (V1, V11, V15). For each of the CGM assessment periods the sensor must be worn for 10 full days and be removed at the visits or as close to the visits as possible at the site visits (V2, V12, V16). This needs to be considered when planning the visits where the sensor is to be fitted and removed.

The CGM system used in this trial will be the Dexcom G6®.

The CGM readings will be blinded to both the subject and investigator and will not be used for any dose adjustments or hypoglycaemic episode reporting.

If a subject withdraws consent during the trial, a site visit should be scheduled in order to remove the CGM sensor and upload the data from the receiver.

CGM fitting and training

The site staff will closely supervise and assist with fitting of the sensor and transmitter on the subject during the site visits. Training in the CGM is the responsibility of the investigator or site staff at the relevant visits. The site should ensure the subject is trained in changing the sensor at home in case the CGM sensor needs to be changed after fitting at site in case it falls off. All subjects will be provided with an extra sensor to bring home in case they need to re-fit the sensor. For information on fitting, and changing of the CGM parts, please refer to the Investigators CGM manual and Subject guide provided.

CGM upload

The subject will return the receiver to site staff at visit (V2, V12, V16) for data upload. Data stored on the CGM receiver must be uploaded at the site by the site staff to the CGM software following the instruction provided to the sites. The upload will be documented by the system directly.

The serial number of the CGM receiver must be recorded and confirmed in the eCRF at the start of each CGM period. In case the CGM receiver is being replaced, the serial number should be updated.

8.1.3 Clinical efficacy laboratory assessments

All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the flowchart and the laboratory manual.

8.2 Safety assessments

Planned time points for all safety assessments are provided in the flowchart (Section 1.2).

A **concomitant illness** is any illness that is already present at the time point from which AEs are collected or found as a result of a screening procedure or other trial procedures performed before exposure to trial products.

Medical history is a medical event that the subject experienced prior to the time point from which AEs are collected. Only relevant and significant medical history as judged by the investigator should be reported in the eCRF at the screening visit. Findings of specific medical history (diabetes history, comorbidities and history of cardiovascular disease) should be described in the designated forms.

In case of an abnormal and clinically significant finding fulfilling the definition of a concomitant illness or medical history, the investigator must record the finding on the Medical History/ Concomitant Illness form.

8.2.1 Physical examinations

A physical examination will include assessments of:

- General appearance
- Head, ears, eyes, nose, mouth, throat, neck
- Respiratory system
- Cardiovascular system
- Abdomen
- Musculoskeletal system
- Central and peripheral nervous system
- Skin
- Thyroid gland
- Lymph node palpation
- Breast (females only).

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2 Vital signs

- Blood pressure and pulse rate measurements should be preceded by at least 5 minutes of rest for the subject in a quiet setting without distractions (e.g. no use of television, cell phones).
- Blood pressure and pulse rate measurements will be assessed sitting with a completely automated device. Manual techniques must be used only if an automated device is not available.
- Blood pressure will consist of 3 systolic and diastolic blood pressure measurements with intervals of at least 1-2 minutes. An additional fourth blood pressure measurement must be performed if the first two readings on systolic or diastolic blood pressure differ by >10 mmHg. Only the last 2 systolic and last 2 diastolic blood pressure readings must be recorded in the eCRF. The eCRF will then calculate the mean for systolic and diastolic blood pressure.
- Pulse rate will be measured in connection to the blood pressure measurements. Record the pulse rate for the last 2 blood pressure measurements in the eCRF. The eCRF will calculate the mean pulse rate values based on the last 2 measurements.

8.2.3 Electrocardiograms

- 12-lead ECG will be obtained as outlined in the flowchart using an ECG machine that automatically calculates the heart rate and measures PR, QRS and QT-intervals.

8.2.4 Eye examination

Subjects with uncontrolled and potentially unstable diabetic retinopathy or maculopathy are not eligible as this indicates retinopathy that has recently progressed to a level that requires intervention or is approaching intervention but has yet to be brought under control.

Results of an eye examination performed by an ophthalmologist or another suitably qualified health care provider (e.g. optometrist) must be available and evaluated by the investigator before randomisation to assess eligibility. The eye examination should be performed as a fundus

photography (e.g. 2-field 60 degree or better, colour or red-free) or by slit-lamp biomicroscopy examination (e.g. using a pre-corneal or corneal contact lens examination). Pharmacological pupil-dilation is a requirement unless using a digital fundus photography camera specified for non-dilated examination.

If the subject had such an eye examination performed within 90 days prior to screening, the investigator may base his/her evaluation upon the results of that examination. The examination must be repeated before randomisation if the subject has experienced worsening of visual function since the last examination. If the applicable eye examination was performed before the subject signed the informed consent form, it must be documented that the reason for performing the examination was not related to this trial.

After randomisation an eye examination performed according to above must be performed as per protocol flowchart (Section 1.2). An eye examination performed within 2 weeks prior to the applicable visits is acceptable, provided that no clinical symptoms suggestive of eye disease have occurred in the meantime in case of which a new examination must be completed. The investigator should indicate the outcome of each eye examination in the eCRF.

The fundus photography or slit-lamp biomicroscopy examination should be used for evaluation of retinopathy or maculopathy. Additional examinations (e.g., optical coherence tomography and/or best corrected visual acuity) can be performed as a supplement for further evaluation. However, in this trial, additional eye examinations including the optical coherence tomography and/or best corrected visual acuity, cannot replace the fundus photography or slit-lamp biomicroscopy examination.

Relevant findings prior to randomisation must be recorded as concomitant illness/medical history. Relevant findings occurring after randomisation should be reported as an AE, please refer to Section 8.3.

8.2.5 Clinical safety laboratory assessments

All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the protocol flowchart.

8.3 Adverse events and serious adverse events

The investigator is responsible for detecting, documenting, recording and following up on events that meet the definition of an AE or SAE.

The definition of AEs and SAEs can be found in Appendix 3, along with a description of AEs requiring additional data collection, please refer to Table 8-1.

Hypoglycaemic episodes

Hypoglycaemic episodes require additional data collection on a hypoglycaemic episode form. As opposed to AEs requiring additional data collection (Table 8-1), non-serious hypoglycaemic episodes do not require an AE form to be filled in. If the hypoglycaemic episode fulfils the criteria for an SAE, then, in addition to the hypoglycaemic episodes form, an AE form and a safety

information form must be filled in, please refer to Appendix 3. For more information on hypoglycaemic episodes, please refer to Appendix 7.

Table 8-1 AEs requiring additional data collection (serious and non-serious AEs)

Event type	AE requiring additional data collection
Medication error	X
Misuse and abuse	X
Acute gallbladder disease	X
Acute pancreatitis	X
Diabetic retinopathy	X
Hypersensitivity reaction	X
Injection site reaction	X

Information on misuse and abuse AEs are captured on the medication error form.

A detailed description of the events mentioned in the above table can be found in Appendix 3.

8.3.1 Time period and frequency for collecting AE and SAE information

All AEs and SAEs must be collected from the screening visit and until the 'end of trial' visit at the time points specified in the flowchart.

Medical occurrences that take place or have onset prior to the time point from which AEs are collected will be recorded as concomitant illness/medical history. AE and SAE reporting timelines can be found in Appendix 3. All SAEs must be recorded and reported to Novo Nordisk or designee within 24 hours, and the investigator must submit any updated SAE data to Novo Nordisk or designee within 24 hours of it being available.

Investigators are not obligated to actively seek for AE or SAE in former trial subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discontinued from/completed the trial, and the investigator considers the event to be possibly/probably related to the trial products or related to trial participation, the investigator must promptly notify Novo Nordisk.

8.3.2 Method of detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

Care should be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about events.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, should be followed until final outcome of the event or the subject is lost to follow-up as described in Section 7.3. Further information on follow-up and final outcome of events is given in Appendix 3.

