Cover Page for Protocol

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Protocol

Including Amendment 1, dated 22 January 2021

Including Amendment 2, dated 19 February 2021

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STEP HFpEF DM

Protocol title:
Effect of Semaglutide 2.4 mg once-weekly on function and symptoms in subjects with obesity-related heart failure with preserved ejection fraction, and type 2 diabetes

Substance name: Semaglutide

Universal Trial Number: U1111-1257-5069

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Trial phase: 3a

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Protocol amendment summary of changes table

DOCUMENT HISTORY		
Document version	**Date**	**Applicable in country(-ies) and/or site(s)**
Protocol version 7.0 (including amendment 6)	09 Sep 2022	All
Protocol version 6.0 (including amendment 5)	29 Apr 2022	Czech Republic
Protocol version 5.0 (including amendment 4)	01 Oct 2021	India
Protocol version 4.0 (including amendment 3)	24 Mar 2021	Japan
Protocol version 3.0 (including amendment 2)	19 Feb 2021	Germany Japan
Protocol version 2.0 (including amendment 1)	22 Jan 2021	All
Protocol version 1.0	08 Dec 2020	All

Protocol version 7.0 (09 September 2022)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.[1]

Overall rationale for preparing protocol, version 7.0:

The overall rationale for the changes implemented in the amended protocol is an increasing interest in reporting results in a manner that reflects the clinical relevance across different domains including patient-reported outcomes combined with objective measures and events.

Section # and name	Description of change	Brief rationale
Section 1.1 Synopsis	Win ratio composite endpoint added to confirmatory secondary endpoints	See overall rationale
Section 3.1 Primary, secondary and exploratory objectives and estimand?	Secondary objectives changes to address added confirmatory secondary endpoint	See overall rationale
Section 3.2.2.1 Confirmatory secondary endpoints	Win ratio composite endpoint added to confirmatory secondary endpoints	See overall rationale
Section 3.2.2.2 Supportive secondary endpoints	Endpoints related to weight loss, KCCQ-CSS and 6MWD added to supportive secondary endpoints	Alignment with SAP
Section 3.2.3 Exploratory endpoints	KCCQ endpoints added to exploratory endpoints	Alignment with SAP
Section 6.1.1 Medical devices	Follow label instructions for storage and in-use time conditions descriptions on the labels.	Clarification
Section 8.1.2 Clinical outcome assessment	Reference to user guide	Clarification
Section 9.1 Statistical hypotheses	Statistical hypotheses updated to reflect changes to testing hierarchy	See overall rationale
Section 9.2 Sample size determination	Power calculation on confirmatory secondary endpoints updated to reflect changes to the testing hierarchy	See overall rationale

Section 9.4.3.1 Statistical analyses Confirmatory secondary endpoints	Description of statistical analyses updated to reflect inclusion of Win Ratio composite endpoint in confirmatory secondary endpoints	See overall rationale

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Protocol attachment I Global list of key staff and relevant departments and suppliers.

Protocol attachment II Country list of key staff and relevant departments.

1 Protocol summary

1.1 Synopsis

Rationale:

Heart failure with preserved ejection fraction (HFpEF) in patients with obesity and type 2 diabetes (T2D) is associated with decreased health-related quality of life, worse heart failure symptoms, greater systemic inflammation and lower exercise capacity compared to HFpEF patients without obesity. A study of subjects with HFpEF and obesity has indicated that a weight loss of 3-7 kg increases exercise tolerance and HF-specific health-related quality of life.

Objectives and endpoints:

Primary objective

To investigate the effects of semaglutide subcutaneous (s.c.) 2.4 mg once-weekly on physical function, symptoms and body weight compared with placebo, both added to standard of care, in subjects with obesity-related HFpEF and T2D.

Secondary objectives

To investigate the effects of semaglutide s.c. 2.4 mg once-weekly in improving the overall clinical benefit compared with placebo, both added to standard of care, in subjects with obesity-related HFpEF and T2D.

To investigate the effects of semaglutide s.c. 2.4 mg once-weekly on walking distance, biomarker of inflammation, disease specific aspects, social limitation, change in body composition and health-related quality of life, and glycaemic control and hypoglycaemia compared with placebo, both added to standard of care, in subjects with obesity-related HFpEF and T2D.

Primary estimand

The estimand will quantify the average change from baseline in Kansas City Cardiomyopathy Questionnaire (KCCQ) clinical summary score and average change from baseline in body weight of semaglutide s.c. 2.4 mg once-weekly relative to placebo, both added to standard of care, after 52 weeks, in all randomised subjects regardless of adherence to randomised treatment ("treatment policy" estimand).

Multiple primary endpoints

Endpoint title	Time frame	Unit
Change in KCCQ clinical summary score	From baseline (week 0) to end of treatment (week 52)	Score (no unit, range; 0-100)
Change in body weight	From baseline (week 0) to end of treatment (week 52)	%

Confirmatory secondary endpoints

Endpoint title	Time frame	Unit
Change in 6-minute walking distance	From baseline (week 0) to end of treatment (week 52)	Metres
Hierarchical composite of: Time to all-cause death, number of heart failure events requiring hospitalisation or urgent heart failure visit, time to first heart failure event requiring hospitalisation or urgent heart failure visit, difference at least 15 in KCCQ clinical summary score change from baseline to 52 weeks, difference at least 10 in KCCQ clinical summary score change from baseline to 52 weeks, difference at least 5 in KCCQ clinical summary score change from baseline to 52 weeks, difference at least 30 metres in six-minute walking distance change from baseline to 52 weeks (assessed by the win ratio)	From baseline (week 0) to end of study (week 57)	Total wins for each treatment group
Change in C-Reactive Protein	From baseline (week -2) to end of treatment (week 52)	Ratio to baseline (no unit)

Overall design:

This is a 52-week, randomised, placebo-controlled, double-blinded, multi-centre clinical trial comparing semaglutide s.c. 2.4 mg with placebo in subjects with obesity-related HFpEF and T2D.

Eligible subjects will be randomised in a 1:1 manner to receive either semaglutide s.c. 2.4 mg or placebo once-weekly as add-on to standard of care.

Key inclusion criteria:

- Male or female, age above or equal to 18 years at the time of signing informed consent.
- Body mass index (BMI) $\geq$ 30.0 kg/m^2
- New York Heart Association (NYHA) Class II-IV
- Left ventricular ejection fraction (LVEF) $\geq$ 45% at screening
- Diagnosed with T2D $\geq$ 90 days prior to the day of screening
- HbA_{1c} of $\leq$ 10.0% as measured at the screening visit

Key exclusion criteria:

- A self-reported change in body weight > 5 kg (11 lbs) within 90 days before screening irrespective of medical records
- Uncontrolled and potentially unstable diabetic retinopathy or maculopathy. Verified by a fundus examination performed within 90 days prior to 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:

610 subjects will be randomly assigned to trial product.

Treatment groups and duration:

The total trial duration for the individual subject will be approximately 59 weeks. The trial includes a screening period of approximately 2 weeks. Eligible subjects will at visit 2 be randomised in a 1:1 manner to receive either semaglutide 2.4 mg once-weekly or placebo once-weekly as add-on to standard of care. During the first 16 weeks, the dose of semaglutide or placebo will be gradually escalated from 0.25 mg once-weekly until maintenance dose. The treatment will continue until the end-of-treatment visit followed by a 5-week follow-up period.

The following trial products will be supplied by Novo Nordisk A/S:

- Semaglutide D 0.5 mg/mL, solution for injection, DV3396 0.5mL pen-injector
- Semaglutide D 1.0 mg/mL, solution for injection, DV3396 0.5 mL pen-injector
- Semaglutide D 2.0 mg/mL, solution for injection, DV3396 0.5 mL pen-injector
- Semaglutide D 2.27 mg/mL, solution for injection, DV3396 0.75 mL pen-injector
- Semaglutide D 3.2 mg/mL, solution for injection, DV3396 0.75 mL pen-injector
- Semaglutide placebo Ia, solution for injection, 0.5mL pen-injector
- Semaglutide placebo Ib, solution for injection, 0.75 mL pen-injector

1.2 Flowchart

	Protocol section	Screening	Randomisation	Treatment period								End of treatment	End of trial
Visit		V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
Timing of Visit (Weeks)		-2	0	4	8	12	16	20	28	36	44	52	57
Visit Window (Days)		0 to +13	0	±3	±3	±3	±3	±3	±3	±3	±3	±3	0 to +7
Informed Consent and Demography[a)]	10.1.3	X											
Eligibility Criteria	5.1, 5.2	X	X										
Physical Examination	8.2.1	X	X									X	
Eye examination	8.2.5	X										X	
Medical History/Concomitant Illness	8.2		X										
Tobacco Use [b)]			X										
Childbearing Potential	10.4	X											
Concomitant Medication	6.5	X	X	X	X	X	X	X	X	X	X	X	X
Body Weight	8.1.1	X	X	X	X	X	X	X	X	X	X	X	
Height /BMI	8.1.1	X											
Waist Circumference	8.1.1		X					X				X	
Patient Global Impression of Status (PGI-S) for KCCQ	8.1.2	X	X					X		X		X	
Patient Global Impression of Change (PGI-C) for KCCQ	8.1.2		X					X		X		X	
Kansas City Cardiomyopathy Questionnaire (KCCQ)	8.1.2	X	X					X		X		X	
European Quality of Life five Dimensions five Level (EQ-5D-5L)	8.1.2		X					X				X	
Patient Global Impression of Status (PGI-S) for 6MWT	8.1.2	X	X					X				X	
Patient Global Impression of Change (PGI-C) for 6MWT	8.1.2		X					X				X	

	Protocol section	Screening	Randomisation	Treatment period								End of treatment	End of trial
Visit		V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
Timing of Visit (Weeks)		-2	0	4	8	12	16	20	28	36	44	52	57
Visit Window (Days)		0 to +13	0	±3	±3	±3	±3	±3	±3	±3	±3	±3	0 to +7
6-minute walk test (6MWT)	8.1.2	X	X					X				X	
NYHA classification/Vital Signs	8.2.4, 8.2.2	X						X				X	
Electrocardiogram (ECG)	8.2.3	X										X	
Echocardiography	8.1.3	X	X[c)]									X[c)]	
Laboratory Assessments	10.2	X	X		X			X		X		X	
Semaglutide plasma concentration	10.2							X				X	
Pregnancy test[d)]	8.3.5, 10.4	X	X		X	X		X	X	X	X	X	X
Healthy Lifestyle Counselling	5.3		X	X	X	X	X	X	X	X	X	X	
Adverse Event	8.3, 10.3			X	X	X	X	X	X	X	X	X	X
Hypoglycaemic episodes	8.3, 10.7		X	X	X	X	X	X	X	X	X	X	X
Self-measured plasma glucose[e)]	8.2.6			X	X	X	X	X					
Event Adjudication	8.3, 10.3			X	X	X	X	X	X	X	X	X	X
Medication Error, Misuse and Abuse	8.3, 10.3.3			X	X	X	X	X	X	X	X	X	
Drug dispensing			X	X	X	X	X	X	X	X	X		
Drug Accountability	6.2		X	X	X	X	X	X	X	X	X	X	
IWRS Session	6.3	X	X	X	X	X	X	X	X	X	X	X	
Training in trial product, pen-handling	6.1		X	X		X				X			
Hand Out Direction for Use	6.1		X										
Hand Out Dose Reminder Card			X	X	X	X	X						

	Protocol section	Screening	Randomisation	Treatment period								End of treatment	End of trial
Visit		V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
Timing of Visit (Weeks)		-2	0	4	8	12	16	20	28	36	44	52	57
Visit Window (Days)		0 to +13	0	±3	±3	±3	±3	±3	±3	±3	±3	±3	0 to +7
Hand Out ID Card		X											
Hand out and instruct in BG meter	10.7		X										
Hand out and instruct in diary	8		X	X	X	X	X	X	X	X	X	X	
Collect, review and transcribe diary	8			X	X	X	X	X	X	X	X	X	X

a: Demography consists of date of birth, sex, race and ethnicity (according to local regulation – Germany and Hungary: for country-specific requirements, please see Appendix 9 (Section 10.9)).

b: Tobacco use is defined as smoking at least one cigarette or equivalent daily.

c: Only relevant for subjects included in the echocardiographic sub-study. India: for country-specific requirements, please see Appendix 9 (Section 10.9).

d: For women of childbearing potential only. In addition to the planned assessments, urine dipstick pregnancy test should be performed at any time during the trial if a menstrual period is missed, or if pregnancy is suspected (according to local regulation – Czech Republic, United Kingdom and Germany: for country-specific requirements, please see Appendix 9 (Section 10.9)).

e: All subjects treated with insulin should capture SMPG.

2 Introduction

There are currently no clinical trials showing disease modifying benefits of treatment or improvement of outcomes in patients suffering from HFpEF. This could partly be due to the heterogeneity of this group of patients, which may call for different interventions based on sub-phenotype.[2] This trial will focus on a specific phenotype of obesity-related HFpEF with coexisting T2D and study the effect of body weight reduction obtained by semaglutide treatment on various clinical aspects in patients with HFpEF.

Semaglutide

Semaglutide is the next generation glucagon-like peptide-1 (GLP-1) analogue currently under development by Novo Nordisk for the treatment of weight management (NN9536, including the phase 3a STEP programme). Semaglutide has been optimised resulting in a longer half-life of approximately 160 hours, making it suitable for once-weekly dosing.[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] In addition, GLP-1 will provide glycaemic control in patients with type 2 diabetes.

Clinical[5-27] and non-clinical[28] data indicate that the body weight (BW) reducing effect of semaglutide is mainly mediated by reduced energy intake. Semaglutide 2.4 mg once-weekly appeared to have a safe and well-tolerated profile (STEP programme), as seen with previous trials.

A comprehensive review of results from the non-clinical and clinical studies of semaglutide can be found in the current version of the investigator's brochure[29] or any updates hereof.

In the following, unless otherwise stated, "semaglutide 2.4 mg" will refer to semaglutide s.c. 2.4 mg once-weekly.

2.1 Trial rationale

Obesity is rapidly increasing worldwide and is a major risk factor for the development of HFpEF.[30] Patients with obesity and HFpEF show a very specific pathophysiological profile with the main common pathway through systemic inflammation.[2] HFpEF in patients with obesity is associated with decreased health-related quality of life, worse heart failure symptoms, higher occurrence of T2D, greater systemic inflammation and lower exercise capacity compared to HFpEF patients without obesity.[31] Furthermore, T2D is associated with pathophysiological changes enhancing inflammation and other pathways that could lead to worsening of diastolic and endothelial dysfunction.[32] The T2D population eligible for this trial is only restricted by an upper limit of HbA_{1c} of 10% allowing any treatment regimen making the study population resemble patients from a clinical setting.

This supports that obesity-related HFpEF should be treated as a specific entity, and that development of treatments that can promote a weight loss in this patient population is warranted.

Semaglutide 2.4 mg once-weekly has demonstrated substantial lowering of body weight of up to 14.9% by week 68 in subjects with obesity or overweight (NN9536 STEP programme).

To explore if a structural and functional cardiac effect can be seen, an exploratory echocardiographic sub-study is planned only in a subset of subjects to limit subject burden.

The aim of the present trial is to investigate the effects of semaglutide 2.4 mg on symptoms, physical function, health-related quality of life, and weight loss in a population with obesity-related HFpEF and T2D.