8.3.4 Regulatory reporting requirements for SAEs

Prompt notification by the investigator to Novo Nordisk or designee of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a trial product under clinical investigation are met.

Novo Nordisk has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a trial product under clinical investigation. Novo Nordisk will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators. This also includes suspected unexpected serious adverse reactions (SUSARs).

An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g. summary or listing of SAEs) from Novo Nordisk will review and then file it along with the investigator's brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5 Pregnancy

Details of pregnancies in female subjects will be collected after screening visit and until 'end of trial' visit (V17). If a female subject becomes pregnant, the investigator should inform Novo Nordisk within 14 calendar days of learning of the pregnancy and should follow the procedures outlined in Appendix 4 (Section 10.4).

8.3.6 Cardiovascular and death events

Cardiovascular and death events will be handled and reported according to Section 8.3.

8.3.7 Hypersensitivity

In the event of a systemic hypersensitivity reaction to trial products, the subject should be called in as soon as possible to have additional blood samples taken in order to analyse the following parameters:

- tryptase
- total immunoglobulin E (IgE) antibodies
- anti-cagrilintide IgE antibodies
- anti-semaglutide IgE antibodies

The blood sampling should be repeated 2-4 weeks following onset of the systemic hypersensitivity reaction. If possible, the above-mentioned analyses should also be performed on the PK sample from visit 4 (week 4).

For details related to blood sampling, plasma preparation and storage, please refer to the laboratory manual.

For retention of residual hypersensitivity samples, please refer to Appendix 6, Section 10.6.

8.3.8 Technical complaints

Technical complaints will be collected for all products listed on the technical complaint form.

Instructions for reporting technical complaints can be found in Appendix 5, Section 10.5.

In order for Novo Nordisk to perform a complete investigation of reported SAEs, Novo Nordisk might ask the investigator to complete a technical complaint form.

8.4 Treatment of overdose

Overdoses of up to 6.0 mg has been observed with cagrilintide treatment in the phase 2 clinical trial (NN9838-4433). The overdoses were related to non-serious AEs, most commonly GI AEs and dizziness.

Semaglutide overdoses of up to 4.0 mg in a single dose, and up to 4.0 mg in a week (by multiple administrations) have been reported in clinical trials (STEP-programme). The most commonly reported AE was nausea. All subjects recovered without complications.

There is no specific antidote for overdose with either semaglutide or cagrilintide. In the event of an overdose, appropriate supportive treatment should be initiated according to subject's clinical signs and symptoms.

Accidental overdose must be reported as a medication error. Intentional overdose must be reported as misuse and abuse, please refer to Section 8.3 and Appendix 3 for further details.

In the event of an overdose, the investigator should closely monitor the subject for overdose-related AE/SAE and laboratory abnormalities, considering the long half-life of cagrilintide and semaglutide.

Decisions regarding dose interruptions or modifications will be made by the investigator based on the clinical evaluation of the subject.

For more information on overdose, also consult the current version of the cagrilintide and semaglutide investigator's brochure.

8.5 Pharmacokinetics

Plasma samples to be analysed for plasma concentration of semaglutide and cagrilintide will be collected at time points as specified in the flowchart (see Section 1.2 and 10.2). Blood samples for measurement of cagrilintide and semaglutide concentration must be drawn before dosing of trial product (C_{trough} measurement).

Separate plasma samples will be collected for cagrilintide and semaglutide. Sampling and handling will be performed as detailed in the laboratory manual.

Semaglutide and cagrilintide will be assayed in plasma by validated assays. Details of the bioanalysis will be outlined in a bioanalytical study plan.

For retention of residual cagrilintide PK samples, please refer to Appendix 6, Section 10.6.

8.6 Pharmacodynamics

Not applicable for this trial.

8.7 Genetics

Not applicable for this trial.

8.8 Biomarkers

Collection of samples for biomarker research is part of this trial to support the efficacy objectives. The following samples must be collected and processed in accordance with the laboratory manual and Appendix 2, Section 10.2 :

Biomarkers linked to cardiovascular risk and inflammation:

- High sensitive C-reactive protein (hsCRP)

Biomarkers linked to appetite regulation:

- Leptin
- Soluble leptin receptor

8.9 Immunogenicity assessments

Not applicable for this trial.

8.10 Health economics

Not applicable for this trial.

9 Statistical considerations

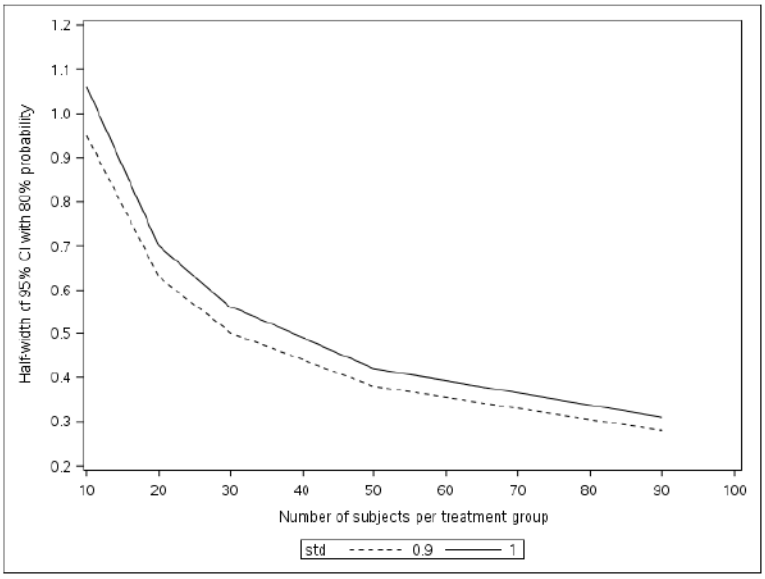
9.1 Statistical hypotheses

No confirmatory statistical hypothesis testing will be done in this trial. Treatment differences will be reported with 2-sided 95% confidence intervals.

9.2 Sample size determination

As the present study is exploratory the sample size calculation is not based on confirmatory testing but aims at quantifying the magnitude of expected variation in the treatment difference for the primary endpoint supporting the primary objective. For the primary estimand a standard deviation of 0.9 (STEP 2) or 1 is assumed for HbA_{1c} change from baseline to week 32. With 30 randomised subjects per treatment arm approximately 80% probability is achieved for obtaining a 95% confidence interval of the treatment difference with half-width 0.5 and 0.56 %-points, respectively. The achievable half-width (with roughly 80% probability) versus sample size is shown in Figure 9-1 for different choices of sample size. Based on this, a sample size of 30 randomised subjects per treatment arm, i.e. a total of 90 randomised subjects, is considered sufficient.

Figure 9-1. Half-width of 95% CI for treatment difference on HbA_{1c} change obtained with 80% power versus sample size by standard deviation (std).



9.3 Populations for analyses

The following population*s* are defined:

Population	Description
Full analysis set (FAS)	All subjects randomised.
Safety analysis set (SAS)	All subjects randomly assigned to trial treatment and who take at least 1 dose of trial product.

The subjects or observations to be excluded from the analysis sets and the reasons for their exclusion must be documented before unblinding and will be described in the CTR. Efficacy endpoints will be analysed using the FAS and safety endpoints will be analysed using the SAS. For both the primary estimand and the additional estimand, subjects contribute to the analysis according to the randomised treatment.

Three observation periods are defined for each subject:

- The in-trial period is defined as the time interval from date of randomisation to date of last contact with trial site.
- The on-treatment period is a subset of the 'in-trial' observation period and represents the time period where subjects are considered exposed to trial product. The observation period starts at the date of first dose of trial product and ends at the first date of any of the following:
    - The date of last dose of trial product +35 days for AEs and hypoglycaemic episodes/ + 14 days for other endpoints
    - The end-date for the 'in-trial' observation period

The on-treatment period will be used for reporting AEs and hypoglycaemic episodes.

The on-treatment without rescue medication period is a subset of the 'on-treatment' observation period and represents the time period where subjects are considered exposed to trial product but

have not initiated any rescue medications. The observation period starts at the date of first dose of trial product and ends at the first date of any of the following:

- Initiation of rescue medication
- The last date of the on-treatment period

The in-trial and on-treatment periods define the patient years of observation (PYO) and patient years of exposure (PYE), respectively, as the total time duration in the periods.

Data points collected outside an observation period will not be included in the analysis. Baseline data will always be included in an observation period.

For the primary estimand, the on-treatment without rescue medication period will be used for reporting of efficacy endpoints. For the additional estimand, data from the in-trial observation period is used.

9.4 Statistical analyses

The statistical analysis plan (SAP) will be finalised prior to the first administrative DBL and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary endpoint.

9.4.1 General considerations

Handling of missing baseline data

The latest available measurement at or prior to randomisation is used as the baseline measurement.

If no measurements have been obtained at or prior to randomisation, the mean value at randomisation across all subjects is used as the baseline value.

9.4.2 Primary endpoint

Analysis addressing the primary estimand

HbA_{1c} (%-point) change from baseline will be analysed using a mixed model for repeated measurements (MMRM). Week 32 assessments for retrieved drop-outs are not used in this analysis. The MMRM will use assessments only from subjects who are taking the randomised treatment until end of treatment or until first discontinuation of randomised treatment defined as 2 consecutive missed doses. The derived date of the second consecutive missed dose will be used as the latest date for using assessments in this MMRM. For subjects who initiate rescue medication before completion or first discontinuation of randomised treatment, the date of starting rescue medication will be used as latest date for using assessments in this MMRM. The MMRM will be fitted using HbA_{1c} change with treatment and stratification factor as factors and baseline HbA_{1c} as covariate – all nested within visit. An unstructured covariance matrix for measurements within the same subject will be employed. If this model is not feasible, the model will be simplified by first excluding the stratification factor from the model and, if necessary, using a compound symmetry covariance matrix.

The present ANCOVA-MMRM model will be used to derive estimates of treatment differences with 95% confidence intervals for cagrilintide 2.4 mg/semaglutide 2.4 mg versus semaglutide 2.4 mg (primary objective) and versus cagrilintide 2.4 mg (secondary objective) together with p-values for the 2-sided tests of no treatment differences.

Analyses addressing the additional estimand

The analysis model for change in HbA_{1c} (%-point) is an ANCOVA with randomised treatment and stratification factor as factors and baseline HbA_{1c} as a covariate. The additional estimand will be based on the FAS using all available week 32 measurements from the in-trial observation period. Missing week 32 data will be imputed from retrieved subjects off treatment by multiple imputation (RDMI) using an ANCOVA model with the same factors and covariate as for the analysis model. If necessary for feasibility, this model will be simplified by excluding the stratification factor.

The present ANCOVA-RDMI model will be used to derive estimates of treatment differences with 95% confidence intervals for cagrilintide 2.4 mg/semaglutide 2.4 mg versus semaglutide 2.4 mg (primary objective) and versus cagrilintide 2.4 mg (secondary objective) together with p-values for the 2-sided tests of no treatment differences.

9.4.3 Secondary endpoint(s)

9.4.3.1 Confirmatory secondary endpoint(s)

Not applicable for this trial.

9.4.3.2 Supportive secondary endpoints

CGM endpoints 'time in target range' and 'time above target range' will be calculated as 100 times the number of recorded measurements in the given glycaemic range, divided by the total number of recorded measurements.

Analysis of other secondary endpoints are described in the SAP.

9.4.4 Exploratory endpoints

Analyses of exploratory endpoints are described in the SAP.

9.4.5 Other safety analyses

All safety analyses will be made on the safety analysis set. The standard safety assessments (AEs, safety laboratory parameters, vital signs, etc.) will be reported descriptively, including any notable changes of clinical interest in laboratory parameters.

9.4.6 Other analyses

For other analyses, please refer to the SAP.

9.4.6.1 Pharmacokinetic modelling

Data from the trial may be used for exploratory pharmacokinetic analysis as needed.

9.5 Interim analyses

In order to prepone a phase 3 stop/go decision and initiate potential phase 3 planning, interim analyses are planned at week 20 for the following endpoints:

- Change from baseline to week 20 in HbA_{1c}
- Change from baseline to week 20 in FPG
- CGM endpoints: Mean glucose change from baseline to week 20, Time in target range at week 20 and time above target range at week 20.
- Change from baseline to week 20 in body weight

Another interim may be conducted after last subject's last treatment in case the interim at week 20 was inconclusive.

A minimum number of Novo Nordisk personnel will be unblinded to perform the interim evaluations. After unblinding, these people cannot be involved in daily trial activities until DBL. No change in trial design can occur and the trial will not be stopped for either positive efficacy or futility at the interim evaluations. It is not considered a protocol deviation if an interim analysis is not performed. Further information on the interim evaluations will be specified in an interim charter before unblinding.

9.6 Data monitoring committee

Not applicable for this trial.

9.7 Reporting of the main part of the trial

A DBL is planned shortly after last subject last visit. The trial will be reported after this DBL.

10 Supporting documentation and operational considerations

10.1 Appendix 1: Regulatory, ethical, and trial oversight considerations

10.1.1 Regulatory and ethical considerations

- This trial will be conducted in accordance with the protocol and with the following:
- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki[28] and applicable ICH Good Clinical Practice (GCP) Guideline[29]
- Applicable laws and regulations
- The protocol, informed consent form, investigator's brochure (as applicable) and other relevant documents (e.g. advertisements) must be submitted to an IRB/IEC and reviewed and approved by the IRB/IEC before the trial is initiated.
- Regulatory authorities will receive the clinical trial application, protocol amendments, reports on SAEs, and the CTR according to national requirements.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the trial design, except for changes necessary to eliminate an immediate safety hazard to trial subjects.
- Before a site is allowed to start screening subjects, written notification from Novo Nordisk must be received.
- The investigator will be responsible for:
    - providing written summaries of the status of the trial annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC and/or regulatory authorities
    - notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
    - providing oversight of the conduct of the trial at the site and adherence to requirements of ICH guidelines, the IRB/IEC, and all other applicable local regulations
    - ensuring submission of the CTR synopsis to the IRB/IEC
    - reporting any potential serious breaches to the sponsor immediately after discovery

10.1.2 Financial disclosure

Investigators and sub-investigators will provide Novo Nordisk with sufficient, accurate financial information as requested to allow Novo Nordisk to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the trial and one year after completion of the trial.
Verification under disclosures per Code of Federal Regulations (CFR) of Financial Conflict of Interest.

10.1.3 Informed consent process

- The investigator or his/her representative will explain the nature of the trial to the subject and answer all questions regarding the trial.

- The investigator must ensure the subject ample time to come to a decision whether or not to participate in the trial.
- Subjects must be informed that their participation is voluntary.
- Subjects must be informed about their privacy rights.
- Subjects will be required to sign and date a statement of informed consent that meets the requirements of local regulations, ICH guidelines[29], Declaration of Helsinki[28] and the IRB/IEC or site.
- The medical record must include a statement that written informed consent was obtained before any trial related activity and the date when the written consent was obtained. The authorised person obtaining the informed consent must also sign and date the informed consent form before any trial related activity.
- The responsibility of seeking informed consent must remain with the investigator, but the investigator may delegate the task to a medically qualified person, in accordance with local requirements.
- Subjects must be re-consented to the most current version of the informed consent forms during their participation in the trial.
- A copy of the informed consent forms must be provided to the subject.