2.2 Background

Heart Failure with Preserved Ejection Fraction

Heart failure (HF) is a haemodynamic disorder where the heart fails to keep up with the circulatory demands of the body (HFrEF), or does so at the expense of raised left ventricular filling pressures (HFpEF).[33] HFpEF is a clinical syndrome of heart failure symptoms combined with normal or near-to-normal LVEF and increased left ventricular filling pressures. The increased pressure can be measured by cardiac catheterization or estimated by echocardiography. Other echocardiographic findings include both structural and functional changes as part of diagnosing HFpEF, and left ventricular diastolic dysfunction (abnormal relaxation) is a key defining feature of HFpEF.[34] The increased pressure generally leads to elevation of NT-proBNP and BNP due to increased ventricular wall tension,[34] but levels of NT-proBNP are inversely related to body weight in both the general population[35] and in the HFpEF patient population.[2]

The prevalence of HFpEF has increased during the last decades and is now more frequent than HFrEF.[36-38] HF, including HFpEF, remains to be a leading cause of morbidity and mortality.[36, 37]

To date, no pharmacological interventions to address HFpEF have been approved, and the current HF therapies do not directly target the fundamental metabolic derangements, thus making it one of the greatest unmet needs in cardiology today.[39]

Obesity-related HFpEF

Obesity, a chronic disease[40] resulting in decreased health-related quality of life and 5-10 years reduced life expectancy,[23, 41, 42] has been identified as a major risk factor for the development of HFpEF. The impact of obesity on HFpEF is probably due to a combination of mechanical mechanisms, volume overload, endocrine-, metabolic- and cellular signalling together with an altered inflammatory status.[30] The aggregate of these factors ultimately lead to cardiomyocyte dysfunction and impaired diastolic function of the heart, while contractility is preserved. More than 83% of patients with HFpEF are found to have either overweight or obesity.[43]

Obesity is associated with systemic inflammation[44] and with increased risk of a variety of comorbidities including T2D, hypertension, dyslipidaemia, cardiovascular diseases, and risk of early death.[12-26] A study of elderly subjects with HFpEF and obesity has indicated that a weight loss of 3-7 kg increases exercise tolerance and improvement in HF-specific health-related quality of life as assessed by the KCCQ.[45]

Lifestyle intervention in the form of diet and exercise is first line treatment for obesity, but most people with obesity struggle to achieve and maintain their weight loss without pharmacotherapy.[40, 46-54] Consequently, semaglutide may serve as a valuable adjunct to lifestyle intervention for individuals with obesity-related HFpEF in order to achieve and sustain a clinically relevant weight loss, to improve complications and health-related quality of life.

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 semaglutide may be found in the investigator's brochure[29] or any update hereof.

2.3.1 Risk assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Trial treatment (semaglutide)		
Gastrointestinal adverse event (AE)	Consistent with findings with other GLP-1 RAs, the most frequently reported AE in clinical trials with semaglutide were gastrointestinal AEs.	A low starting dose and dose escalation steps will be implemented to mitigate the risk of gastrointestinal AEs.
Cholelithiasis	Events of cholelithiasis were the most frequently reported gallbladder events in the phase 2 weight management trial (NN9536-4153) and were in a few instances co-reported with event adjudication committee confirmed acute pancreatitis.	If cholelithiasis is suspected, appropriate clinical follow-up is to be initiated at the investigator's discretion.
Hypoglycaemia (in combination with SU or insulin)	There is a low risk of hypoglycaemic episodes when semaglutide is used as monotherapy. Subjects treated with semaglutide in combination with a sulphonylurea (SU) or insulin have an increased risk of hypoglycaemia.	The risk of hypoglycaemia can be lowered by reducing the dose of SU or insulin when initiating treatment with semaglutide
Diabetic retinopathy	The cardiovascular outcome trial in the semaglutide T2D development programme showed an increased risk of events related to diabetic retinopathy complications in subjects treated with semaglutide compared to placebo, albeit the proportion of subjects with an event of diabetic retinopathy complications was low. The imbalance was driven by subjects with a history of diabetic retinopathy at baseline and subjects who were treated with insulin.	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 and 8.2.5

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Acute pancreatitis	Acute pancreatitis has been observed with the use of GLP-1 RA drug class.	Subjects with a history of chronic pancreatitis or recent acute pancreatitis will not be enrolled in the trial. In addition, trial product should be discontinued in case of suspicion of acute pancreatitis in accordance to Section 7.1.
Medullary thyroid cancer (MTC) (based on non-clinical data)	Proliferative thyroid C-cell changes were seen in the mouse and rat carcinogenicity studies after daily exposure to semaglutide for 2 years. No hyperplasia was observed in monkeys after 52 weeks exposure up to 13-fold above the clinical plasma exposure at 2.4 mg/week. In clinical trials with semaglutide, there have been no clinically relevant changes in calcitonin levels. The C-cell changes in rodents are mediated by the GLP-1 receptor, which is not expressed in the normal human thyroid. Accordingly, the risk of GLP-1 receptor-mediated C-cell changes in humans is low.	Exclusion criteria related to medical history of multiple endocrine neoplasia type 2 (MEN2) or MTC have been implemented.
Pancreatic cancer	There is currently no support from non-clinical studies, clinical trials or post-marketing data that GLP-1 RA based therapies increase the risk of pancreatic cancer, but pancreatic cancer has been classified as a potential class risk of GLP-1 RAs by European Medicines Agency (EMA).	Subjects with a history of malignant neoplasms within the past 5 years prior to screening will be excluded from the trial.
Allergic reactions	As is the case with all protein-based pharmaceuticals, subjects treated with semaglutide are at risk of developing immunogenic and allergic reactions.	Subjects with known or suspected hypersensitivity to semaglutide or related products will not be enrolled.
Risk of COVID-19 infection in relation to trial treatment	Available data does not suggest an increased risk of infection or a more severe progression of infection when treated with s.c. semaglutide.	Detailed information about the known risks for s.c. semaglutide can be found in the investigator's brochure and summary of product characteristics.
Trial procedures		
Cubital haematoma	Venous laboratory samples drawn at screening and selected visits may be associated with slight discomfort and complicated by bruising in the region.	The number of blood samples have been reduced to the extent possible

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Risk of COVID-19 infection in relation to trial participation	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.	The risk of COVID-19 transmission in relation to site visits is overall considered to be low, however this may vary between geographical areas. To minimize the risk as much as possible, the following measure will be taken: Cautious subject recruitment planning to ensure controlled subject enrolment in countries where the COVID-19 pandemic is evaluated to be sufficiently under control
Other		
Pregnancy and fertility (based on non-clinical data)	Studies in animals have shown reproductive toxicity. There is limited data from the use of semaglutide in pregnant women.	Semaglutide should not be used during pregnancy. Exclusion and discontinuation criteria related to pregnancy have been implemented.

2.3.2 Benefit assessment

Subjects will be treated with a regimen anticipated to be better than or equal to the weight management they receive at the time of entry into the trial. Results from the phase 3a weight management programme (NN9536, STEP) demonstrated that s.c. 2.4 mg semaglutide once-weekly, as an adjunct to a reduced calorie diet and increased physical activity, was effective for weight loss in subjects with obesity, while displaying a satisfactory tolerability profile. Weight loss was accompanied by a consistent improvement in weight-related comorbidities, indicated by cardiovascular risk factors, lipid profile and glycaemic factors, as well as improvements in clinical outcome assessments.

Benefits on HF-related symptoms, physical function, and health-related quality of life are to be established by the present trial, but we have indications that semaglutide will improve these measures. The close contact will ensure constant ongoing optimisation of the treatment of any comorbidity.

In addition, it is expected that subjects will benefit from participation through close contact with the trial site and counselling by a qualified healthcare professional, all of which will most likely result in intensified weight management.

2.3.3 Overall benefit-risk conclusion

Necessary precautions have been implemented in the design and planned conduct of the trial in order to minimise the risks and inconveniences of participation in the trial. The safety profile for semaglutide generated from the clinical and non-clinical development programme has not revealed any safety issues that would prohibit administration of semaglutide 2.4 mg. The results of the 3a weight management programme (NN9536, STEP) indicate that semaglutide provides a clinically meaningful weight loss that will provide benefit and is expected to relieve symptoms and improve physical function. The anticipated benefits from healthy lifestyle counselling will include all subjects participating in this trial.

Considering the measures taken to minimise risk to subjects participating in this trial, the potential risks identified in association with semaglutide are justified by the anticipated benefits that may be afforded to subjects with obesity-related HFpEF and T2D.

3 Objectives and endpoints

3.1 Primary, secondary and exploratory objectives and estimand

Primary objective

To investigate the effects of semaglutide s.c. 2.4 mg once-weekly on physical function, symptoms and body weight compared with placebo, both added to standard of care, in subjects with obesity-related HFpEF and T2D.

Secondary objectives

To investigate the effects of semaglutide s.c. 2.4 mg once-weekly in improving the overall clinical benefit compared with placebo, both added to standard of care, in subjects with obesity-related HFpEF and T2D.

To investigate the effects of semaglutide s.c. 2.4 mg once-weekly on walking distance, biomarker of inflammation, disease specific aspects, social limitation, change in body composition, health-related quality of life, and glycaemic control and hypoglycaemia compared with placebo, both added to standard of care, in subjects with obesity-related HFpEF and T2D.

Exploratory objectives

To investigate the effects of semaglutide s.c. 2.4 mg once-weekly versus placebo, both added to standard of care, in subjects with obesity-related HFpEF and T2D regarding:

- Heart failure outcomes
- Change in medications
- Change in biomarkers of myocardial strain
- Echocardiographic parameters of heart failure (in a subset of subjects)

Primary estimand

The estimand will quantify the average change from baseline in KCCQ clinical summary score and average change from baseline in body weight of semaglutide s.c. 2.4 mg once-weekly relative to placebo, both added to standard of care, after 52 weeks, in all randomised subjects regardless of adherence to randomised treatment (“treatment policy” estimand).

The handling of intercurrent events with respect to data collection and analysis is specified in Table 3-1 for the primary endpoints. Apart from the listed examples of intercurrent events, missing data will occur due to non-CV deaths (KCCQ clinical summary score), all deaths (body weight), withdrawn consent, loss to follow-up, or continued follow-up without endpoint evaluation.

Table 3-1 Handling of intercurrent events for the primary endpoints

Intercurrent event	Data collection	Data analysis
Temporary discontinuation of trial treatment	Subjects will be followed, and data collected after intercurrent events	**Primary estimand:** Data collected after intercurrent events used in analysis in line with a treatment-policy strategy CV deaths will be incorporated into the KCCQ clinical summary score by ascribing the outcome an unfavourable value in line with a composite strategy
Initiation of other weight management drugs or bariatric surgery		
CV deaths* for KCCQ- clinical summary score	N/A	

*as determined by the event adjudication committee.

The secondary confirmatory endpoints will use a similar estimand where the strategy for change in 6-minute walking distance will follow the strategy for KCCQ clinical summary score.

For the hierarchical composite endpoint, the intercurrent event of CV death will be handled as part of the endpoint.

3.2 Primary, secondary and exploratory endpoints

3.2.1 Multiple primary endpoints

Endpoint title	Time frame	Unit
Change in KCCQ clinical summary score (see Section 8.1)	From baseline (week 0) to end of treatment (week 52)	Score (no unit, range; 0-100)
Change in body weight	From baseline (week 0) to end of treatment (week 52)	%

3.2.2 Secondary endpoints

3.2.2.1 Confirmatory secondary endpoints

Endpoint title	Time frame	Unit
Change in 6-minute walking distance	From baseline (week 0) to end of treatment (week 52)	Metres
Hierarchical composite of: Time to all-cause death, number of heart failure events requiring hospitalisation or urgent heart failure visit, time to first heart failure event requiring hospitalisation or urgent heart failure visit, difference at least 15 in KCCQ clinical summary score change from baseline to 52 weeks, difference at least 10 in KCCQ clinical summary score change from baseline to 52 weeks, difference at least 5 in KCCQ clinical summary score change from baseline to 52 weeks,	From baseline (week 0) to end of study (week 57)	Total wins for each treatment group

difference at least 30 metres in six-minute walking distance change from baseline to 52 weeks (assessed by the win ratio)		
Change in C-Reactive Protein	From baseline (week -2) to end of treatment (week 52)	Ratio to baseline (no unit)

3.2.2.2 Supportive secondary endpoints

Endpoint title	Time frame	Unit
Subject achieving 10% weight loss or more (Yes/No)	From baseline (week 0) to end of treatment (week 52)	Count of subjects
Subject achieving 15% weight loss or more (Yes/No)	From baseline (week 0) to end of treatment (week 52)	Count of subjects
Subject achieving 20 % weight loss or more (Yes/No)	From baseline (week 0) to end of treatment (week 52)	Count of subjects
Subject improving 5 points or more in KCCQ clinical summary score (see Section 8.1) (Yes/No)	From baseline (week 0) to end of treatment (week 52)	Count of subjects
Subject improving 10 points or more in KCCQ clinical summary score (Yes/No)	From baseline (week 0) to end of treatment (week 52)	Count of subjects
Change in KCCQ overall summary score (see Section 8.1)	From baseline (week 0) to end of treatment (week 52)	Score (no unit, range 0-100)
Subject achieving threshold for clinically meaningful within-subject change in KCCQ-CSS	From baseline (week 0) to end of treatment (week 52)	Count of subjects
Subject achieving threshold for clinically meaningful within-subject change in 6MWD	From baseline (week 0) to end of treatment (week 52)	Count of subjects
Change in waist circumference	From baseline (week 0) to end of treatment (visit 52)	cm
Change in systolic blood pressure	From baseline (week -2) to end of treatment (week 52)	mmHg
Change in HbA_{1c}	From baseline (week 0) to end of treatment (week 52)	%-point
Number of treatment emergent severe or clinically significant hypoglycaemia episodes	From baseline (week 0) to end of trial (week 57)	Count of events

India: for country-specific requirements, please see Appendix 9 (Section 10.9).

3.2.3 Exploratory endpoints

Endpoint title	Time frame	Unit
Change in antihypertensive medication	From baseline (week 0) to end of treatment (week 52)	Category (no unit; decrease / no change / increase)
Change in loop diuretic medication	From baseline (week 0) to end of treatment (week 52)	Category (no unit, decrease / no change / increase)
Change in NT-proBNP	From baseline (week -2) to end of treatment (week 52)	pg/mL
Change in EQ-5D-5L score	From baseline (week 0) to end of treatment (week 52)	Score (no unit, range per item; 1-5)
Subject worsening 5 points or more in KCCQ clinical summary score (Yes/No)	From baseline (week 0) to end of treatment (week 52)	Count of subjects
Subject worsening 10 points or more in KCCQ clinical summary score (Yes/No)	From baseline (week 0) to end of treatment (week 52)	Count of subjects
Subject improving 5 points or more in KCCQ overall summary score (Yes/No)	From baseline (week 0) to end of treatment (week 52)	Count of subjects
Subject improving 10 points or more in KCCQ overall summary score (Yes/No)	From baseline (week 0) to end of treatment (week 52)	Count of subjects
Subject worsening 5 points or more in KCCQ overall summary score (Yes/No)	From baseline (week 0) to end of treatment (week 52)	Count of subjects
Subject worsening 10 points or more in KCCQ overall summary score (Yes/No)	From baseline (week 0) to end of treatment (week 52)	Count of subjects
Change in subscales of KCCQ (total symptom score, physical limitations score, social limitations score, and health-related quality of life)	From baseline (week 0) to end of treatment (week 52)	Score (no unit, range 0-100)
Subject experiencing improvement in NYHA Class (Yes/No)	From baseline (week -2) to end of treatment (week 52)	Count of subjects
Subject experiencing deterioration in NYHA Class (Yes/No)	From baseline (week -2) to end of treatment (week 52)	Count of subjects
Time to first heart failure event (hospitalisation or urgent visit)	From baseline (week 0) to end of treatment (week 52)	Days
Subject achieving HbA_{1c} below 7.0%	From baseline (week 0) to end of treatment (week 52)	Count of subjects
Subject achieving HbA_{1c} below 6.5%	From baseline (week 0) to end of treatment (week 52)	Count of subjects
Echocardiographic sub-study		
Change in left atrial volume	From baseline (week 0) to end of treatment (week 52)	Ratio to baseline (no unit)
Change in left ventricular (LV) filling pressure (diastolic function) (E/e´)	From baseline (week 0) to end of treatment (week 52)	Ratio to baseline (no unit)
Change in global longitudinal strain	From baseline (week 0) to end of treatment (week 52)	%

4 Trial design

4.1 Overall design

This is a 52-week, randomised, placebo-controlled, double-blinded, multi-centre clinical trial comparing semaglutide s.c. 2.4 mg with placebo in subjects with obesity-related HFpEF and T2D.