10.1.4 Information to subjects during trial

The site will be offered a communication package for the subject during the conduct of the trial. The package content is issued by Novo Nordisk. The communication package will contain written information intended for distribution to the subjects. The written information will be translated and adjusted to local requirements and distributed to the subject at the discretion of the investigator. The subject may receive a "welcome to the trial letter" and a "thank you for your participation letter" after completion of the trial. Further, the subject may receive other written information during the trial.

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

10.1.5 Data protection

- Subjects will be assigned a 6-digit unique identifier, a subject number. Any subject records or datasets that are transferred to Novo Nordisk will contain the identifier only. No direct identifiers from the subject are transferred to Novo Nordisk.
- The subject and any biological material obtained from the subject will be identified by subject number, visit number and trial ID. Appropriate measures such as encryption or leaving out certain identifiers will be enforced to protect the identity of subjects as required by local, regional and national requirements.
- The subject must be informed about his/her privacy rights, including that his/her personal trial related data will be used by Novo Nordisk in accordance with local data protection law. The disclosure of the data must also be explained to the subject.
- The subject must be informed that his/her medical records may be examined by auditors or other authorised personnel appointed by Novo Nordisk, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.6 Committees structure

10.1.6.1 Novo Nordisk safety committee

Novo Nordisk will perform ongoing safety surveillance. If new safety signals are identified, these will be evaluated by an internal safety committee. The safety committee may recommend unblinding of any data for further analysis, and in this case an internal trial independent ad hoc group will be established in order to maintain the blinding of the trial personnel.

10.1.6.2 Trial safety group

Not applicable for this trial.

10.1.6.3 Data monitoring committee

Not applicable for this trial.

10.1.6.4 Event adjudication committee

Not applicable for this trial.

10.1.7 Dissemination of clinical trial data

Information of the trial will be disclosed at clinicaltrials.gov and novonordisk-trials.com. It will also be disclosed according to other applicable requirements, such as those of the International Committee of Medical Journal Editors (ICMJE)[30], the Food and Drug Administration Amendment Act (FDAAA)[31], European Commission Requirements[32-34] and other relevant recommendations or regulations. If a subject request 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.

The primary completion date (PCD) is the last assessment of the primary endpoint and is for this trial last subject first treatment (LSFT) + 32 weeks corresponding to 'end of treatment visit (visit 16). If the last subject is withdrawn early, the PCD is considered the date when the last subject would have completed visit 16. The PCD determines the deadline for results disclosure at clinicaltrials.gov according to FDAAA.

10.1.8 Data quality assurance

10.1.8.1 Case report forms

- Novo Nordisk or designee is responsible for the data management of this trial including quality checking of the data.
- All subject data relating to the trial will be recorded on electronic CRFs unless transmitted electronically to Novo Nordisk or designee (e.g. laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Corrections to the CRF data may be made by the investigator or the investigator's delegated 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 delegated staff after the date when the investigator signed the CRF, the CRF must be signed and dated again by the investigator.

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

The following will be provided as paper CRFs:

- Pregnancy forms

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

- AE forms
- Safety information forms
- Technical complaint forms (also to be used to report complaints on trial product not yet allocated to a subject)

10.1.8.2 Monitoring

- The investigator must permit trial-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data 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 site staff should be available for discussions at monitoring visits and between monitoring visits (e.g. by telephone).
- Trial monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorised site personnel are accurate, complete and verifiable from source documents; that the safety and rights of subjects are being protected, to monitor drug accountability and collect completed paper CRF pages, if applicable, and that the trial is being conducted in accordance with the currently approved protocol and any other trial agreements, ICH GCP, and all applicable regulatory requirements.
- Monitoring will be conducted using a risk-based approach including risk assessment, monitoring plans, centralised monitoring (remote assessment of data by Novo Nordisk) and visits to sites.
- Monitors will review the subject's medical records and other source data, e.g. the diaries to ensure consistency and/or identify omissions compared to the CRF.

10.1.8.3 Protocol compliance

Deviations from the protocol should be avoided. If deviations do occur, the investigator must inform the monitor without delay 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 CRF or via listings from the trial database.

10.1.9 Source documents

- All data entered in the eCRF must be verifiable in source documentation other than the CRF.
- CGM data is considered intermediate data until it has been transferred to the service provider's database. CGM data transferred to this database will be considered source data. After database lock, site specific CGM data will be provided to sites for site archival.
- The original of the completed diaries must not be removed from the site, unless they form part of the CRF and a copy is kept at the site.
- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the site.
- Data reported on the paper CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents, or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records. Also, current medical records must be available.
- It must be possible to verify subject's medical history in source documents, such as subject's medical record.
- The investigator must document any attempt to obtain external medical information by noting the date(s) when information was requested, and who was contacted.
- Definition of what constitutes source data can be found in a source document agreement at each site. There will only be one source document defined at any time for any data element.

10.1.10 Retention of clinical trial documentation

- Records and documents, including signed informed consent forms, pertaining to the conduct of this trial must be retained by the investigator for 15 years after end of trial unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of Novo Nordisk. No records may be transferred to another location or party without written notification to Novo Nordisk.
- The investigator must be able to access his/her trial documents without involving Novo Nordisk in any way. If applicable, electronic CRF (eCRF) and other subject data will be provided in an electronic readable format to the investigator before access is revoked to the systems and/or electronic devices supplied by Novo Nordisk. Site-specific CRFs and other subject data (in an electronic readable format or as paper copies or prints) must be retained by the site. A copy of all data will be stored by Novo Nordisk.
- Subject's medical records must be kept for the maximum period permitted by the hospital, institution or private practice.

10.1.11 Trial and site closure

Novo Nordisk reserves the right to close the site or terminate the trial at any time for any reason at the sole discretion of Novo Nordisk. If the trial is suspended or terminated, the investigator must inform the subjects promptly and ensure appropriate therapy and follow-up. The investigator and/or Novo Nordisk must also promptly inform the regulatory authorities and IRBs/IECs and provide a detailed written explanation.

Sites will be closed upon trial completion. A site is considered closed when all required documents and trial supplies have been collected and a site closure visit has been performed.

The investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a site by Novo Nordisk or investigator may include but are not limited to:

- failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, Novo Nordisk procedures or GCP guidelines
- inadequate recruitment of subjects by the investigator
- discontinuation of further trial product development.

10.1.12 Responsibilities

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

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

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

The investigator will take all necessary technical and organisational safety measures to prevent accidental or wrongful destruction, loss or deterioration of data. The investigator will prevent any unauthorised access to data or any other processing of data against applicable law. This also includes ensuring that no indirect sharing of user credentials for IT systems used in this study takes place (e.g., by not sharing IT equipment with others in a way where user credentials have the possibility of being shared). The investigator must be able to provide the necessary information or otherwise demonstrate to Novo Nordisk that such technical and organisational safety measures have been taken.

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

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

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

10.1.13 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.

10.1.14 Publication policy

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

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

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

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

One investigator will be appointed by Novo Nordisk to review and sign the CTR (signatory investigator) on behalf of all participating investigators.

10.1.14.1 Communication of results

Novo Nordisk commits to communicate and disclose results of trials regardless of outcome. Disclosure includes publication of a manuscript in a peer-reviewed 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. Novo Nordisk reserves the right to defer the release of data until specified milestones are reached, for example when the CTR is available. This includes the right not to release the results of interim analyses, because the release of such information may influence the results of the entire trial.

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

In all cases, the trial results will be reported in an objective, accurate, balanced and complete manner, with a discussion of the strengths and limitations. 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.

10.1.14.2 Authorship

Novo Nordisk will work with one or more investigator(s) and other experts who have contributed to the trial concept or design, acquisition, analysis or interpretation of data to report the results in one or more publications.

Authorship of publications should be in accordance with the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals by the International Committee of Medical Journal Editors.[35]

All authors will be provided with the relevant statistical tables, figures, and reports needed to evaluate the planned publication.

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

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

For a multicentre 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. Thus, Novo Nordisk may deny a request or ask for deferment of the publication of individual site results until the primary manuscript is accepted for publication. In line with Good Publication Practice, such individual reports should not precede the primary manuscript and should always reference the primary manuscript of the trial.

10.1.14.4 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.

10.2 Appendix 2: Clinical laboratory tests

- The tests detailed in Table 10-1 and Table 10-2 will be performed by the central or special laboratory.
- Additional tests may be performed at any time during the trial as determined necessary by the investigator or required by local regulations. Only laboratory samples specified in the protocol should be sent to the central laboratory for analysis; if additional laboratory sampling is needed, e.g. to follow up on AEs, this must be done at a local laboratory.
- The central laboratory will communicate to the investigator abnormal values of parameters not requested in the protocol but identified by the laboratory equipment and/or their processes according to their lab SOPs. These data will not be transferred to the trial database. The investigator should review such values for AEs and report these according to this protocol.
- The investigator must review all laboratory results for concomitant illnesses and AEs.
- For haematology samples (differential count) where the test result is not normal, then a part of the sample may be kept for up to two years or according to local regulations.
- Results of pharmacokinetics, Leptin and Soluble leptin receptor will not be shared with site.
- Outcome of hypersensitivity tests will be communicated to site. Results of tryptase, total immunoglobulin E (IgE), anti-cagrilintide IgE and anti-semaglutide IgE will not be shared with site.
- Laboratory samples will be destroyed no later than at finalisation of the CTR except for samples described in Section 10.6.

Table 10-1 Protocol-required efficacy laboratory assessments

Laboratory assessments	Parameters	Visits
Glucose metabolism	• $HbA1_c$	1, 2, 4, 6, 8, 12, 14, 16
	• Fasting plasma glucose[1]	2, 4, 6, 8, 12, 16
	• Fasting Serum Insulin • C-Peptide • Proinsulin • Glucagon	2, 6, 12, 16
Lipids	• Cholesterol • High density lipoprotein (HDL) cholesterol • Low density lipoprotein (LDL) cholesterol • Very-low-density lipoprotein (VLDL) cholesterol • Triglycerides	2, 6, 12, 16
Biomarker	• High sensitive C-reactive protein (hsCRP) • Leptin • Soluble leptin receptor	2, 6, 12, 16
NOTES: [1]An FPG result ≤3.9 mmol/L (70 mg/dL) in relation to planned fasting visits should not be reported as a hypoglycaemic episode but as an AE at the discretion of the investigator (Section 10.3).		

Table 10-2 Protocol-required safety laboratory assessments

Laboratory assessments	Parameters	Visits
Haematology	• Haemoglobin • Haematocrit • Erythrocytes • Thrombocytes • Leucocytes • Basophils • Eosinophils • Lymphocytes • Monocytes • Neutrophils	1, 4, 6, 8, 12, 16
Biochemistry[1]	• Alanine Aminotransferase (ALT)[3] • Albumin • Albumin corrected calcium • Alkaline phosphatase • Aspartate Aminotransferase (AST)[3] • Bilirubin • Calcium • Creatine kinase • Creatinine • Gamma Glutamyl Transferase (GGT) • Magnesium	1, 4, 6, 8, 12, 16
	• Potassium • Sodium	1, 2, 4, 6, 8, 12, 16, 17
Hormones	• Aldosterone • Plasma renin activity • Aldosterone-to-renin activity ratio	1, 2, 4, 6, 8, 12, 16, 17
	• Thyroid stimulating hormone (TSH) • Follicle-stimulating hormone (FSH) (female subjects only)[4]	1
Pregnancy Testing	• Highly sensitive urine human chorionic gonadotropin (hCG) pregnancy test (only postmenopausal female subjects who have stopped menstruating within the last 5 years)[2]	1, 2, 4, 6, 8, 10, 12, 14,16, 17
Pharmacokinetics	• Semaglutide plasma concentration • Cagrilintide plasma concentration	4, 6, 12, 16,
Other tests	• eGFR calculated by the central laboratory based on the creatinine value using the CKD-EPI equation	1, 4, 6, 8, 12, 16
	• tryptase • total immunoglobulin E (IgE) antibodies • anti-cagrilintide IgE antibodies • anti-semaglutide IgE antibodies	Only in case of systemic hypersensitivity, see section 8.3.7

Notes:
[1]Details of required actions and follow-up assessments for increased liver parameters including any discontinuation criteria are given in Section 10.3 (Hy's Law) and Section 7.1
[2]Local urine testing will be standard unless serum testing is required by local regulation or IRB/IEC. A pregnancy test should be performed every 4 weeks and at the End of trial (after 5weeks off treatment) (refer to flowchart, Section 1.2 and Appendix 4).

[3]If ALT or AST > 3 upper normal limit (UNL), additional blood sample should be taken from the subject to analyse international normalised ratio (INR) by central laboratory (except at screening visit). Repeat testing of the abnormal laboratory assessments should be performed via central laboratory for the subject until abnormalities return to normal or baseline state.

[4]Applicable for postmenopausal women only to confirm postmenopausal status (see Appendix 4, Section 10.4)

10.3 Appendix 3: Adverse events: Definitions and procedures for recording, evaluation, follow-up, and reporting

10.3.1 Definition of AE

AE definition
An AE is any untoward medical occurrence in a clinical trial subject that is temporally associated with the use of an investigational medicinal product (IMP), whether or not considered related to the IMP. An AE can therefore be any unfavourable and unintended sign, including an abnormal laboratory finding, symptom or disease (new or exacerbated) temporally associated with the use of an IMP.

Events meeting the AE definition
• Any abnormal laboratory test results or safety assessments considered clinically significant in the medical and scientific judgment of the investigator, including events that have worsened from prior to the time point from which AEs are collected • Conditions detected or diagnosed after IMP administration even though it may have been present prior to the time point from which AEs are collected • Exacerbation/worsening of a chronic or intermittent condition including either an increase in frequency and/or intensity of the condition • Signs, symptoms or the clinical sequelae of a suspected drug-drug interaction • Signs, symptoms or the clinical sequelae of a suspected overdose of IMP regardless of intent A "lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition.
Events NOT meeting the AE definition
• Conditions present prior to the time point from which AEs are collected and anticipated day-to-day fluctuations of these conditions, including those identified during screening or other trial procedures performed before exposure to IMP. • Note: Conditions present or occurring prior to the time point from which AEs are collected should be recorded as concomitant illness/medical history. • Medical or surgical procedures (e.g. endoscopy, appendectomy). The condition that leads to the procedure is the AE. • Medical or surgical procedures not preceded by an AE or worsening of a known condition.

10.3.2 Definition of an SAE

An SAE is an AE that fulfils at least one of the following criteria:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' 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 were more severe.
c. Requires inpatient hospitalisation or prolongation of existing hospitalisation • Hospitalisation signifies that the subject has been detained at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other seriousness criteria, the event is serious. When in

doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious.