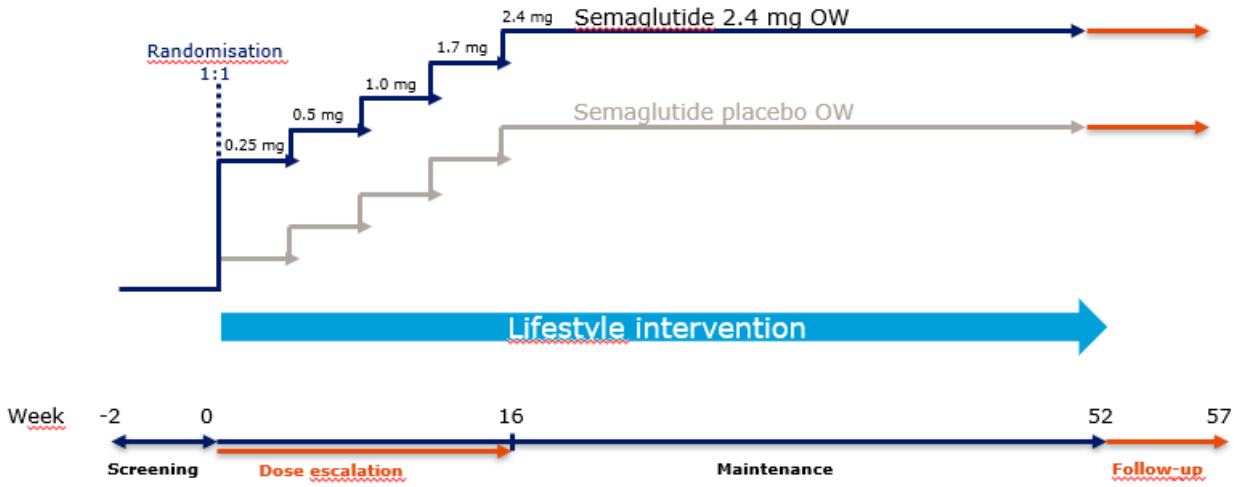
Eligible subjects will be randomised in a 1:1 manner to receive either semaglutide s.c. 2.4 mg or placebo once-weekly as add-on to standard of care (Figure 4-1).

The trial includes a screening visit to assess the subject's eligibility followed by a randomisation visit. A period of 16 weeks of dose escalation is planned to minimise potential gastrointestinal adverse events with a dose increase every 4th week. Hereafter a visit will take place every 8th week until end of treatment (week 52). Follow-up period is 5 weeks after end of treatment.

A subset of 240 randomised subjects will undergo echocardiography at randomisation to ensure that at least 180 subjects will undergo echocardiography at the end of treatment. Measures of diastolic dysfunction will be evaluated as exploratory endpoints in order to gain mechanistic insights associated with weight loss on semaglutide treatment.

Randomisation will be stratified by BMI into two subgroups (BMI < 35.0 and BMI ≥35.0). To ensure sufficient statistical power for subgroup analyses according to BMI, a maximum of 50% of subjects will be included in the lower BMI subgroup.

Figure 4-1 A schematic diagram of the trial design



4.2 Scientific rationale for trial design

The trial population will consist of subjects with HFpEF (symptoms of HF, signs of HF, LVEF ≥ 45 %, and relevant structural heart disease and/or diastolic dysfunction), obesity (BMI ≥30.0 kg/m^2), and T2D (see Section 5.1).[55] The trial population is chosen to optimise the likelihood of clinical benefit of weight loss by including subjects where the mechanism behind their HF is likely to be obesity. Furthermore, T2D is associated with pathophysiological changes enhancing inflammation and other pathways that could lead to worsening of diastolic and endothelial dysfunction.[32] The T2D population eligible for this trial is only restricted by an upper limit of

HbA_{1c} of 10% allowing any treatment regimen making the study population resemble patients from a clinical setting. Improvement in the glycaemic control could also be expected to add to the beneficial effects of semaglutide on inflammation and HFpEF.

Trial duration of 52 weeks has been chosen based on the STEP programme for weight management, in order to ensure enough time to realise full treatment effect on weight loss potential of the intervention as well as downstream effects on symptoms and function related to HF. The treatment length will be 52 weeks consisting of 36 weeks at maintenance dose of semaglutide 2.4 mg after 16 weeks of dose escalation. A 5 week follow-up period after end of treatment is planned in order to collect safety data. The follow-up period of 5 weeks has been chosen to account for the long half-life of semaglutide.

Efforts will be made to ensure that the technician administering the 6-minute walk test (6MWT) is unaware of other assessments that could reveal treatment group.

4.3 Justification for dose

Results from the phase 3a weight management programme (NN9536, STEP) showed that a maintenance dose of semaglutide s.c. 2.4 mg once-weekly leads to clinically meaningfully reductions in body weight while displaying an acceptable tolerability profile. Since weight loss is expected to be part of symptom relief and better physical function in HFpEF patients, a large weight loss is attractive also in patients with obesity-related HFpEF and T2D. The once-weekly dosing is anticipated to ease the burden of drug administration in clinical practice. Subjects will initiate treatment with a once-weekly dose of 0.25 mg and follow a fixed dose escalation regimen, with dose escalation every 4 weeks (to doses of 0.5, 1.0 and 1.7 mg/week), until the 2.4 mg maintenance dose is reached after 16 weeks.

It is well known that to mitigate gastrointestinal adverse events with GLP-1 RA treatment, slow dose escalation to the maintenance dose is required.

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.

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

5 Trial population

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted. The eligibility criteria consists of the inclusion and exclusion criteria outlined below.

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. Male or female, age above or equal to 18 years at the time of signing informed consent.
3. BMI ≥ 30.0 kg/m^2.
4. NYHA Class II-IV.
5. LVEF ≥ 45% at screening.
6. No hospitalisations due to heart failure between screening (V1) and randomisation (V2).
7. Able to perform the 6MWT at screening with a minimum distance of 100 metres.
8. KCCQ clinical summary score < 90 at screening.
9. At least one of the following:
    a. Mean pulmonary wedge pressure ≥15 mmHg or left ventricular end diastolic pressure (LVEDP) ≥15 mmHg documented during catheterisation at rest *or* pulmonary artery (PA) diastolic pressure measured by implantable monitor ≥15 mmHg *or* pulmonary wedge pressure or LVEDP ≥25 mmHg documented during catheterisation at exercise.
    b. If BMI < 35.0: NT-proBNP ≥ 220 pg/mL (for patients with sinus rhythm) or NT-proBNP ≥660 pg/mL (for patients with persistent/permanent atrial fibrillation); if BMI ≥ 35.0: NT-proBNP ≥ 125 pg/mL (for patients with sinus rhythm) or NT-proBNP ≥ 375 pg/mL (for patients with persistent/permanent atrial fibrillation) at screening (NT-proBNP analysed by the central laboratory) in combination with at least one of the following (documented by echocardiography within 12 months prior to or at screening):
        i. Septal é < 7cm/sec or lateral é < 10 cm/sec or average E/é ≥ 15
        ii. PA systolic pressure >35mmHg
        iii. Left atrial (LA) enlargement (LA width ≥3.8 cm or LA length ≥ 5.0cm or LA area ≥ 20.0cm^2 or LA volume ≥ 55mL or LA volume index ≥ 29mL/m^2)
        iv. LV hypertrophy with septal thickness or posterior wall thickness ≥1.2cm
    c. Hospitalisation with a primary diagnosis of decompensated heart failure which required intravenous loop diuretic treatment, within the previous 12 months in combination with at least two of the following (documented by echocardiography within 12 months prior to or at screening):
        i. Septal é < 7cm/sec or lateral é < 10cm/sec or average E/é ≥ 15
        ii. PA systolic pressure > 35mmHg
        iii. LA enlargement (LA width ≥ 3.8cm or LA length ≥ 5.0cm or LA area ≥ 20.0cm^2 or LA volume ≥ 55mL or LA volume index ≥ 29mL/m^2)
        iv. LV hypertrophy with septal thickness or posterior wall thickness ≥ 1.2cm

v. Ongoing use of diuretic therapy for at least 30 days prior to screening

10. Diagnosed with T2D ≥ 90 days prior to the day of screening.
11. Subject treated with diet, exercise, and/or glucose lowering treatment* according to local label in stable dosing for at least 30 days prior to screening:
    - *OAD(s): unchanged drug(s), dose and dosing frequency
    - *Insulin(s): unchanged regimen (basal, basal+bolus, premix combination) with stable total daily insulin dose as judged by the investigator
12. HbA_{1c} of ≤ 10.0% as measured at the screening visit.

Japan: for country-specific requirements, please see Appendix 9 (Section 10.9).

5.2 Exclusion criteria

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

Cardiovascular-related:

1. Myocardial infarction, stroke, hospitalisation for heart failure, unstable angina pectoris or transient ischemic attack within 30 days prior to the day of screening.
2. Systolic blood pressure > 160 mmHg at screening.
3. Planned coronary, carotid or peripheral artery revascularization.
4. Any other condition judged by the investigator to be the primary cause of dyspnoea (such as heart failure due to restrictive cardiomyopathy or infiltrative conditions (e.g. amyloidosis), hypertrophic obstructive cardiomyopathy, primary pulmonary arterial hypertension, chronic obstructive pulmonary disease, right heart failure due to pulmonary disease, complex congenital heart disease, anaemia, or more than moderate heart valve disease).

Obesity-related:

5. Bariatric surgery prior to screening or planned bariatric surgery within the trial time course.
6. A self-reported change in body weight > 5 kg (11 lbs) within 90 days before screening irrespective of medical records.

Glycaemia-related:

7. History of type 1 diabetes (history of gestational diabetes is allowed).
8. Treatment with any GLP-1 receptor agonist within 90 days prior to the day of screening.
9. Uncontrolled and potentially unstable diabetic retinopathy or maculopathy. Verified by a fundus examination performed within 90 days prior to 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.
10. Recurrent severe hypoglycaemic episodes within the last year as judged by the investigator.
11. Treatment with continuous subcutaneous insulin infusion

General health and safety:

12. Personal or first-degree relative(s) history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma.
13. Presence of acute pancreatitis within the last 180 days prior to screening.
14. History or presence of chronic pancreatitis.

15. End-stage renal disease or chronic or intermittent haemodialysis or peritoneal dialysis.
16. Presence or history of malignant neoplasm within 5 years prior to the day of screening. Basal and squamous cell cancer and any carcinoma *in-situ* are allowed.
17. Known or suspected hypersensitivity to trial product or related products.
18. Participation in any clinical trial of an approved or non-approved device for the treatment of heart failure, diabetes or obesity within 30 days before screening.
19. Receipt of any investigational medicinal product within 30 days before screening.
20. Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using a highly effective contraceptive method.
21. Major surgery scheduled for the duration of the trial, affecting walking ability in the opinion of the investigator.
22. Any disorder, including severe psychiatric disorder, suicidal behaviour within 90 days before screening, and suspected drug abuse, which in the investigator´s opinion might jeopardise subject´s safety or compliance with the protocol.

The criteria will be assessed at the investigator's discretion unless otherwise stated.

Czech Republic, Germany and Spain: for country-specific requirements, please see Appendix 9 (Section 10.9).

5.3 Lifestyle considerations

At every visit the subject should be offered individualised healthy lifestyle counselling (including diet and physical activity).

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 and eligibility criteria.

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 are allowed to be rescreened once. 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 randomisation criteria and dosing day criteria

Not applicable for this trial.

6 Treatments

6.1 Treatments administered

Investigational medicinal products (IMP)

The investigational medicinal products (IMP, trial products) provided by Novo Nordisk are listed in Table 6-1 .

Table 6-1 Investigational medicinal products provided by Novo Nordisk

Trial product name	Dose	Dosage form	Route of administration	Dosing instructions	Delivery device
Semaglutide D 0.5 mg/mL DV3396	0.25 mg	Solution for injection	s.c.	Once-weekly	0.5 mL DV3396 pen-injector
Semaglutide D 1.0 mg/mL DV3396	0.5 mg	Solution for injection	s.c.	Once-weekly	0.5 mL DV3396 pen-injector
Semaglutide D 2.0 mg/mL DV3396	1.0 mg	Solution for injection	s.c.	Once-weekly	0.5 mL DV3396 pen-injector
Semaglutide placebo Ia DV3396	N/A	Solution for injection	s.c.	Once-weekly	0.5 mL DV3396 pen-injector
Semaglutide D 2.27 mg/mL DV3396	1.7 mg	Solution for injection	s.c.	Once-weekly	0.75 mL DV3396 pen-injector
Semaglutide D 3.2 mg/mL DV3396	2.4 mg	Solution for injection	s.c.	Once-weekly	0.75 mL DV3396 pen-injector
Semaglutide placebo Ib DV3396	N/A	Solution for injection	s.c.	Once-weekly	0.75 mL DV3396 pen-injector

- The investigator must document that directions for use are given to the subject verbally and in writing as a direction for use (DFU) document, at the first dispensing visit (as specified in the flowchart in Section 1.2).
- It is recommended that the investigator consults Novo Nordisk in case of persistent deviations from the planned escalation regimen.
- Dose escalation of semaglutide/placebo should take place during the first 16 weeks after randomisation as described in Table 6-2 . All subjects should aim at reaching the recommended maintenance dose of semaglutide 2.4 mg once-weekly, or placebo, but individual escalation and dosing are allowed (see later in this section).

Table 6-2 Dose escalation and maintenance of semaglutide/semaglutide placebo

Trial product name	Dose	Delivery device	Duration
Dose escalation period			
Semaglutide D 0.5 mg/mL DV3396/ semaglutide placebo Ia DV3396	0.25 mg	0.5 mL DV3396 pen-injector	4 weeks
Semaglutide D 1.0 mg/mL DV3396/ semaglutide placebo Ia DV3396	0.5 mg	0.5 mL DV3396 pen-injector	4 weeks
Semaglutide D 2.0 mg/mL DV3396/ semaglutide placebo Ia DV3396	1.0 mg	0.5 mL DV3396 pen-injector	4 weeks
Semaglutide D 2.27 mg/mL DV3396/ semaglutide placebo Ib DV3396	1.7 mg	0.75 mL DV3396 pen-injector	4 weeks
Maintenance period			
Semaglutide D 3.2 mg/mL DV3396/ semaglutide placebo Ib DV3396	2.4 mg	0.75 mL DV3396 pen-injector	36 weeks

Subjects will be instructed to inject semaglutide/placebo once-weekly at the same day of the week (to the extent possible) throughout the trial.

Injections may be administered in the thigh, abdomen or upper arm, at any time of day irrespective of meals.

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

If ≥ 2 consecutive doses of trial product are missed, the subject should be encouraged to recommence the treatment if considered safe as per the investigator's discretion and if the subject does not meet any of the discontinuation criteria (Section 7). The trial product should be continued as early as the situation allows. The missed doses should not affect the scheduled dosing day of the week. The start dose for re-initiation of trial product is at the investigator's discretion but the following guidance can be used:

- If ≤ 3 consecutive doses are missed, once-weekly regimen can be resumed as prescribed without dose reduction
- If 4-5 consecutive doses are missed, it is recommended to resume treatment at 1.0 mg for 4 weeks, and then escalate to 2.4 mg, using 1.7 mg as the intermediate dose for 4 weeks
- If ≥ 6 consecutive doses are missed, it is recommended to restart treatment at 0.25 mg semaglutide and escalate to 2.4 mg, using the standard dose escalation regimen

In case of questions related to re-initiation of trial product, the investigator should consult Novo Nordisk.

If a subject does not tolerate the recommended maintenance dose of 2.4 mg once-weekly, the subject may stay at a lower dose level. To prevent premature trial treatment discontinuation and

ensure as much exposure as possible, dose reductions, extensions of dose-escalation intervals and treatment pauses are allowed e.g. if treatment with the trial product is associated with unacceptable AEs or due to other circumstances. Dose adjustments are at the discretion of the investigator. It is recommended that the subject makes at least one attempt to re-escalate to the recommended maintenance dose of 2.4 mg once-weekly.

Date and dose are to be reported in the electronic case report form (eCRF) when trial product dose is initiated or changed (reason for change should also be reported).

Auxiliary supplies

Auxiliary supplies will be provided in accordance with the trial materials manual (TMM) and Table 6-3 .

Table 6-3 Auxiliary supplies provided by Novo Nordisk

Auxiliary supply	Details
Direction for use (DFU)	DFU for DV3396 pen-injector Not included in the dispensing unit and to be handed out separately
Needles	The DV3396 pen-injector comes with an integrated and hidden needle of 6 mm in length (29G), therefore no additional/separate needles are required to be used with this pen-injector
Blood glucose (BG) meter	BG meter and related auxiliaries

6.1.1 Medical devices

Information about the DV3396 pen-injector may be found in the investigator's brochure[29] and any updates hereof. Information about the use of the drug-device combination products can be found in the DFU.

Training in the DV3396 pen-injector

Site staff will train subjects according to the flowchart (Section 1.2). Novo Nordisk will train the site staff and only trained site staff can be allocated the task to train and supervise subjects. All training must be documented.

The following should be emphasised during training of subjects:

- use of the pen-injector (according to instruction guidelines given in the DFU)
- subjects should be informed to follow label instructions for storage and in-use time conditions descriptions on the labels and in the TMM. In-use time starts if removed from the refrigerator.

The investigator must document that DFU are given to the subjects orally and in writing at the first dispensing visit and that subjects are trained. Training must be repeated as specified in the flowchart (Section 1.2) and, if needed, during the trial at regular intervals in order to ensure correct use of the pen-injector. Training is the responsibility of the investigator or delegate.

The first dose of trial product must be taken on the day of randomisation (V2) at the clinical site by self-administration under supervision by trained site staff.

6.2 Preparation/handling/storage/accountability

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

- Acceptable temperature ranges and conditions for storage and handling of each trial product when not in use and when in use are described in the TMM.
- Each site will be supplied with sufficient trial products for the trial on an ongoing basis. Trial product 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 on a pen-injector level and must be documented in the IWRS.
- The subject must return all used and unused trial product including empty packaging materials during the trial as instructed by the investigator.
- 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, 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.

Japan: for country-specific requirements, please see Appendix 9 (Section 10.9).

6.2.1 Shipment of trial product to subject's home

For selected countries and if permitted by local regulations, the investigator may offer to send trial product 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 patients' homes" document. The document contains detailed instructions for preparing packaging and setting up the pick-up of trial product, handover of trial product from the trial site or pharmacy staff to the courier,

required temperature monitoring of trial product, delivery to and receipt of trial product 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/pharmacy 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 product will be dispensed/allocated at the trial visits summarised in the flowchart.

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

The active drug and placebo are visually identical for the following trial products:

- Semaglutide D 0.5 mg/mL, Semaglutide D 1.0 mg/mL, Semaglutide D 2.0 mg/mL DV3396 and Semaglutide placebo Ia
- Semaglutide D 2.27 mg/mL, Semaglutide D 3.2 mg/mL and Semaglutide placebo Ib

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 source documentation.

The person breaking the blind must print the "code break confirmation" notification generated by the IWRS, sign and date the document. If the IWRS is not accessible at the time of blind break, the IWRS helpdesk should be contacted. Contact details are listed in Attachment I.

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 product(s) at home, compliance with trial product administration will be assessed and the assessment documented in source documents at each visit where information is available. If any suspicion of non-compliance arises, the site must enter into a dialogue with the patient, 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:

- Drug accountability information; visual inspection of pen-injectors
- Questioning of subjects about missed doses and current treatment dose at every visit

Information on treatment dose and periods >14 days without treatment will be recorded in the eCRF. Treatment start and stop dates will be recorded in the eCRF.

6.5 Concomitant medication

Initiation of any GLP-1 RA must be avoided during the trial. The investigators are encouraged to ensure constant ongoing optimisation of the treatment of any comorbidity.

Other than the trial product, only medications that the subject is receiving at the time of screening or during the trial, for the following indications, must be recorded in the eCRF:

- To treat or prevent HF or cardiovascular diseases (e.g. antihypertensives, diuretics, lipid-lowering agents, anticoagulants, aspirin and other antiplatelet agents).
- To treat overweight or obesity.
- To treat a serious adverse event (SAE) or medication which may provide further information on the SAE i.e. alternative aetiology.
- To treat diabetes and diabetes complications.
- COVID-19 vaccine.

The information collected for each concomitant medication includes start date and stop date or continuation, dose (only to be collected for loop diuretics and glucose lowering medication) and related AE number when applicable.

Changes in concomitant medication listed above must be recorded at each visit. If a change is due to an SAE, then this must be reported according to Section 8.3.

During the trial, subjects should not initiate any weight management drugs or treatment which is not part of the trial procedures. If such treatment is initiated, the subjects should be instructed to stop the treatment.

6.5.1 Glucose lowering medication

Generally, glucose lowering medication should be selected according to American Diabetes Association (ADA)/ European Association for the Study of Diabetes (EASD) guidelines[56] (excluding GLP-1 RAs) and local guidelines and should preferably be weight-neutral. Modification of background glucose lowering treatment or addition of new treatment, should be implemented at the discretion of the investigator to mitigate persistent hyperglycaemia or risk of hypoglycaemia.

In this trial, trial product may be added to existing glucose-lowering background medication that includes SUs as well as insulins. To mitigate the potential for hypoglycaemia the investigator should consider reducing SU dose by e.g. 50%, and consider reducing insulin dose by e.g. 20% at randomisation. For subjects on prandial insulin consider reducing the prandial doses with e.g. 50%

and non-prandial dose with e.g. 20% at randomisation. For guidance on insulin titration during the trial please see appendix 8 (Section 10.8).

During the trial drug escalation phase the total daily insulin dose should preferably not exceed the total daily dose prior to randomisation unless needed to avoid acute hyperglycaemic complications

Glucose lowering medication should be documented in medical records and reported on the concomitant medication form in the eCRF.

6.6 Dose modification

Please refer to Section 6.1 for description of missed doses.

6.7 Treatment after end of trial

After the end of trial, the subject should be treated at the discretion of the investigator.

Argentina: for country-specific requirements, please see Appendix 9 (Section 10.9).

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.

Efforts must be made to have subjects, who discontinue trial product, to continue in the trial. Subjects must be educated about the continued scientific importance of their data, even if they discontinue trial product. Only subjects who withdraw consent will be considered as withdrawn from the trial.

Temporary or permanent discontinuation of treatment with trial product will not lead to withdrawal from the trial.

7.1 Discontinuation of trial treatment

Discontinuation of trial treatment can be decided by both the investigator and the subject.

Subjects who discontinue trial product should be encouraged to continue with the scheduled visits and assessments to ensure continued healthy lifestyle counselling and data collection.

If the subject does not wish to attend the scheduled clinic visits, efforts should be made to have the visits converted to phone contacts. However, all effort should be made to have the subject attend at least the end-of-treatment visit (V11) containing the final data collection of primary and confirmatory secondary efficacy endpoints and participate in the end-of-trial visit (V12).

The end-of-trial visit is scheduled 5 weeks after the end-of-treatment visit, to ensure the safety of the subject. If the subject has discontinued trial product >5 weeks prior to the end-of-treatment visit, and the requirements for the follow-up period prior to the end-of-trial visit is fulfilled, then the end-of-trial visit can be performed in combination with the end-of-treatment visit.

If the subject is unwilling to attend the end-of-treatment visit and/or end-of-trial visit, information about the attempts to follow up with the subject must be documented in the subject's medical record.

The trial product 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. Intention of becoming pregnant
5. Simultaneous use of an approved or non-approved investigational medicinal product in another clinical trial. Simultaneous participation in a COVID-19 vaccine trial is however allowed at the discretion of the investigator without discontinuation of trial product.

Japan: for country-specific requirements, please see Appendix 9 (Section 10.9).

If acute pancreatitis is suspected appropriate actions should be initiated, including local measurements of amylase and lipase (see Section 10.3.3 for reporting).

Subjects meeting discontinuation of trial product criterion no. 2 can resume trial product if the Atlanta criteria[57] are not fulfilled and thus, the suspicion of acute pancreatitis is not confirmed. Trial product may be resumed for subjects with a gallstone-induced pancreatitis in case of cholecystectomy.

Subjects meeting discontinuation of trial product criteria no. 1, 3 and 4 can resume trial product, if the criteria are no longer met (see Section 7.1.1).

The primary reason for discontinuation of trial product must be specified in the end-of-treatment-form in the eCRF, and final drug accountability must be performed.

7.1.1 Temporary discontinuation of trial treatment

If a subject has discontinued trial product due to temporary safety concern not related to trial product and treatment with trial product is allowed to be resumed, the guide for missed doses should be followed (Section 6.1). Similarly, a subject who discontinues trial product on their own initiative should be encouraged to resume trial product (Section 6.1).

If a 'treatment status' session previously has been made in IWRS to indicate discontinuation of treatment, a new "treatment status" session must be made to resume trial product.

In case of suspicion of acute pancreatitis, the trial product should promptly be interrupted; however, a 'treatment status' session to discontinue treatment should not be made in IWRS before diagnosis of acute pancreatitis is confirmed. Appropriate actions should be initiated, including local measurement of amylase and lipase (see appendix 3 (Section 10.3) for AE reporting). If acute pancreatitis is confirmed, treatment with trial product should not be restarted, and a 'treatment status' session should be made in IWRS.

7.2 Subject discontinuation/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 the end-of-treatment visit (V11). 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 discontinuation 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.

Publicly available data sources should also be searched for withdrawn subjects to establish vital status at end of trial (unless prohibited by local regulation).

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 product 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 source document.
- 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'.
- If establishing direct contact is not possible, vital status (dead or alive) should be obtained. Publicly available data sources should also be searched at end of trial (unless prohibited by local regulation).

8 Trial assessments and procedures

- The following sections describe the assessments and procedures, while their timing is summarised in the flowchart (Section 1.2) and Appendix 2 (Section 10.2).
- 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 (Section 1.2), is essential and required for trial conduct.
- Paper diaries will include the following in relation to the visit they support:
    - Instruction on how to use the diary
    - Information to be recorded:
        - self-measured plasma glucose (according to Section 8.2.6)
        - hypoglycaemic event(s) (according to Appendix 7 in Section 10.7)
- Review of diaries, ECG, laboratory reports etc. must be documented either on the documents or in the subject's medical records. If clarification of entries or discrepancies in the diary is needed, the subject must be questioned, and a conclusion made in the subject's source documents. 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).

8.1.1 Body measurements

Body weight should be measured without shoes and only wearing light clothing. It should be measured on a digital scale and recorded in kg or lb (one decimal with a precision of 0.1 kg or lb) using preferably the same scale throughout the trial. The scale must be calibrated according to manufacturer's recommendation.

Height is measured without shoes in centimetres or inches (one decimal with a precision of 0.1 centimetres or inches). At screening BMI will be calculated by the eCRF and must agree with inclusion criterion no. 3.

Waist circumference is defined as the abdominal circumference located midway between the lower rib margin and the iliac crest. Measurement must be obtained in standing position with a non-stretchable measuring tape and to the nearest cm or inch.

The measuring tape should touch the skin but not compress soft tissue and twists in the tape should be avoided. The subject should be asked to breathe normally. The same measuring tape should be used throughout the trial. The measuring tape will be provided by Novo Nordisk to ensure standardisation.

8.1.2 Clinical outcome assessments

Subjects should be given the opportunity to complete the questionnaires by themselves without interruption. Subjects must transcribe directly into a site-pad/web-solution. Subjects are not allowed to answer the questions on paper. Site staff should activate and verify completion of the questionnaires (as specified in the TrialMax Slate® and TrialManager® Site User Guide).

The following electronic patient-reported outcome (ePRO) questionnaires will be used:

- Patient Global Impression of Status (PGI-S) for KCCQ version 1.0.
- Patient Global Impression of Change (PGI-C) for KCCQ version 1.0.
- Kansas City Cardiomyopathy Questionnaire (KCCQ) version 2.0.

  The KCCQ is a disease-specific health status instrument composed of 23 items that quantify the domains of physical limitation, symptoms, self-efficacy, social limitation, and health-related quality of life limitation from heart failure. The overall summary score and all domains have been independently demonstrated to be valid, reliable, and responsive to clinical change. Scores range from 0 to 100.[58]

- EuroQoL five dimensions five level (EQ-5D-5L).

  The EQ-5D-5L will be used to estimate the impact on patients' health-related quality of life and provides a description of patient's problems by dimensions (descriptive system), a score for overall self-rated health (visual analogue scale (VAS) as well as an index score (EQ-5D-5L index)). EQ-5D index score range: 0 to 1 and EQ-5D-VAS: range 0 to 100. A higher score indicates better self-reported health status. If clarification of the test is needed, care must be taken not to bias the subject

- Patient Global Impression of Status (PGI-S) for 6MWT version 1.0.
- Patient Global Impression of Change (PGI-C) for 6MWT version 1.0.

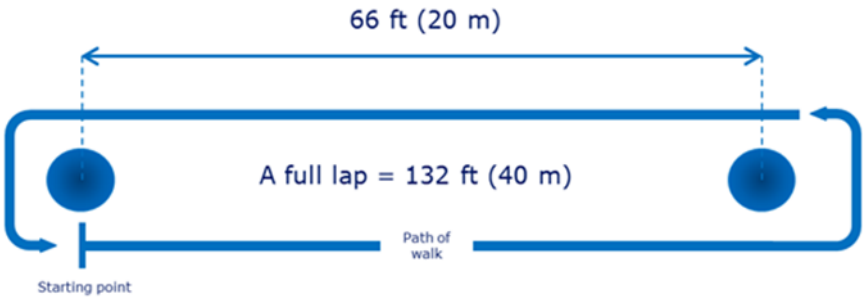
The following functional test will be performed:

- 6-minute walk test (6MWT)

The 6MWT assesses the distance a subject can walk in six minutes. It is a direct and timed measure of walking ability, which is technically simple, reproducible, and when administrators are well trained, readily standardised. The goal is for the subject to walk as far as possible in six minutes without running. The subject can self-pace and rest as needed as they traverse back and forth along a marked walkway of 66 feet (20 m) (Figure 8-1). The primary outcome is the distance covered over six minutes.

The 6MWT must be performed in accordance with the manual provided by Novo Nordisk.

Figure 8-1 Walkway marking for the 6-minute walk test



In order to assess the subject's perception of the allocated treatment a question regarding this will be posed at the end-of-treatment visit.

8.1.3 Echocardiography

Echocardiography must be performed in all subjects at the screening visit assessing only the LVEF to ensure agreement with inclusion criterion number 5.

Only for subjects participating in the sub-study:

The echocardiography must be performed as outlined in the flowchart (Section 1.2). The echocardiography must be performed in accordance with the manual from the supplier.

India: for country-specific requirements, please see Appendix 9 (Section 10.9).