- Hospitalisation for elective treatment (e.g. elective medical or surgical procedures) of a condition that was present prior to the time point from which AEs are collected, and that did not worsen, is not considered an AE.
  Note:
  - Hospitalisations for administrative, trial related, social and convenience reasons do not constitute AEs and should therefore not be reported as AEs or SAEs.
  - Hospital admissions for medical or surgical procedures, planned before trial inclusion, are not considered AEs or SAEs.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experience of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g. sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Important medical event:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations. This includes important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious and reported as SAEs using the important medical event criterion.
- The following adverse events must always be reported as SAEs using the important medical event criterion if no other seriousness criteria are applicable:
  - Suspicion of transmission of infectious agents via the IMP
  - Risk of liver injury defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 x UNL and total bilirubin >2 x UNL where no alternative aetiology exists (Hy's law)

10.3.3 Description of AEs requiring additional data collection

Description of AEs requiring additional data collection (on specific event form)

Adverse events requiring additional data collection

Event type	Description
Medication error, misuse and abuse	Medication error: A medication error is an unintended failure in the IMP treatment process that leads to, or has the potential to lead to, harm to the subject, such as: • administration of wrong drug or use of wrong device Note: Use of wrong DUN is not considered a medication error unless it results in administration of wrong drug. • wrong route of administration, such as intramuscular instead of subcutaneous • accidental administration of higher dose than intended. The administered dose must deviate from the intended dose to an extent where clinical consequences for the trial subject were likely to happen as judged by the investigator, although they did not necessarily occur.

	Misuse and abuse: • Situations where the IMP is intentionally and inappropriately used not in accordance with the protocol (e.g. overdose to maximise effect) • Persistent or sporadic, intentional excessive use of an IMP which is accompanied by harmful physical or psychological effects (e.g. overdose with the intention to cause harm) Medication error, misuse and abuse must always be reported as an AE (e.g. accidental overdose, intentional overdose or other) on a separate AE form, and a medication error, misuse and abuse form must be completed. In case of a medication error and/or misuse and abuse resulting in a clinical consequence (e.g. hypoglycaemia or other), this must be reported on an additional AE form.
Acute gallbladder disease	Events of symptomatic acute gallbladder disease (including gallstones and cholecystitis).
Acute pancreatitis	The diagnosis of acute pancreatitis requires two of the following three features: • abdominal pain consistent with pancreatitis (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 pancreatitis on imaging.
Diabetic retinopathy	New onset or worsening of diabetic retinopathy.
Hypersensitivity reaction	For all types of hypersensitivity reactions additional information need to be collected including information about the type of reaction and signs and symptoms associated with the event. In case of systemic hypersensitivity reactions relevant immunological tests should be performed please see Section 8.3.7.
Injection site reaction	For all types of injection site reactions additional information need to be collected including information about the objective findings (e.g. erythema, haematoma, ecchymosis) and local symptoms (e.g. burning, pain, numbness, itching).

10.3.4 Recording and follow-up of AE and/or SAE

AE and SAE recording

- The investigator will record all relevant AE/SAE information in the CRF.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory and diagnostics reports) related to the event.
- There may be instances when copies of source documents (e.g. medical records) for certain cases are requested by Novo Nordisk. In such cases, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the source documents before submission to Novo Nordisk.
- 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. For sign-off of SAE related forms, refer to "AE and SAE reporting via paper CRF later in this section.
- Novo Nordisk products used as concomitant medication or NIMP: if an AE is considered to have a causal relationship with a Novo Nordisk marketed product used as NIMP or 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.

Assessment of severity

The investigator will assess severity for each event reported during the trial and assign it to one of the following categories:

- **Mild**: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- **Moderate**: An event that causes sufficient discomfort and interferes with normal everyday activities.
- **Severe**: An event that prevents normal everyday activities.
  Note: An AE that is assessed as severe should not be confused with a SAE. Both AEs and SAEs can be assessed as severe.

Assessment of causality

- The investigator is obligated to assess the relationship between IMP and the occurrence of each AE/SAE.
- Relationship between an AE/SAE and the relevant IMP(s) should be assessed as:
  - 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 IMP.
- Alternative aetiology, such as underlying disease(s), concomitant medication, and other risk factors, as well as the temporal relationship of the event to IMP administration, will be considered and investigated.
- The investigator should use the investigator's brochure for the assessment. For each AE/SAE, the investigator must document in the medical records that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report. However, **it is important that the investigator always makes an assessment of causality for every event before the initial transmission of the SAE data.**
- The investigator may change his/her opinion of causality, in light of follow-up information, and update the causality assessment in the CRF.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Final outcome

The investigator will select the most appropriate outcome:

- **Recovered/resolved:** The subject has fully recovered, or by medical or surgical treatment the condition has returned to the level observed when first documented
- **Recovering/resolving:** The condition is improving, and the subject is expected to recover from the event. This term may be applicable in cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE).
- Note: For SAEs, this term is only applicable if the subject has completed the follow-up period and is expected to recover.
- **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.

Note: This term may be applicable in cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE).

- **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 a fatal outcome must be reported as an SAE.
- **Unknown:** This term is only applicable if the subject is lost to follow-up.

Follow-up of AE and SAE

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Novo Nordisk to elucidate the nature and/or causality of the AE or SAE as fully as possible (e.g. severe hypersensitivity reactions). This may include additional laboratory tests (e.g. skin prick test) or investigations, histopathological examinations, or consultation with other health care professionals.

If a subject dies during participation in the trial or during a recognised follow-up period, the investigator should provide Novo Nordisk with a copy of autopsy report including histopathology.

New or updated information will be recorded in the CRF.

10.3.5 Reporting of SAEs

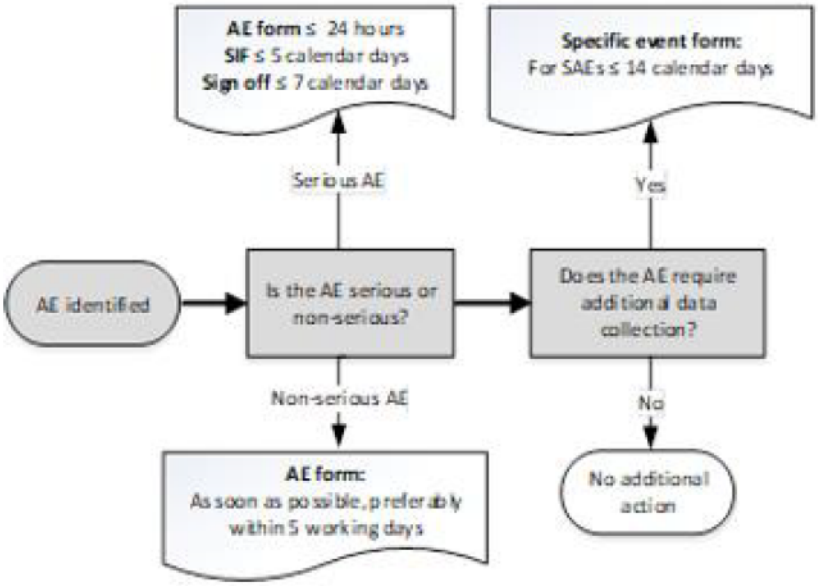
SAE reporting via electronic CRF

- Relevant forms (AE and safety information form) must be completed in the eCRF.
- For reporting and sign-off timelines, see Figure 10-1 below.
- If the eCRF is unavailable for more than 24 hours, then the site will use the paper AE form, and if the eCRF is unavailable for more than 5 calendar days, then the site will use the paper safety information form (see box below).
- The site will enter the SAE data into the eCRF as soon as it becomes available.
- After the trial is completed, the trial database will be locked, and the eCRF will be decommissioned to prevent the entry of new data or changes to existing data. If a site receives a report of a new SAE from a subject or receives updated data on a previously reported SAE after CRF decommission, then the site can report this information on a paper AE and safety information form (see box below) or to Novo Nordisk by telephone.