8.1.4 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 (Section 1.2) and the laboratory manual.

Czech republic: for country-specific requirements, please see Appendix 9 (Section 10.9).

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 product.

Medical history is a medical event that the subject experienced prior to the time point from which AEs are collected.

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 signs of HF, the cardiovascular, respiratory, and gastrointestinal system, as well as general appearance.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2 Vital signs

The method for measuring pulse rate and systolic and diastolic blood pressure needs to follow the standard clinical practice at site, however as a minimum:

- Vital sign assessment 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 with a completely automated device. Manual techniques must be used only if an automated device is not available.

8.2.3 Electrocardiograms

- 12-lead ECG will be obtained as outlined in the flowchart (Section 1.2) using an ECG machine that automatically calculates the heart rate and measures PR and QRS intervals.
- The investigator must perform review of the ECG for clinically significant abnormal findings.

8.2.4 New York Heart Association classification

The investigator must assess the functional status of the subject based on below:

- Class I: No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea.
- Class II: Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea.
- Class III: Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnoea.
- Class IV: Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

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

Germany: for country-specific requirements, please see Appendix 9 (Section 10.9).

8.2.6 Self-measured plasma glucose

During the trial, all subjects treated with insulin, should perform SMPG measurements for 3 consecutive days prior to selected visits (see Section 1.2). The investigator will use the SMPGs to decide if adjustment to glucose lowering treatment is required. The SMPG measurements should be done pre-breakfast in a fasting state (defined as six hours). For subjects on a twice daily insulin regimen an additional pre-dinner measurement should be done (not required to be fasting). For subjects on multiple daily injections measurements are expected pre-breakfast, pre-lunch, predinner, and at bedtime. The investigator may advise subjects to measure more frequently based on clinical judgement. Additional SMPG measurements are supportive for investigators' treatment and should be filed at site.

An insulin titration guide is provided in Appendix 8 (Section 10.8).

Subjects will be provided with a BG meter including auxiliaries as well as instructions for use. The subjects will be instructed how to use the device. The investigator should ensure that the subject is able to correctly measure BG at any time.

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

The BG meter provided by Novo Nordisk should be used for the measurements required in the protocol as outlined in the flowchart (Section 1.2) and in case a hypoglycaemic episode is suspected. Please refer to Appendix 7 (Section 10.7) for SMPG measurement in relation to hypoglycaemic episodes.

Subjects should be instructed in how to record the results of the SMPG values in the diaries. The record of each SMPG value should include date, time and value. SMPG values required as per the flowchart in Section 1.2 must be transcribed from the diary into the eCRF during or following the contact. If obtained via phone, and a discrepancy is later detected, the values in the eCRF must be

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

8.2.7 Clinical safety laboratory assessments

All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the protocol flowchart (Section 1.2).

8.3 Adverse events and serious adverse events

The investigator is responsible for detecting, documenting, recording and following up on all the events listed below:

- SAEs
- Following AEs irrespective of seriousness:
  - AEs leading to premature treatment discontinuation
  - AEs of COVID-19
    - Note: suspected COVID-19 should be reported if the clinical presentation is suggestive of COVID-19, even in the absence of a COVID-19 test or without a positive COVID-19 test result. In the absence of clinical symptoms, a positive COVID-19 test (antigen or antibody) should be reported, if available.
  - AEs requiring additional data collection (Table 8-1)
- AEs for adjudication (Table 8-1)
- Pregnancies
- Obesity-related surgical procedures
  - The procedure (e.g. bariatric surgery) must be reported as an AE.

The definition of AEs and SAEs can be found in Appendix 3 (Section 10.3), along with a description of event(s) for adjudication and AEs requiring additional data collection.

Some AEs require additional data collection on a specific event form. This always includes medication error, misuse and abuse of IMP. The relevant events are listed below in Table 8-1 , together with events for adjudication.

Events for adjudication require data collection on an adjudication form. Event adjudication will be performed in randomised subjects and will be evaluated by an independent external event adjudication committee (EAC) in a blinded manner, please refer to Section 10.1.6.2

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

Event type	AE requiring additional data collection	Event for adjudication
Acute pancreatitis	X	
Diabetic retinopathy	X	
Medication error	X	
Misuse and abuse	X	
Heart failure hospitalisation or urgent heart failure visits		X

Death		X

A detailed description of the events mentioned in the above table can be found in Appendix 3 (Section 10.3).

There are four ways to identify events relevant for adjudication as described below:

1. Investigator-reported events for adjudication: investigator selects the appropriate AE category relevant for adjudication (see Appendix 3, Section 10.3.3).

2. AEs reported with fatal outcome.

3. AE search (standardised screening): All AEs not reported with an AE category relevant for adjudication will undergo screening to identify potential events for adjudication. Investigators will be notified of these events in the eCRF.

4. EAC-identified events: Unreported events relevant for adjudication identified by the EAC during review of source documents provided for another event for adjudication. Investigators will be notified of these events in the eCRF and has the option to report the EAC-identified event.

For each event relevant for adjudication an event type specific adjudication form should be completed in the eCRF within 14 days.

Copies of source documents should be uploaded to the event adjudication system (EAS) as soon as possible and preferably within 4 weeks. In cases where the EAS is not accessible the investigator should ensure that the relevant source documents are collected and saved locally until the EAS is ready. If no, or insufficient source documents are provided to the adjudication supplier, the investigator can be asked to complete a clinical narrative to be uploaded to the EAS.

If new information becomes available for an event sent for adjudication, it is the responsibility of the investigator to ensure the new information is uploaded to the EAS.

An Event Adjudication Site Manual will be provided to each site detailing which source documents are relevant and how these should be provided to the adjudication supplier. The anonymization and labelling requirements are also described in the site manual.

Germany and Japan: for country-specific requirements, please see Appendix 9 (Section 10.9).

Hypoglycaemic episodes

All hypoglycaemic episodes must be recorded on a hypoglycaemic form. 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 (Section 10.3). For more information on hypoglycaemic episodes, please refer to Appendix 7 (Section 10.7).

8.3.1 Time period and frequency for collecting AE and SAE information

As per AE definition (ICH E2A) an AE is temporally associated with the use of a trial product, hence AEs are collected from the first administration of trial product. In this trial there is no invasive screening procedures that warrant collection of AEs from screening.

All events specified in Section 8.3 (for events related to pregnancy, see Appendix 4, Section 10.4) must be collected and reported. The events must be collected from the randomisation visit and until end of trial visit, at the time points specified in the flowchart (Section 1.2).

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, Section 10.3. 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 product 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, Section 10.3.4.

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 (SUSAR).

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 first exposure to trial product and until the end of trial.

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.

Argentina and Austria: for country-specific requirements, please see Appendix 9 (Section 10.9).

8.3.6 Cardiovascular and death events

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

8.3.7 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 10.5.2.

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 4 mg in a single dose, and up to 4 mg in a week have been reported in clinical trials. The most commonly reported AE was nausea. All subjects recovered without complications.

There is no specific antidote for overdose with semaglutide. 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 or abuse, please refer to Section 8.3 and Appendix 3, Section 10.3.3 for further details.

In the event of an overdose, the investigator should closely monitor the subject for overdose-related AE/SAE. A prolonged period of observation and treatment may be necessary, considering the long half-life of semaglutide of approximately one week.

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 investigator's brochure[29] or any updates hereof.

8.5 Pharmacokinetics

- Blood samples for measuring plasma concentration of semaglutide will be drawn at visit 7 and visit 11 according to the flowchart (Section 1.2)
- The dosing information should be transcribed into the CRF for the date and time of the last two doses (approx. -2 and -1 week) of trial product prior to the PK assessment.
- The exact timing of obtaining the PK sample must be recorded on the laboratory form.
- The purpose of measuring plasma semaglutide levels is to evaluate exposure-response relationship.
- Blood samples for PK assessments must be collected, handled and shipped according to the description in the laboratory manual supplied by the central laboratory. The bioanalysis of semaglutide PK will be performed by a special laboratory. Semaglutide PK samples will be stored at the special laboratory responsible for PK until final CTR in case Novo Nordisk requests further analysis of the PK samples. Details of the bioanalysis will be outlined in a bioanalytical study plan issued by the special laboratory.

8.6 Pharmacodynamics

Not applicable for this trial.

8.7 Genetics

A blood sample for genetic analysis will be collected from subjects who have consented to participate in the optional biobank component of the trial. Subjects who do not wish to participate in the genetic research may still participate in the trial.

Refer to Section 8.8 and Appendix 6, Section 10.6 for further details.

Israel: for country-specific requirements, please see Appendix 9 (Section 10.9).

8.8 Biomarkers

Collection of samples for biomarker research is part of this trial. The following samples are required and will be collected from all subjects in this trial:

- N-terminal pro-brain natriuretic peptide (NT-proBNP)
- C-reactive protein (CRP)

Collection of biosamples for future analysis (stored in a biobank) is a component of this trial. Participation in the biobank component is optional. Subjects who do not wish to participate in the biobank component may still participate in the trial. For the biobank, samples will be collected according to Table 10-1 and stored for future use.

The samples are collected for the purpose of allowing future analyses of biomarkers, both genetic and circulating, at a later point in time when new knowledge or improved measurement techniques may have become available. The analyses may include biomarkers currently known or discovered in the future.

Genetic analyses may include analysis of candidate genes or genetic markers throughout the genome with the purpose of understanding and predicting the response to semaglutide as well as to understand obesity, cardiovascular, metabolic, or related conditions.

Analyses of circulating biomarkers will measure hormones, metabolites or other non-genetic serum entity with the purpose of understanding and predicting response to semaglutide as well as understanding obesity, cardiovascular, metabolic, or related conditions.

The analyses are likely to be performed after the trial has come to an end, and results will therefore not be part of the clinical trial report. The biobank samples may be stored at a central laboratory up to 15 years after the study has been reported.

For further details, refer to Appendix 6, Section 10.6.

Israel: for country-specific requirements, please see Appendix 9 (Section 10.9).

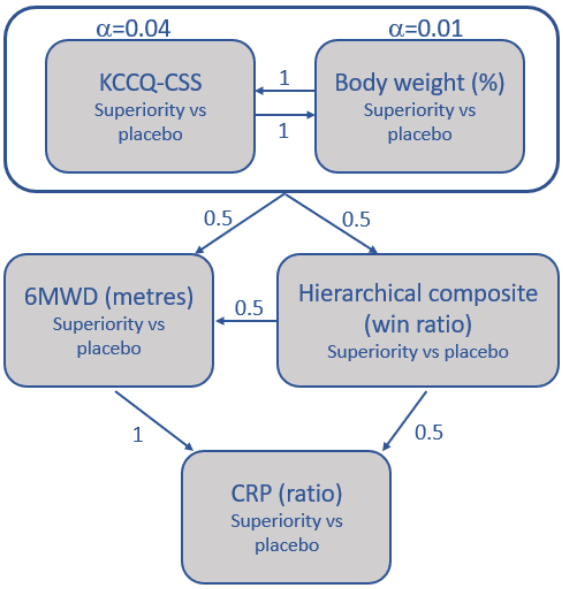
8.9 Immunogenicity assessments

Not applicable for this trial.

9 Statistical considerations

9.1 Statistical hypotheses

The tests of superiority of semaglutide s.c. 2.4 mg once weekly versus placebo for the primary and confirmatory secondary endpoints are performed using a graphical testing system (Figure 9-1) that preserves the overall study-wise type I error of 5%.



KCCQ-CSS: Kansas City Cardiomyopathy Questionnaire; CRP: C-Reactive Protein; 6MWD: six-minute walking distance. Hierarchical composite endpoint as defined in Section 3.2.2.1.

Figure 9-1 Tests of superiority of semaglutide s.c. 2.4 mg once weekly versus placebo for the primary and confirmatory secondary endpoints

First, the multiple primary endpoints are tested, where for these two endpoints the alpha is split in 1% for weight change and 4 % for change in KCCQ-CSS. The tests for the multiple endpoint will follow the weighted Holm-Bonferroni procedure[57] (with weights one) such that if one of the two endpoints is superior then the full alpha can be recycled for the other endpoint and hence the remaining primary endpoint will be tested at the 5% significance level (two-sided).

If both hypotheses are rejected and superiority is confirmed for both primary endpoints, then the confirmatory secondary endpoint will be tested according to the flow and weights as specified in Figure 9-1. The 5% alpha will be 50/50 split between 6MWD and the hierarchical composite endpoint, so that the hierarchical composite endpoint will be tested at 2.5% significance level, and if superiority is confirmed, the 6MWD will be tested at 3.75% significance level. If superiority is not confirmed for the hierarchical composite endpoint, the 6MWD will be tested at 2.5% significance level. If superiority is confirmed for both 6MWD and the hierarchical composite endpoint, CRP will be tested at 5% significance level, but if only 6MWD is confirmed CRP will be tested at 2.5% significance level, or if only the hierarchical composite is confirmed, CRP will be tested at 1.25% significance level.

9.2 Sample size determination

610 subjects will be randomly assigned to trial product.

The trial is designed with a marginal power of at least 90% to detect differences on each of the dual primary endpoints with a study-wise type I error rate of 5%.

The calculations for the primary endpoints and confirmatory secondary endpoints 6MWD and CRP are based on a t test on the mean difference assuming equal variances in the arms. The calculations for the composite hierarchical secondary endpoint are based on the win ratio.

In the trial NN9536-4374 (STEP-2) which included 1210 randomised obese subjects with T2D, a treatment difference of 7.3% was observed for change in body weight between semaglutide 2.4 mg once-weekly and placebo at 52 weeks for completers with a standard deviation of 6.5. This can also be expected in the current HF population with T2D.

Although the specific magnitude of clinical relevance between groups for change in KCCQ-CSS can be deliberated, it is assumed that in this HF population we can expect a treatment difference of 5 points[60] between semaglutide 2.4 mg once-weekly and placebo at week 52 with a standard deviation of 15.

This is based on the results in the study by Kitzman et al, where a difference of 7 points was estimated between 92 completed subjects for KCCQ-OSS randomised to either diet or no dietary restrictions in an obese population with HFpEF adjusted for baseline.[45] Furthermore, in this trial the standard deviation across the groups were approximately 12 using the published 95% CIs assuming KCCQ-OSS and KCCQ-CSS have similar variability. Furthermore, using results from DEFINE-HF (a HFrEF population which includes subjects with T2D) the standard deviation for KCCQ-CSS was calculated to be 13.7 and 13.7 for placebo and active group, respectively, at 3 months also adjusted for baseline KCCQ-CSS.[61]

In the PARADIGM-HF trial[62] the calculated standard deviation for KCCQ-CSS was 14.9 at 1 year adjusted for baseline. The PARADIGM-HF trial included subjects with HFrEF of which 35% had T2D at baseline. As the current trial will include obese subjects with T2D we expect more variability in the KCCQ-CSS endpoint as compared to the standard deviations from 12-14 seen above and hence we assume a standard deviation of 15 at 52 weeks.

In the DEFINE-HF trial based on the same assumptions as above a standard deviation of 72 and 75 was derived for 6MWD in the placebo group and the active group, respectively.[61] By personal communication the standard deviation in the PANACHE trial for 6MWD was 60 and in the SECRET trial it was much lower with a standard deviation of 40. As a treatment difference of 30 metres in the 6MWD is considered as having a clinical relevance we will assume this difference of 30 metres at week 52 between semaglutide 2.4 mg once-weekly versus placebo with a standard deviation of 75.

Using data from NN9536-4374 a mean ratio of 0.67 and 0.57 (semaglutide 2.4 mg versus placebo) were estimated at 20 and 68 weeks adjusted for baseline CRP. A coefficient of variation was estimated to be 1.05 using the residual variance on the log scale back transformed. Hence, we assume a mean ratio of 0.70 for completers between semaglutide 2.4 mg once-weekly versus placebo in the present trial at 52 weeks with a coefficient of variation of 1.05.

For the power calculations on the hierarchical composite endpoint, it is assumed that 10 all-cause deaths (with a treatment effect corresponding to a hazard ratio of 0.9) and 15 subjects with heart failure hospitalisation (with a treatment effect corresponding to a hazard ratio of 0.8) will occur

during the trial. A correlation of 0.5 between the KCCQ-CSS and 6MWD is assumed for this endpoint. The power calculations for this endpoint are based on simulation of 10000 datasets.

In relation to treatment effects in non-completers using data from NN9536-4374 we assume that 25% of subjects discontinue permanently and 50% of these are retrieved at week 52. All subjects in the placebo arm are assumed to have same effect as subjects who complete the trial on placebo. Retrieved subjects in the semaglutide s.c. 2.4 mg once-weekly arm are assumed to have an effect corresponding to half the treatment difference (compared to placebo) of subjects who complete the trial on semaglutide s.c. 2.4 mg OW. Non-retrieved subjects in the semaglutide s.c. 2.4 mg once-weekly arm are assumed to have an effect corresponding to placebo. The attenuation of the assumed mean differences between treatment groups using these assumptions can be seen in Table 9-1.

Table 9-1 Assumptions and power for the confirmatory endpoints given with an anticipated number of 610 randomised subjects

Endpoint	Mean difference/ratio Completers	Mean Difference/ratio #	Standard deviation /CV	Two-sided significance level (%)*	Marginal Power (%)
Body weight	-7.3%	-5.93%	6.5	1	>99.9%
KCCQ-CCS	5.0 points	4.0625 points	15	4	90
6MWD	30 metres	24.375 metres	75	2.5	96%
Hierarchical composite	N/A	N/A	N/A	2.5	90%
CRP	0.70 Mean ratio	0.748 Mean ratio	1.05 CV	1.25	95%

CRP is characterised by mean ratio and coefficient of variation (CV).

#Assumed that 25% discontinue treatment with 50% retrieval with a halved treatment effect in retrieved subjects which corresponds to that 75% of subjects have a treatment effect as completers, 12.5% would have a halved treatment effect as completers and 12.5% would have no treatment effect. *Minimum significance level it can be tested on.

The sample size in this trial would essentially be governed by the assumptions of the mean difference and the standard deviation of KCCQ-CSS. Different scenarios can be observed in Table 9-2 .

Table 9-2 Sample size for KCCQ-CSS according to different assumptions of the mean difference and standard deviation with a significance level of 4% and a power of 90%

Standard deviation	Mean difference	Sample size
14	5	352
15	5	404
16	5	458
14	4.0625	532
15	*4.0625*	*610*
16	4.0625	694
14	4	548
15	4	628
16	4	716

9.3 Populations for analyses

The following population*s* are defined:

Population	Description
Randomised	All subjects randomised
Full analysis set (FAS)	All subjects randomised. Exclusion of data from analyses should be used restrictively, and normally no data should be excluded from the FAS. Subjects will be analysed according to the randomised treatment
Safety analysis set (SAS)	All subjects randomly assigned to trial treatment and who take at least 1 dose of trial product. Subjects are analysed according to the treatment they received.

Two observation periods are defined for each subject:

- In-trial: The in-trial period is defined as the uninterrupted time interval from date of randomisation to date of last contact with trial site.
- On-treatment (with trial product): A time-point is considered as 'on-treatment' if any dose of trial product has been administered within the prior 2 weeks (14 days). The on-treatment period is defined as all times which are considered on-treatment.

In general, the on-treatment period will therefore be from the date of first trial product administration to date of last trial product administration excluding potential off-treatment time intervals triggered by at least two consecutive missed doses.

For the evaluation of AEs, the lag time for each on-treatment time interval is 5 weeks (35 days).

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.

Efficacy endpoints will be analysed using the FAS; safety endpoints will be analysed using the SAS.

9.4 Statistical analyses

The statistical analysis plan (SAP) will be written, including a more technical and detailed elaboration of the statistical analyses. The SAP will be finalised before breaking the blind to treatment assignment.

9.4.1 General considerations

The comparison presented from a statistical analysis will be semaglutide 2.4 mg once-weekly versus placebo and results will be presented by the estimated treatment contrast with associated two-sided 95% confidence intervals and p-values corresponding to two-sided tests of no difference.

The last available and eligible observation at or before randomisation is used as the baseline value.

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

9.4.2 Primary endpoints

The primary endpoints are change in the KCCQ clinical summary score (score) and change in BW in percentage (BW-%) from baseline (week 0) to end of treatment (week 52) as listed in Section 3.

All tests are tests of superiority of semaglutide s.c. 2.4 mg once-weekly to placebo.

Analyses addressing the primary estimand

The following statistical analyses and imputation methods are designed to address the primary estimand.

The primary analysis model for change in the KCCQ-CSS (score) or change in BW (%) is a linear regression (ANCOVA) with randomised treatment, and with baseline KCCQ (score) and baseline BW (kg), respectively, as covariates. The factor BMI subgroup (BMI < 35.0 kg/m^2 versus BMI ≥ 35.0 kg/m^2) is included in the model as it is used as a stratification variable in the randomisation scheme.

The estimated treatment difference between semaglutide s.c. 2.4 mg once-weekly and placebo will be reported together with the associated two-sided 95% CI and corresponding p-value. All available data at week 52 are used, missing values at week 52 will be imputed and the endpoint will be derived from the imputed values. The imputation approach for the primary analysis is a multiple imputation similar to the one described by McEvoy et al.[63] For subjects in the semaglutide s.c. 2.4 mg once-weekly and the placebo groups, missing primary endpoint measurements at week 52 for non-retrieved subjects are imputed using assessments from retrieved subjects in each treatment group. This will be done according to the timing of last available observation during the on-treatment period of KCCQ-CSS or BW.

Missing measurements for the primary endpoints at week 52 for subjects on randomised treatment (at week 52) are imputed by sampling from available measurements at week 52 from subjects on randomised treatment in the relevant randomised treatment arms. Details of the imputation approach will be provided in the SAP e.g. variables used in the imputation and assignment of unfavourable values in case of CV deaths.

Sensitivity analyses will address the primary estimand using a non-parametric methods.

9.4.3 Secondary endpoints

9.4.3.1 Confirmatory secondary endpoints

The confirmatory secondary endpoints are change in CRP and 6MWD (metres) from baseline (week -2 and 0, respectively) to end of treatment (week 52) as well as the hierarchical composite endpoint as listed in Section 3.

All tests are tests of superiority of semaglutide s.c. 2.4 mg once-weekly to placebo.

Analyses addressing the primary estimand

The secondary confirmatory endpoints CRP and 6MWD will be analysed using the primary imputation approach used for the primary endpoint and to address the primary estimand. The

statistical model for change in CRP and 6MWD will be the same as for the primary endpoints. The linear regression for CRP will be based on the log-transformed values at week 52 and log-transformed baseline values.

The analysis of the hierarchical composite endpoint will be based on direct comparisons of each subject randomised to semaglutide s.c. 2.4 mg OW versus each subject randomised to placebo within each stratum. For each of these pairs, a 'treatment winner' based on similar observation time will be declared based on the endpoint hierarchy. The win ratio (i.e. the proportion of winners randomised to semaglutide s.c. 2.4 mg OW divided by the winners randomised to placebo) will be reported together with the associated two-sided 95% CI and corresponding p-value. Furthermore, the contribution of wins from each individual component of the hierarchical composite endpoint will be summarised.

9.4.3.2 Supportive secondary endpoints

For details on analyses of additional supportive secondary endpoints, please refer to the SAP.

9.4.4 Exploratory endpoints

For details on analyses of exploratory endpoints, please refer to the SAP.

9.4.5 Other analyses

9.5 Pharmacokinetic modelling

Exposure-response analyses will be used as supportive evidence for the evaluation of efficacy and safety and further to support the investigated dose of semaglutide in subjects with HFpEF, obesity and T2D. Plasma semaglutide concentrations will be used to derive model-based estimates of steady-state average concentrations for each subject, utilizing a population pharmacokinetic modelling approach that leverages information from the STEP programme. Relevant efficacy and safety endpoints will be related to steady-state average concentrations and subjected to model-based exposure-response analysis. A modelling analysis plan will be prepared prior to database lock outlining details of the analyses. The results from the exposure-response analysis will be reported separately from the CTR.

9.6 Interim analyses

No interim analyses are planned.

9.7 Data monitoring committee

Not applicable for this trial.

9.8 Reporting of the main part of the trial

Not applicable for this trial.

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[65] and applicable ICH Good Clinical Practice (GCP) Guideline[66]
  - 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

Japan: for country-specific requirements, please see Appendix 9 (Section 10.9).

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.
For US sites: 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[66], Declaration of Helsinki[65] 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 form*(s)* 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.

United Kingdom: for country-specific requirements, please see Appendix 9 (Section 10.9).

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 Event adjudication committee

An independent external EAC is established to perform ongoing blinded adjudication of selected AEs and deaths (see Table 8-1).

The EAC will evaluate events sent for adjudication using pre-defined definitions and guidelines in accordance with the EAC charter. The evaluation is based on review of pre-defined clinical data collected by the sites. The EAC is composed of permanent members covering all required medical specialities. EAC members must disclose any potential conflicts of interest and must be independent of Novo Nordisk. The EAC will have no authority to impact trial conduct, trial protocol or amendments. The assessments made by both the event adjudication committee and the investigator will be evaluated and included in the CTR.

10.1.6.3 Steering committee

A steering committee will provide scientific and operational leadership for the trial. The committee will consist of experts from outside Novo Nordisk, and designated Novo Nordisk employees. The committee will operate under a charter agreed with Novo Nordisk.

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)[67], the Food and Drug Administration Amendment Act (FDAAA)[68], European Commission Requirements[1, 69, 70] and other relevant recommendations or regulations. If a subject requests to be included in the trial via the Novo Nordisk e-mail contact at these web sites, Novo Nordisk may disclose the investigator's contact details to the subject. As a result of increasing requirements for transparency, some countries require public disclosure of investigator names and their affiliations.

The primary completion date (PCD) is the last assessment of the primary endpoint, and is for this trial last subject first treatment (LSFT) + 52 weeks corresponding to visit 11. If the last subject is withdrawn early, the PCD is considered the date when the last subject would have completed visit 11. 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 eCRFs unless transmitted electronically to Novo Nordisk or designee (e.g. laboratory and electronic PRO data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- Data from the paper diaries will be transcribed into the eCRF.
- The investigator must ensure that data is recorded in the eCRF as soon as possible after the visit.

- The following will be provided as paper CRFs:
  - Pregnancy forms
- The following will be provided as paper CRFs to be used when access to the eCRF is revoked or the eCRF 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)

- Corrections to the eCRF data may be made by the investigator or the investigator's delegated staff. An audit trail will be maintained in the eCRF application containing as a minimum: the old and the new data, identification of the person entering the data, date and time of the entry and reason for the correction. If corrections are made by the investigator's delegated staff after the date when the investigator signed the eCRF, the eCRF must be signed and dated again by the investigator.
- The investigator must ensure that data is recorded in the eCRF 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.

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 eCRF 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 eCRF.

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.
- For ePROs, data in the service providers' database is considered source data.
- 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.
- If source data is entered directly in a paper CRF, each data entry or clear series of data entries must be signed and dated separately by the trial staff making the entry.
- 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.
- 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.

Canada and Spain: for country-specific requirements, please see Appendix 9 (Section 10.9).

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.[71]

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.

10.2 Appendix 2: Clinical laboratory tests

- The tests detailed in Table 10-1 will be performed by the central laboratory unless otherwise specified.
- All laboratory results from visit 1 will be disclosed to the investigator. In addition, all HbA_{1c}, creatinine and eGFR (calculated from creatinine) results will be disclosed to the investigator.
- 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 lab 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.
- Laboratory samples, with the exception of biobank samples for future use (see Appendix 6, Section 10.6), will be destroyed no later than at finalisation of the CTR.
- Human biosamples for retention will be stored as described in Appendix 6 (Section 10.6).

Table 10-1 Protocol-required laboratory assessments

Laboratory assessments	Parameters
Glucose metabolism Visit: V1, V2, V4, V7, V9, V11	• HbA_{1c}
Biochemistry Visit: V1, V4, V7, V9, V11	• Creatinine • eGFR calculated by the central laboratory based on the creatinine value using the CKD-EPI equation
Biomarkers Visit: V1, V7, V11	• N-terminal pro-brain natriuretic peptide (NT-proBNP) • high sensitivity C-Reactive Protein (hsCRP)
Pregnancy testing Visit: V1, V2, V4, V5, V7, V8, V9, V10, V11, V12	• Urine human chorionic gonadotropin pregnancy test (as needed for women of childbearing potential)[1]
Biobank[2] Visit: V2, V7, V11	• Whole blood (for genetic analysis) (visit 2 only) • Serum (for analyses of circulating biomarkers)
Pharmacokinetics Visit: V7 and V11	• Plasma semaglutide
[1]Local urine testing will be standard unless serum testing is required by local regulation or IRB/IEC. [2]Subjects must sign and date a separate informed consent form before samples are collected.	

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

For trials with investigational medical device(s), please refer to Appendix 7, Section 10.7.

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 • Obesity-related surgical procedures 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. Exceptions include obesity-related surgical procedures where the procedure (e.g. bariatric surgery) should be reported as 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 events for adjudication and AEs requiring additional data collection

Description of events for adjudication and AEs requiring additional data collection (on specific event form)
Events for adjudication: An event for adjudication is a selected AE or death evaluated by an independent external EAC in a blinded manner, please refer to Section 10.1.6.2 and Figure 10-1. • **Death:** All cause death • **Heart failure hospitalisations or urgent heart failure visit:** New episode or worsening of existing heart failure leading to an urgent, unscheduled hospital admission or clinic/office/emergency department visit.

Adverse events requiring additional data collection:

Acute pancreatitis
Diagnosis of acute pancreatitis requires two of the following three features:
1. abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back)
2. serum lipase activity (and/or amylase activity) at least three times greater than the upper limit of normal
3. characteristic findings of acute pancreatitis on imaging.

Diabetic retinopathy
New onset or worsening of diabetic retinopathy.

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
  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.

Note: missed doses or drug pauses are not to be reported as a medication error.

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. gastrointestinal AE, hypoglycaemia or other), this must be reported on an additional AE form.

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

AE and SAE recording
• SAEs and AEs listed in Section 8.3 and AEs/SAEs in connection with pregnancies, must be recorded by the investigator 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: if an AE is considered to have a causal relationship with a Novo Nordisk marketed product used as concomitant medication in the trial, it is important that the suspected relationship is reported to Novo Nordisk, e.g. in the alternative aetiology section on the safety information form. Novo Nordisk may need to report this adverse event to relevant regulatory authorities.

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 die 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 eCRF.