AE and SAE reporting via paper CRF

- Relevant CRF forms (AE and safety information form) must be forwarded to Novo Nordisk in accordance with Section 10.1.5.
- For SAEs, initial notification via telephone is acceptable, although it does not replace the need for the investigator to complete the AE and safety information form within the designated reporting timelines (as illustrated in the figure below):
  - AE form within 24 hours
  - Safety information form within 5 calendar days
  - Both forms must be signed within 7 calendar days after first knowledge by the investigator.
- The specific event form for AEs requiring additional data collection within 14 calendar days

Figure 10-1 Decision tree for determining the event type and the respective forms to complete with associated timelines



- **Timelines** are from the awareness of an AE.
- **Hypoglycaemic episodes** should be reported on the hypoglycaemic episodes form. If the hypoglycaemic episode fulfils the criteria for an SAE then an AE form and a safety information form must also be filled in.
- **Queries and follow-up** requests to be resolved ≤ 14 calendar days.
- In general, data must be recorded in the CRF as soon as possible, preferably within 5 working days (see Appendix 1)

AE: Adverse Event, **SAE:** Serious Adverse Event, **SIF:** Safety Information Form

Contact details for SAE reporting can be found in the investigator trial master file.

10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information

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

10.4.1 Definitions

Woman of childbearing potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile.
If fertility is unclear (e.g. amenorrhea in adolescents or athletes), and a menstrual cycle cannot be confirmed before first dose of trial treatment, additional evaluation should be considered.

Females in the following categories are not considered WOCBP

1. Females with one or more of the following:
   - Documented total hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

Females with permanent infertility due to an alternate medical cause other than the above (e.g. Müllerian agenesis, androgen insensitivity), investigator discretion should be applied in determining trial enrolment.

2. Postmenopausal female:
   - A postmenopausal state is defined as amenorrhoea for 12 months without an alternative medical cause in a female >45 years of age. Alternative medical causes for amenorrhoea include, but are not limited to, hormonal contraception or hormonal replacement therapy.
   - Females ≥ 60 years of age can be considered postmenopausal.

A FSH measurement may be used to confirm postmenopausal status (see Appendix 2, Section 10.2).

Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt are considered of childbearing potential and are not eligible to participate in this trial.

Note: Documentation regarding categories 1-2 can come from the site staff's review of subject's medical records, medical examination or medical history interview.

10.4.2 Contraception guidance

Male subjects
No contraception measures are required for male subjects, as the risk of teratogenicity/fetotoxicity caused by transfer of cagrilintide in seminal fluid is unlikely[22].

Female subjects
Female subjects of childbearing potential are not eligible to participate.

Pregnancy testing

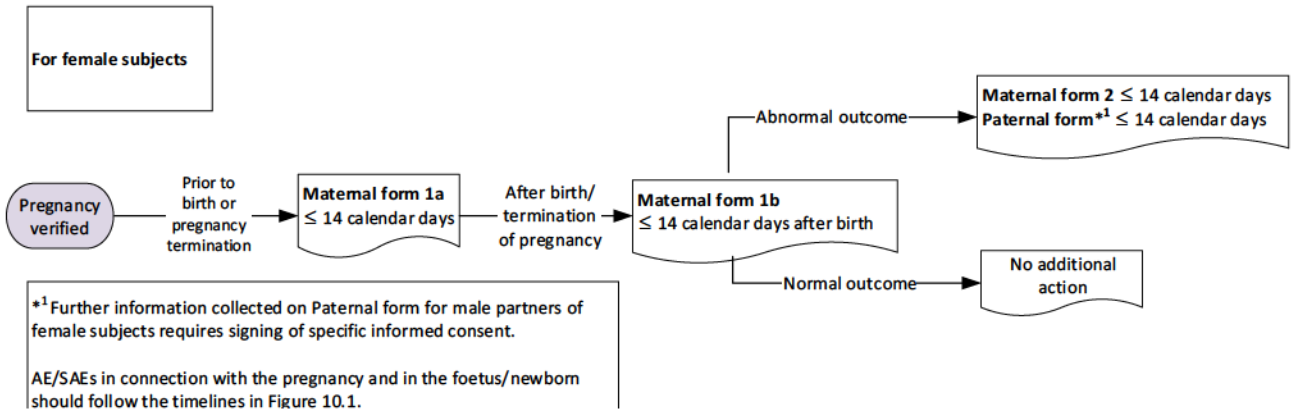
- Postmenopausal female subjects who have stopped menstruating within the last 5 years must have urine pregnancy tests performed at clinic visits as outlined in the flowchart (Section 1.2).
- Pregnancy testing must be performed at home in addition to clinic visits according to the flowchart and home-testing kits must be handed out according to flowchart (see Section 1.2).
- Pregnancy testing must be repeated at any time during the trial if the subject experiences a late or missed menstrual cycle or if pregnancy is otherwise suspected. Trial products must be discontinued until a pregnancy test has been confirmed negative by the investigator.

10.4.3 Collection of pregnancy information

Female subjects who become pregnant

- Investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this trial.
- Information will be recorded on the appropriate form and submitted to Novo Nordisk within 14 calendar days of learning of a subject's pregnancy (see Figure 10-2).
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on subject and neonate which will be forwarded to Novo Nordisk within 14 calendar days. Generally, follow-up will not be required for longer than 1 month beyond the delivery date.
- Any termination of pregnancy will be reported, regardless of foetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any adverse event in connection with pregnancy or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. If relevant, consider adding 'gestational', 'pregnancy related' or a similar term when reporting the AE/SAE.
- Pregnancy outcome should be documented in the subject's medical record. Abnormal pregnancy outcome (e.g. spontaneous abortion, foetal death, stillbirth, congenital anomalies and ectopic pregnancy) is considered an SAE. In case of abnormal pregnancy outcome, paternal information should be recorded in the appropriate form after obtaining the necessary signed paternal informed consent.
- If the investigator learns of an SAE occurring as a result of a post-trial pregnancy which is considered related to the IMP by the investigator, the SAE should be reported to Novo Nordisk as described in Appendix 3 (Section 10.3).

Figure 10-2 Decision tree for determining the forms to complete with associated timelines for pregnancy.



Any female subject who becomes pregnant while participating in the trial will discontinue IMP.

10.5 Appendix 5: Technical complaints: Definition and procedures for recording, evaluation, follow-up and reporting

10.5.1 Definition of technical complaint

Technical complaint definition
• 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:

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

Time period for detecting technical complaints
All technical complaints which occur from the time of receipt of the product at site until the time of the last usage of the product must be collected for products predefined on the technical complaint form.

10.5.2 Recording and follow-up of technical complaints

Reporting of technical complaints to Novo Nordisk
Contact details for Customer Complaint Center, please refer to Attachment I. Technical complaints must be reported on a separate technical complaint form: 1. One technical complaint form must be completed for each affected DUN. 2. If DUN is not available, a technical complaint form for each batch, code or lot number must be completed.

Timelines for reporting of technical complaints to Novo Nordisk
The investigator must complete the technical complaint form in the eCRF within: • 24 hours if related to an SAE • 5 days calendar for all other technical complaints If the eCRF is unavailable, or when reporting a technical complaint on a trial product that is not yet allocated to subject, the information must be provided on a paper form 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.

Follow-up of technical complaints
The investigator is responsible for ensuring that new or updated information will be recorded on the originally completed form.

Collection, storage and shipment of technical complaint samples
The investigator must collect the technical complaint sample and all associated parts that were packed in the same DUN and notify the monitor within 5 calendar days of obtaining the sample at site. The sample and all associated parts must be sent as soon as possible to Customer Complaint Center, Novo Nordisk, together with a copy of the completed technical complaint form. The technical complaint sample should contain the batch, code or lot number and, if available, the DUN. If the technical complaint sample is unobtainable, the reason must be stated on the technical complaint form. If several samples are shipped in one shipment, the sample and the corresponding technical complaint form should be kept together. Storage of the technical complaint sample must be done in accordance with the conditions prescribed for the product.