10.3.5 Reporting of SAEs

SAE reporting via electronic CRF

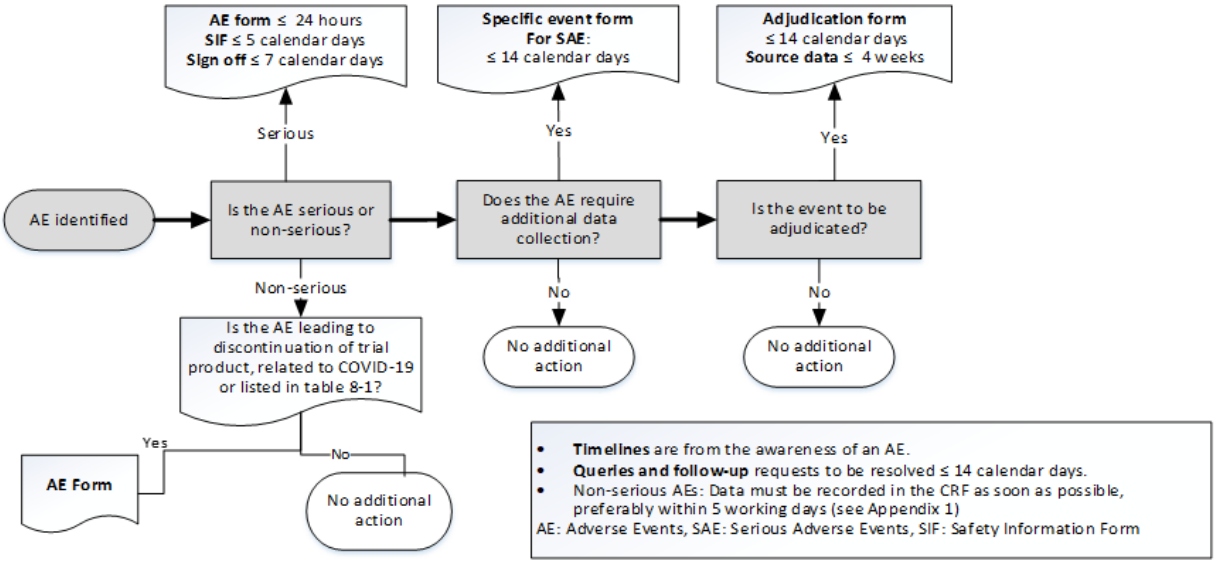
- Relevant forms (AE and safety information form) must be completed in the eCRF.
- For reporting and sign-off timelines, see Figure 10-1 below.
- If the eCRF is unavailable for more than 24 hours, then the site will use the paper AE form, and if the eCRF is unavailable for more than 5 calendar days, then the site will use the 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 CRF 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



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

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. Premenarcheal
2. 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.

3. Postmenopausal female:
   - A postmenopausal state is defined as amenorrhoea for 12 months without an alternative medical cause.
   - Females ≥ 50 years of age can be considered postmenopausal (irrespective of treatment with a hormonal contraception or hormone replacement therapy (HRT)) if they have both:
     - Amenorrhoea and
     - Documentation of 2 high follicle stimulating hormone (FSH) measurements in the postmenopausal range and one of these was observed ≥1 year prior to screening.
   - Females ≥ 60 years of age can be considered postmenopausal.

Females on HRT and whose menopausal status is in doubt are considered of childbearing potential and will be required to use one of the highly effective contraception methods.

Note: Documentation regarding categories 1-3 can come from the site staff's review of subject's medical records, medical examination or medical history interview.

Contraception guidance

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

Female subjects
Female subjects of childbearing potential are eligible to participate if they agree to use methods of contraception consistently and correctly as described in the table below:

Table 10-2 Highly effective and acceptable contraceptive methods

CONTRACEPTIVES[a] ALLOWED DURING THE TRIAL INCLUDE:

• **Highly effective methods[b, d] that have low user dependency** (Failure rate of < 1% per year when used consistently and correctly):
  • Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
  • Intrauterine device (IUD)
  • Intrauterine hormone-releasing system (IUS)[b]
  • Bilateral tubal occlusion
  • Vasectomized partner
  Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential, and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.
 	
• **Highly effective methods[b,d] that are user dependent** (Failure rate of < 1% per year when used consistently and correctly):
  • Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c]
  ○ oral
  ○ intravaginal
  ○ transdermal
  ○ injectable
  • Oral/injectable progestogen-only hormonal contraception associated with inhibition of ovulation
  • Sexual abstinence
  Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject.

NOTES a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical trials. b) Failure rate of < 1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. d) Contraception should be utilised during the treatment period and for at least 35 days (corresponding to time needed to eliminate trial product) after the last dose of trial product.

Argentina, Germany and Spain: for country-specific requirements, please see Appendix 9 (Section 10.9).

Pregnancy testing

- Additional pregnancy testing should be performed during the treatment period, if required locally (Appendix 9, Section 10.9).

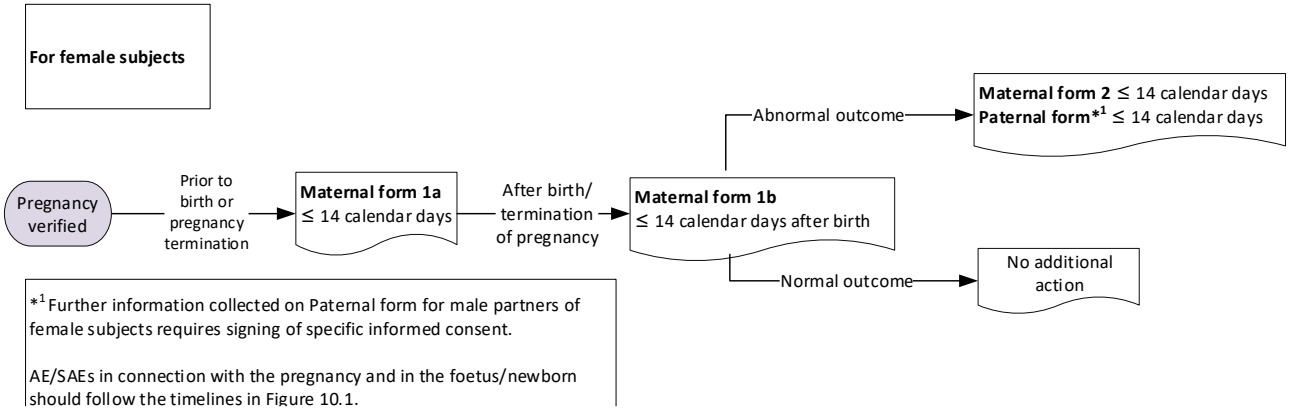
- Women/WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test (refer to Appendix 2, Section 10.2).
- A pregnancy test should be performed at the end of relevant systemic exposure (refer to Appendix 2, Section 10.2).
- Pregnancy testing should be performed whenever a menstruation is missed or when pregnancy is otherwise suspected.

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.
- Any SAE occurring as a result of a post-trial pregnancy which is considered possibly/probably related to the IMP by the investigator will be reported to Novo Nordisk as described in Section 10.3. While the investigator is not obligated to actively seek this information in former subjects, he or she may learn of an SAE through spontaneous reporting.

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.

10.6 Appendix 6: Retention of human biosamples and genetics

In countries where applicable, the trial will involve collection of human biosamples to be stored in a central archive for future use. Subjects must sign and date a separate informed consent form before biosamples are collected.

The following samples will be collected and stored according to Appendix 2, Section 10.2:

- Whole blood (for genetic analysis)
- Serum (for analysis of circulating biomarkers)

As new biomarkers related to the disease and/or safety, efficacy or mechanism of action of semaglutide may evolve during the conduct of the trial, the analyses of the stored biosamples may also include biomarkers that are unknown at present or have not been included in the scientific hypotheses at initiation of the trial.

The biosamples will be stored at a central storage facility contracted by Novo Nordisk. Only Novo Nordisk and storage facility employees will be able to access the stored biosamples. The biosamples may be transferred to other countries for analysis and will be destroyed at the latest 15 years after the trial has been reported.

Patients may withdraw from the biobank component of the trial at any time, independent of participation in the trial. The patient can choose to do so at any given time while in the trial or after the end of the trial. If a patient withdraws from the biobank component all stored biosamples obtained from their own body will be destroyed.

Israel: for country-specific requirements, please see Appendix 9 (Section 10.9).

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[72], ADA[73], ISPAD[74], type 1 diabetes outcomes program[75], ATTD[76]. Severe hypoglycaemia as defined by Seaquist[77] and ISPAD[74].		

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.[77]

Nocturnal hypoglycaemia

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

Reporting of hypoglycaemic episodes

Reporting of hypoglycaemic episodes by BG meters:
Plasma glucose (PG) should always be recorded in the diary/eCRF when a hypoglycaemic episode is suspected.
Hypoglycaemic episodes should be reported according to the instructions below. When a subject experiences 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 to 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.[77]

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.[77]

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 source documents 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.[78, 79]

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 source documents.

10.8 Appendix 8: Titration guideline

Titration guidelines have been developed, providing recommended dose adjustments at different PG levels to ensure that subjects receive an optimal treatment. However, it is recognised that insulin treatment should be individualised, and the specific titration algorithms may not be applicable in certain clinical situations. Hence, it is important that other information, such as symptoms of hypo-/hyperglycaemia, previous response to dose adjustments, other glucose measurements and other indicators of the subject's level of glycaemic control, is taken into consideration when decisions on dosing of insulin and other glucose lowering treatment are made. The investigator is responsible for the treatment of the subjects and can therefore overrule the guidelines to avoid safety hazards.

Initiation of trial product

Since the trial product may be added to background glucose lowering treatment that includes insulin and SUs the investigator is responsible for considering adjustment of background treatment at randomisation. Please refer to Section 6.5.

Dose adjustment of insulin treatment during the trial

After randomisation the investigator should evaluate insulin treatment in connection with the scheduled visits (see Flowchart Section 1.2) as described below. Additional adjustment may be necessary during both the trial drug dose escalation and the maintenance phase and additional SMPG measurements should be performed as directed by investigators' recommendation and subjects' preference to support treatment adjustment decisions.

Once daily insulin regimen:

- The dose of basal insulin should be titrated based on the mean of the three most recent pre-breakfast SMPG values measured before the contact in accordance with Table 10-4 and Table 10-5 .
- If one or more SMPGs values are missing, the adjustment should be performed based on the remaining SMPG value(s).
- If one of the SMPG values is below target (< 4.0 mmol/L or 71 mg/dL), then the insulin dose should be reduced in accordance with Table 10-4.

Twice daily insulin regimen:

- The pre-breakfast dose of basal insulin should be titrated based on the mean of the three most recent pre-dinner SMPG values measured before the contact.
  The pre-dinner dose of basal insulin should be titrated based on the mean of the three most recent pre-breakfast SMPG values measured before the contact.
  Doses should be adjusted in accordance with Table 10-4 and Table 10-5 .
- If one or more SMPGs values are missing, the adjustment should be performed based on the remaining SMPG value(s).
- If one of the SMPG values is below target (< 4.0 mmol/L or 71 mg/dL), then the insulin dose should be reduced in accordance with Table 10-4.

Table 10-4 Reduction of basal insulin dose

Lowest pre-breakfast or pre-dinner SMPG value		Reduction of basal insulin dose*
mmol/L	mg/dL	U
3.1 – 3.9	56 – 70	- 2
< 3.1	< 56	- 4

*Adjust using the most recent dose

Table 10-5 Increase of basal insulin dose

Mean pre-breakfast or pre-dinner SMPG values		Increase of basal insulin dose*
mmol/L	mg/dL	U
4.0 – 7.0	71 – 126	No adjustment
7.1 – 8.0	127 – 144	+ 2
8.1 – 9.0	145 – 162	+ 4
> 9.0	> 162	+ 6

*Adjust using the most recent dose

Bolus insulin regimen:

- Adjustment should be based on the mean SMPG value from the three most recent days before the contact in accordance with Table 10-6. Breakfast dose should be adjusted according to the pre-lunch SMPG values, lunch dose according to the pre-dinner SMPG values and dinner dose according to the bedtime SMPG values. Additional bolus doses should be documented under "extra bolus insulin" in the eCRF.

Table 10-6 Adjustment of bolus insulin

Mean pre-prandial or bedtime SMPG values			**Adjustment of insulin dose***
mmol/L	mg/dL	No. of measurements	U
< 4.0	< 71	≥ 1 SMPG below target	-1
4.0 – 7.0	71– 126	0 or 1 SMPG above target No SMPG below target	0
7.1 – 9.0	127 – 162	0 or 1 SMPG above target No SMPG below target	+1
>9.0	>162	≥ 2 SMPG above target No SMPG below target	+2

*Adjust using the most recent dose

If a subject practices carbohydrate counting the insulin dose should be adjusted with the guidance of the investigator.

10.9 Appendix 9: Country-specific requirements

For Argentina:

Section 8.3.5 Pregnancy:
Monthly testing with highly sensitive urine pregnancy tests is required for WOCBP.

Appendix 4, Section 10.4 Contraceptive guidance and collection of pregnancy information:
The contraceptive methods and pregnancy tests will be reimbursed by the sponsor.

Section 6.6: In reference to treatment after end of trial: the sponsor commits to comply with what is stated in point 6.8 of the current local regulation, disposition 6677/10. According to it, commits to comply with the following: "For Argentina, after the conclusion of subject´s participation in the study, trial doctor will discuss with subjects the best alternatives for future treatment. If trial doctor, based on his/her adequately justified medical analysis, decides that the Sponsor's study drug is the best available treatment option for the subject, trial doctor will prescribe the study drug, which must be approved by the Ethics Committee. The Sponsor (Novo Nordisk Pharma Argentina S.A.) will provide access to the Sponsor's study drug to the subject for the time the Ethics Committee decides or until access is ensured by any other means and in accordance with the applicable provisions in Argentina. Subjects must visit trial doctor to receive the Sponsor's study drug and will have to provide information about health status and any possible side effects that may have been experienced since last visit.

For Austria:

Section 8.3.5 Pregnancy:
A monthly pregnancy test is mandatory for female subjects of childbearing potential.

For Canada:

Appendix 1, Section 10.1.10 Retention of clinical trial documentation:
Retention period is 25 years.

For Czech Republic:

Section 1.2 Flowchart, Section 5.2, exclusion criteria #20, Appendix 2, Section 10.2 and Appendix 4, Section 10.4:
A monthly pregnancy test (urine) is required for all women of childbearing potential.

For Germany:

Section 1.2 Flowchart:
Subject's full Date of Birth is not allowed to be collected and must be shortened to year of birth

Section 1.2 Flowchart, Section 5.2, exclusion criteria #20, Appendix 2, Section 10.2 and Appendix 4, Section 10.4:
A monthly pregnancy test (urine) is required for all women of childbearing potential.

Section 5.2 Exclusion criteria and Appendix 4 (Section 10.4) Contraceptive guidance and collection of pregnancy information:

Contraceptive measures considered adequate include highly effective contraceptive methods in accordance with the CTFGs "Recommendations related to contraception and pregnancy testing in clinical trials", as listed in Table 10-2.

Section 8.2.5 Eye examination:
Fundus photography has to be performed by an ophthalmologist. Performance of fundus photography by an optimetrist or another qualified health care provider is not allowed.

Section 8.3 and Appendix 3, Section 10.3: All AEs, irrespective of seriousness, should be collected from the day of randomisation and until the follow-up visit/end of trial visit, at the time points specified in the flowchart.

For Hungary:

Section 1.2 Flowchart:
Subject's full Date of Birth is not allowed to be collected and must be shortened to year of birth

For India:

Section 1.2 Flowchart and Section 8.1.3 Echocardiography:
Indian subjects not participating in the echocardiography sub-study, shall undergo echocardiography at the Screening (V1) and End of Treatment (V11) visits. The echocardiographic examination should be conducted and documented in accordance with local practice; any adverse event identified will be assessed as described in Appendix 3, Section 10.3.

Section 3.2.2.2 Supportive secondary endpoints:
Heart failure mortality will be assessed descriptively as supportive secondary endpoint for subjects participating in the study from India and will be reported in a separate report. The assessment will be based on adjudicated deaths from heart failure (count of subjects who died from heart failure from baseline (week 0) to end of trial).

For Israel:

Section 8.7 Genetics, 8.8 Biomarkers and Appendix 6, Section 10.6 Retention of human biosamples and genetics:
No subjects from Israel will participate in the optional biobank part of the trial, and no genetic testing will be performed for Israeli subjects.

For Japan:

Section 5.1 Inclusion criteria:
Inclusion criteria 2: ≥ 20 years at the time of signing informed consent.

Section 6.2 Preparation/handling/storage/accountability:
The head of the study site or the trial product storage manager assigned by the head of the study site (a pharmacist in principle) is responsible for control and accountability of the trial products.

Section 7.1 Discontinuation of trial treatment:
The following sentence is not applicable to Japan: Simultaneous participation in a COVID-19

vaccine trial is however allowed at the discretion of the investigator without discontinuation of trial product.

Section 8.3 and Appendix 3, Section 10.3: All AEs, irrespective of seriousness, should be collected from the day of randomisation and until the follow-up visit/end of trial visit, at the time points specified in the flowchart.

Appendix 1, Section 10.1.1 Regulatory and ethical considerations:
A name and seal is accepted as a signature.

For Spain:

Section 5.2 Exclusion criteria and Appendix 4, Section 10.4 Contraceptive guidance and collection of pregnancy information:
Contraceptive measures considered adequate include highly effective contraceptive methods in accordance with the CTFGs "Recommendations related to contraception and pregnancy testing in clinical trials", as listed in Table 10-3 .

Appendix 1, Section 10.1.10 Retention of clinical trial documentation:
Retention period is 25 years.

For United Kingdom:

Appendix 1, Section 10.1.5 Data protection:
The IRB/IEC do not have access to the subjects' medical records.

Section 1.2 Flowchart, Section 5.2, exclusion criteria #20, Appendix 2, Section 10.2 and Appendix 4, Section 10.4:
A monthly pregnancy test (urine) is required for all women of childbearing potential.

For Poland:

Section 5.2, exclusion criteria #20 and Appendix 4, Section 10.4:
Contraceptive measures considered adequate include highly effective contraceptive methods in accordance with the Clinical Trial Facilitation Group: Recommendations related to contraception and pregnancy testing in clinical trials.

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

10.10 Appendix 10: Abbreviations

6MWD	6-minute walking distance
6MWT	6-minute walk test
ADA	American Diabetes Association
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BG	blood glucose
BMI	body mass index
BNP	brain natriuretic peptide
BW	body weight
CFR	Code of Federal Regulations
COVID-19	Coronavirus disease 2019
CRF	case report form
CRP	C-reactive protein
CTFG	Clinical Trial Facilitation Group
CTR	clinical trial report
CV	cardiovascular
DFU	directions for use
DUN	dispensing unit number
EAC	event adjudication committee
EAS	event adjudication system
EASD	European Association for the Study of Diabetes
ECG	electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
EQ-5D-5L	European Quality of Life five Dimensions five level
FAS	full analysis set
FDA	U.S. Food and Drug Administration
FDAAA	FDA Amendments Act
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GLP-1	glucagon-like peptide-1
GLP-1 RA	glucagon-like peptide-1 receptor agonist
HbA_{1c}	glycated haemoglobin

HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HRT	hormone replacement therapy
hsCRP	High-sensitivity C-reactive protein
ICH	International Council for Harmonisation
IEC	independent ethics committee
IMP	investigational medicinal product
IRB	institutional review board
IWRS	interactive web response system
KCCQ	Kansas City Cardiomyopathy Questionnaire
KCCG-CSS	Kansas City Cardiomyopathy Questionnaire clinical summary score
LA	left atrial
LAO-OT	last available observation during the on-treatment period
LSFT	last subject first treatment
LV	left ventricular
LVEDP	left ventricular end diastolic pressure
LVEF	left ventricular ejection fraction
MEN2	multiple endocrine neoplasia type 2
MTC	medullary thyroid cancer
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
OAD	Oral anti-diabetic
OW	Once-weekly
PA	Pulmonary artery
PCD	primary completion date
PG	plasma glucose
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Status
PK	pharmacokinetic
PRO	patient-reported outcome
PYE	patient years of exposure
PYO	patient years of observation
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
s.c.	subcutaneous

SMPG	self-measured plasma glucose
SOP	standard operating procedure
SU	sulphonylurea
SUSAR	suspected unexpected serious adverse reaction
T2D	type 2 diabetes
TMM	trial materials manual
UNL	upper normal limit
WOCBP	woman of childbearing potential

10.11 Appendix 11: Mitigations to ensure participant safety and data integrity during an emergency situation

Definition and scope of appendix

In case local restrictions, e.g. due to a COVID-19 outbreak, lead to lock-down of a site, the site must contact Novo Nordisk to allow for implementation of mitigations mentioned in this appendix based on mutual agreement.

Table 10-7 indicates the minimum requirements for assessments that should be performed during a lock-down, but sites should always try to follow the assessments outlined in Section 1.2 (original flowchart) to the extent possible. Implementation of specific mitigations should be based on assessment of feasibility at the individual site.

Sites should comply with local regulations, requirements and/or guidelines.

Visits

Screening (Visit 1) and randomisation/baseline (Visit 2) should always be performed as physical on-site visits. If a site is unable to perform these visits on-site, screening and randomisation of new participants at that site should be on hold until on-site visits are possible. Participants that cannot attend on-site visits 1 and 2 should not be included.

Visits 7 and 11 should be performed as physical on-site visits, if in any way possible. If not, assessments can be conducted remotely using telemedicine or as home visits. The visit window for visit 11 can be extended for up to 4 weeks. If the assessments at visit 7 cannot be performed on-site, using telemedicine or home visits, the visit window can be extended for up to 8 weeks.

Other on-site visits (Visits 3, 4, 5, 6, 8, 9 and 10) can be converted to telemedicine (video, phone or similar) or home visits.

At each visit the investigator must indicate in the eCRF how the visit was performed and specify the reason for the preferred assessment method.

Assessments

Local laboratories or diagnostic facilities can be used at the investigator's discretion if on-site visits are not possible or in case of temporary lockdown of the central laboratory. Only findings meeting the definition for an AE should be reported in the eCRF, refer to Section 10.1.12 for further details.

If the assessments indicated in Table 10-7 cannot be performed as on-site visits, using telemedicine or at a local laboratory or diagnostic facility, they should be performed at the first possible time point following the originally scheduled visit.

Assessments used for the primary and secondary endpoints at Visits 7 and 11 (weight, outcome assessments and lab samples) should be prioritised. In addition, all participants must have ECG performed at Visit 11 and all participants of the sub-study must have an echocardiography performed at Visit 11. Pregnancy tests can be shipped to the subject of childbearing potential if on-site visits are not possible. The site is responsible for contracting a suitable courier and costs will be reimbursed by Novo Nordisk. It must be documented in medical records that the subject has

consented to this process, and, if required locally, the subject might have to sign a separate informed consent form.

Paper diaries should be shipped to sites in case of lockdown.

Study intervention

Alternative dispensing methods may be implemented, and details will be communicated and documented. The dispensing options will be provided by Novo Nordisk A/S and will be based on options and requirements at country level and if permitted by local regulations.

Table 10-7 Minimum assessments following randomisation to be performed during lockdown

Please refer to Section 1.2 for the full flowchart.

Procedures marked with a black X should be prioritised. If deemed necessary because of the lockdown, Visits 3, 4, 5, 6, 8, 9 and 10 can be fully converted to phone visits and procedures marked with a red X will subsequently be cancelled.

	Protocol section	Screening	Randomisation	Treatment period								End of treatment	End of trial
Visit		V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
Timing of Visit (Weeks)		-2	0	4	8	12	16	20	28	36	44	52	57
Visit Window (Days)		0 to +13	0	±3	±3	±3	±3	±3	±3	±3	±3	±3	0 to +7
Informed Consent and Demography[a)]	10.1.3	X											
Eligibility Criteria	5.1, 5.2	X	X										
Physical Examination	8.2.1	X	X									X	
Eye examination	8.2.5	X										X	
Medical History/Concomitant Illness	8.2		X										
Tobacco Use[b)]			X										
Childbearing Potential	10.4	X											
Concomitant Medication	6.5	X	X	X	X	X	X	X	X	X	X	X	X
Body Weight	8.1.1	X	X	X	X	X	X	X	X	X	X	X	
Height /BMI	8.1.1	X											
Waist Circumference	8.1.1		X					X				X	
Patient Global Impression of Status (PGI-S) for KCCQ	8.1.2	X	X					X		X		X	
Patient Global Impression of Change (PGI-C) for KCCQ	8.1.2		X					X		X		X	
Kansas City Cardiomyopathy Questionnaire (KCCQ)	8.1.2	X	X					X		X		X	
European Quality of Life five Dimensions five Level (EQ-5D-5L)	8.1.2		X					X				X	

	Protocol section	Screening	Randomisation	Treatment period								End of treatment	End of trial
Visit		V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
Timing of Visit (Weeks)		-2	0	4	8	12	16	20	28	36	44	52	57
Visit Window (Days)		0 to +13	0	±3	±3	±3	±3	±3	±3	±3	±3	±3	0 to +7
Patient Global Impression of Status (PGI-S) for 6MWT	8.1.2	X	X					X				X	
Patient Global Impression of Change (PGI-C) for 6MWT	8.1.2		X					X				X	
6-minute walk test (6MWT)	8.1.2	X	X					X				X	
NYHA classification/Vital Signs	8.2.4, 8.2.2	X						X				X	
Electrocardiogram (ECG)	8.2.3	X										X	
Echocardiography	8.1.3	X	X[c])									X[c])	
Laboratory Assessments	10.2	X	X		X			X		X		X	
Semaglutide plasma concentration	10.2							X				X	
Pregnancy test[d])	8.3.5, 10.4	X	X		**X**	**X**		X	**X**	**X**	**X**	X	X
Healthy Lifestyle Counselling	5.3		X	X	X	X	X	X	X	X	X	X	
Adverse Event	8.3, 10.3			X	X	X	X	X	X	X	X	X	X
Hypoglycaemic episodes	8.3, 10.7		X	X	X	X	X	X	X	X	X	X	X
Self-measured plasma glucose[e])	8.2.6			X	X	X	X	X					
Event Adjudication	8.3, 10.3			X	X	X	X	X	X	X	X	X	X
Medication Error, Misuse and Abuse	8.3, 10.3.3			X	X	X	X	X	X	X	X	X	
Drug dispensing	6		X	**X**	**X**	**X**	**X**	X	**X**	**X**	**X**		
Drug Accountability	6.2		X	X	X	X	X	X	X	X	X	X	

	Protocol section	Screening	Randomisation	Treatment period								End of treatment	End of trial
Visit		V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
Timing of Visit (Weeks)		-2	0	4	8	12	16	20	28	36	44	52	57
Visit Window (Days)		0 to +13	0	±3	±3	±3	±3	±3	±3	±3	±3	±3	0 to +7
IWRS Session		X	X	X	X	X	X	X	X	X	X	X	
Training in trial product, pen-handling	6.1		X	X		X				X			
Hand Out Direction for Use	6.1		X										
Hand Out Dose Reminder Card			X	X	X	X	X						
Hand Out ID Card		X											
Hand out and instruct in BG meter	10.7		X										
Hand out and instruct in diary	8		X	X	X	X	X	X	X	X	X	X	
Collect, review and transcribe diary				X	X	X	X	X	X	X	X	X	X

a: Demography consists of date of birth, sex, race and ethnicity (according to local regulation – Germany and Hungary: for country-specific requirements, please see Appendix 9 (Section 10.9)).

b: Tobacco use is defined as smoking at least one cigarette or equivalent daily.

c: Only relevant for subjects included in the echocardiographic sub-study. India: for country-specific requirements, please see Appendix 9 (Section 10.9).

d: For women of childbearing potential only. In addition to the planned assessments, urine dipstick pregnancy test should be performed at any time during the trial if a menstrual period is missed, or if pregnancy is suspected (according to local regulation – Czech Republic, United Kingdom and Germany: for country-specific requirements, please see Appendix 9 (Section 10.9)).

e: All subjects treated with insulin should capture SMPG.

10.12 Appendix 12: Protocol amendment history

The protocol amendment summary of changes table for the current updated protocol is located directly before the Table of Contents.

Protocol version 6.0 (29 April 2022)

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.[1] because it neither significantly impacts the safety nor physical/mental integrity of subjects nor the scientific value of the trial.

Overall rationale for preparing protocol, version 6.0:

The overall rationale for the changes implemented in the amended protocol is to address expected requirements from health authorities.

Section # and name	Description of change	Brief rationale
Section 10.9: Appendix 9 Country-specific Requirements Czech Republic	A monthly pregnancy test is mandatory for female subjects of childbearing potential.	See overall rationale

Protocol version 5.0 (01 October 2021)

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.[1] because it neither significantly impacts the safety nor physical/mental integrity of subjects nor the scientific value of the trial.

Overall rationale for preparing protocol, version 5.0:

The overall rationale for the changes implemented in the amended protocol is to address expected requirements from health authorities.

Section # and name	Description of change	Brief rationale
Section 10.9: Appendix 9 Country-specific Requirements India	Indian subjects not participating in the echocardiography sub-study, shall undergo echocardiography at the Screening (V1) and End of Treatment (V11) visits.	See overall rationale
Section 10.9: Appendix 9 Country-specific Requirements India	Heart failure mortality will be assessed descriptively as supportive secondary endpoint for subjects participating in the study from India	See overall rationale

Protocol version 4.0 (24 March 2021)

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.[1] because it neither significantly impacts the safety nor physical/mental integrity of subjects nor the scientific value of the trial.

Overall rationale for preparing protocol, version 4.0:

The overall rationale for the changes implemented in the amended protocol is to address expected requirements from health authorities.

Section # and name	Description of change	Brief rationale
Section 10.9: Appendix 9 Country-specific Requirements Japan	The following is not applicable for Japan: Section 7.1, discontinuation criterion #5: The following sentence is not applicable to Japan: Simultaneous participation in a COVID-19 vaccine trial is however allowed at the discretion of the investigator without discontinuation of trial product.	Simultaneous co-participation in COVID-19 vaccine trials is not recommended in Japan following feedback from local health authority.

Protocol version 3.0 (19 February 2021)

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.[1] because it neither significantly impacts the safety nor physical/mental integrity of subjects nor the scientific value of the trial.

Overall rationale for preparing protocol, version 3.0:

The overall rationale for the changes implemented in the amended protocol is to address expected requirements from health authorities.

Section # and name	Description of change	Brief rationale
Section 10.9: Appendix 9 Country-specific Requirements Germany	All AEs, irrespective of seriousness, should be collected from the day of randomisation and until the follow-up visit/end of trial visit, at the time points specified in the flowchart	See overall rationale
Section 10.9: Appendix 9 Country-specific Requirements Japan	All AEs, irrespective of seriousness, should be collected from the day of randomisation and until the follow-up visit/end of trial visit, at the time points specified in the flowchart	See overall rationale

Protocol version 2.0 (22 January 2021)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.[1]

Overall rationale for preparing protocol, version 2.0:

The overall rationale for the changes implemented in the amended protocol is to align internally with other Novo Nordisk trials, following health authority feedback.

Section # and name	Description of change	Brief rationale
Section 7.2	Inclusion of obtainment of vital status for subjects 'lost to follow up'.	See overall rationale

Subject discontinuation/withdrawal from the trial		
Section 7.3 Lost to follow-up	Inclusion of obtainment of vital status for subjects 'lost to follow up'.	See overall rationale
Section 10.1.12 Appendix 1 Responsibilities	Inclusion of elaboration of responsibilities of the investigator in relation to prevention of unauthorised access to data or any other processing of data against applicable law.	See overall rationale
Section 10.9: Appendix 9 Country-specific Requirements United Kingdom	A monthly pregnancy test is mandatory for female subjects of childbearing potential.	See overall rationale
Section 10.9: Appendix 9 Country-specific Requirements Germany	A monthly pregnancy test is mandatory for female subjects of childbearing potential.	See overall rationale
Section 10.9: Appendix 9 Country-specific Requirements Poland	Contraceptive measures considered adequate include highly effective contraceptive methods.	See overall rationale

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