10.5.3 Reporting of technical complaints

Reporting of technical complaints for Novo Nordisk products not included in technical complaint form
Technical complaints on Novo Nordisk products not included in the technical complaint form should be reported to local Novo Nordisk.

10.6 Appendix 6: Retention of human biosamples

The samples will be pseudoanonymised (so personal data can no longer be attributed to a specific data subject without the use of additional information such as a unique sample ID, visit number, trial identification number and sampling date). Confidentiality and personal data protection will be ensured during storage after the end of trial and no direct identification of the subject will be stored together with the samples.

Potential further analyses of the samples will not have any consequences for the subject.

The biosamples will be stored at a central laboratory, at a central storage facility or Novo Nordisk for up to 15 years after end of trial. Only relevant Novo Nordisk, consultants, research organisations or laboratories working for or collaborating with Novo Nordisk as well as storage facility employees will be able to access the stored biosamples and associated data. The biosamples may be transferred to other countries for analysis and will be destroyed at the latest 15 years after end of trial.

The following human biosamples may be retained until marketing authorisation approval:

Residual cagrilintide PK samples

- The residual PK samples may be retained for later analysis of metabolites or assay validation purposes if needed.
- The residual PK samples may be used for hypersensitivity reaction analysis.

Residual hypersensitivity samples

- In case of a systemic hypersensitivity reaction, the residual hypersensitivity samples (please refer to Section 8.3.7) may be retained to follow-up on the hypersensitivity reaction. If deemed relevant by Novo Nordisk, relevant exploratory analysis may be performed, e.g., histamine release (basophil activation), complement analysis, prick tests and/or intra-dermal tests.

10.7 Appendix 7: Hypoglycaemic episodes

Table 10-3 Classification of hypoglycaemia

Classification of hypoglycaemia		
Level	Glycaemic criteria	Description
Hypoglycaemia alert value (level 1)	< 3.9 mmol/L (70 mg/dL) and ≥ 3.0 mmol/L (54 mg/dL)	Sufficiently low for treatment with fast-acting carbohydrate and dose adjustment of glucose-lowering therapy
Clinically significant hypoglycaemia (level 2)	< 3.0 mmol/L (54 mg/dL)	Sufficiently low to indicate serious, clinically important hypoglycaemia
Severe hypoglycaemia (level 3)	No specific glucose threshold	[1]Hypoglycaemia associated with severe cognitive impairment requiring external assistance for recovery
Notes: The Novo Nordisk terms are adapted from IHSG[36], ADA[37], ISPAD[38], type 1 diabetes outcomes program[39], ATTD[40]. Severe hypoglycaemia as defined by Seaquist[41] and ISPAD[38].		

Severe hypoglycaemia

[1]Severe hypoglycaemia is an event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.[41]

Nocturnal hypoglycaemia

Nocturnal hypoglycaemic episodes: episodes occurring between 00:01 and 05:59 both inclusive.

Reporting of hypoglycaemic episodes

Plasma glucose (PG) should always be measured by the trial BG meter and hypoglycaemic episodes should be recorded in the diary/eCRF. The following should be reported in the diary as hypoglycaemic episodes:

- PG values < 3.9 mmol/L (70 mg/dL)
- Severe hypoglycaemic episodes without confirmed PG values

Hypoglycaemic episodes should be reported according to the instructions below. If a subject experience a hypoglycaemic episode, the subject should record the general information in relation to the hypoglycaemia (timing, PG measurements, symptoms etc.) as described in the diary. The investigator should ensure correct reporting of the hypoglycaemic episode and report the hypoglycaemic episode on the hypoglycaemic episodes form in the eCRF. In case a subject is not able to fill in the diary (e.g. in case of hospitalisation), the investigator should still report the hypoglycaemic episode on the hypoglycaemic episodes form in the eCRF.

If the hypoglycaemic episode fulfils the criteria for an SAE then in addition to the above, an AE form and a safety information form must also be filled in. One AE form and safety information form can cover several hypoglycaemic episode forms, if the subject has not recovered between the episodes.

Upon onset of a hypoglycaemic episode the subject is recommended to measure PG every 15 minutes until the PG value is ≥3.9 mmol/L (70 mg/dL) and/or symptoms have been resolved in accordance with current guidelines.[41]

Repeated PG measurements and/or symptoms will by default be considered as one hypoglycaemic episode until a succeeding PG value is ≥ 3.9 mmol/L (70 mg/dL) and/or symptoms have been resolved and should be reported as only one hypoglycaemic episode. In case of several low PG values within the hypoglycaemic episode, the lowest value is the one that will be reported as the PG value for the hypoglycaemic episode, but the start time of the episode will remain as the time for the first low PG value and/or symptom. The remaining values will be kept as source data.

If the severity of a hypoglycaemic episode changes, only one hypoglycaemic episode will be reported, reflecting the most severe degree of hypoglycaemia.

Regarding the question: "To feel better, did you need help to get a sugary drink, food, or medicine?" the investigator must instruct the subjects to answer "Yes", if the episode was an event that required 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.[41]

Additional information (e.g. description of symptoms, alleviation of symptoms, seizure or coma) in relation to severe hypoglycaemic episodes must be recorded in the hypoglycaemic episode eCRF.

Diary review

At each contact the investigator must review the diary data for correct reporting of PG values and hypoglycaemic episodes. In case of incomplete or incorrect data in the diary, the subject must be questioned whether there have been any severe hypoglycaemic episodes since the last visit and report accordingly.

For low PG values for hypoglycaemic episodes with incomplete reporting information:

- If a hypoglycaemic episode form in the diary is not completed by the subject within 7 calendar days of the PG measurement, the episode should be described in the medical records and reported by the investigator on a hypoglycaemic episode eCRF with as much information as possible. If the subject did not need help to get a sugary drink, food, or medicine, Novo Nordisk will only ask for start date due to recall bias.[42, 43]

Re-training of subjects

The subject must be re-trained in how to report hypoglycaemic episodes if the investigator identifies low PG values not reported as hypoglycaemic episodes. The training should be documented by the investigator in the medical records.

10.8 Appendix 8: Abbreviations

ADA	American Diabetes Association
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BG	blood glucose
BMI	body mass index
CGM	continuous glucose monitoring
CRF	case report form
CTR	clinical trial report
DBL	database lock
DFU	directions for use
DUN	dispensing unit number
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
FAS	full analysis set
FDA	U.S. Food and Drug Administration
FDAAA	FDA Amendments Act
FPG	fasting plasma glucose
FSH	follicle-stimulating hormone
GI	gastrointestinal
GLP-1	glucagon-like peptide-1
GCP	Good Clinical Practice
$HbA1_c$	glycated haemoglobin
HRT	hormone replacement therapy
ICH	International Council for Harmonisation
IEC	independent ethics committee
IB	investigator's brochure
IMP	investigational medicinal product
IRB	institutional review board
IWRS	interactive web response system
LDL	low-density lipoprotein
MMRM	Mixed model for repeated measurements
NIMP	non-investigational medical product
OAD	oral anti-diabetic

PCD	primary completion date
PG	plasma glucose
PK	pharmacokinetics
s.c.	subcutaneus
SAE	serious adverse event
SAP	statistical analysis plan
SGLT2	Sodium-glucose co-transporter-2
SUSAR	suspected unexpected serious adverse reaction
T2D	type 2 diabetes
TMM	trial materials manual
UNL	upper normal limit
WOCBP	woman of child-bearing potential

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16.1.01 Protocol Attachment

Protocol Attachment I is located in the Trial Master File.

If applicable, Protocol Attachment II is also located in the Trial Master File.

Content: Global key staff and Country key staff.