Cover Page for Protocol

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NCT number	NCT04560998
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Official title of study:	Effect of semaglutide on functional capacity in patients with type 2 diabetes and peripheral artery disease
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Protocol

Trial ID: NN9535-4533

Effects of semaglutide on functional capacity in patients with type 2 diabetes and peripheral arterial disease

Substance: Semaglutide s.c

Universal Trial Number: U1111-1238-7071

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Trial Phase: 3b

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

Protocol amendment summary of changes table

DOCUMENT HISTORY		
Document version	Date	Applicable in country(-ies) and/or site(s)
7.0	18 April 2023	All
6.0	06 June 2022	Austria, Canada, Czech Republic, Denmark, Greece, India, Malaysia, Sweden, Thailand and United States
5.0	15 October 2021	All
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1.0	26 May 2020	All

Protocol version 7.0 (18 April 2023)

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 to strengthen our approach of submitting a single trial to have the PAD information accepted into the label. This is achieved by elevating the supportive endpoint "Follow-up change in maximum walking distance on a constant load treadmill test" to confirmatory secondary endpoint with the purpose of ensuring that the follow-up period results are taken into consideration by regulators.

Additionally, this amendment includes the inversion of confirmatory endpoints "Change in pain-free walking distance on a constant load treadmill test" and "Change in Vascular Quality of Life Questionnaire-6 (VascuQoL-6) score", as well as a small change in the wording of the secondary objective related to VascuQoL-6 questionnaire, to clarify the measured concepts. This will strengthen our position to submit a label containing the VascuQoL-6 results.

New text is written as *italic*.

Section # and name	Description of change	Rationale
Section 1.1 Synopsis	Description of objectives and endpoints updated as specified below.	To align synopsis with protocol updates
Section 1.2 Flowchart	Footnote added for V9A *a) EOT follow-up visit (V9A) to be performed 5 weeks after V8A.* Subsequent footnote numbering updated accordingly.	For clarification
Section 1.2 Flowchart	*PK sampling* ~~Semaglutide plasma concentration~~	Renamed to clarify that this refers to PK sampling.
Section 1.2 Flowchart	Severe Hypoglycaemic episodes have been added to the high-level flowchart	For completeness
Section 1.2 Flowchart	Footnote added for Treadmill assessments [f]	To increase flexibility for the sites

Section # and name	Description of change	Rationale
	f) The treadmill assessments at visits 6, 8 and 9 can be performed at a later day than the other assessments and procedures at the given visit, provided that all assessments are completed within the visit window (visit windows are calculated from the randomisation date). Subsequent footnote numbering updated accordingly.	
Section 1.2 Flowchart	Footnote added for eye examination *k) Fundus photography/dilated fundoscopy should be performed:* • *within 90 days prior to screening or within the period between screening and randomisation, see details in Section 8.2.2* • *at V8 and V8A or within +/- 2 weeks of those visits* Subsequent footnote numbering updated accordingly.	To increase flexibility for the sites
Section 3.1.1 Primary objective and estimands	The primary estimand will be the ~~treatment ratio of the~~ median *treatment* ratio to baseline at week 52 in maximum walking distance (…) *Two*~~A~~ secondary estimand*s* for the primary objective will be the ~~treatment ratio of the~~ median *treatment* ratio to baseline *(i) at week 57 in maximum walking distance and (ii)* at week 52 in pain free walking distance (…) The rationale for ~~this~~ *pain-free walking estimand* (…)	See rationale above the table
Section 3.1.1 Primary objective and estimands	Table 3-1 updated to include two additional secondary estimands for the primary objective.	The supportive secondary endpoint "Follow-up change in maximum walking distance on a constant load treadmill test" has been elevated to a confirmatory secondary endpoint
Section 3.1.2 Secondary objectives and estimands	~~PAD specific health related quality of life~~ *Patient reported symptoms and impacts of intermittent claudication* (VascuQoL-6)	To specify. The questionnaire is assessing the proximal concept of symptoms and impacts of intermittent claudication, that can be more directly associated with PAD defining concepts. At the same time, "quality of life" is a distal concept that could be influenced by multiple contextual factors that the questionnaire does not assess (whether environmental or personal, e.g. psychosocial factors, ethnicity, etc.)

Section # and name	Description of change	Rationale
		The FDA is not likely to accept data related to quality of life, which they consider a broad and subjective term
Section 3.2.2 Secondary endpoints	Elevation of supportive endpoint to confirmatory and inversion of the other confirmatory endpoints **Confirmatory secondary endpoints:** • *Follow-up change in maximum walking distance on a constant load treadmill test* • ~~Change in pain-free walking distance on a constant load treadmill test~~ • Change in Vascular Quality of Life Questionnaire-6 (VascuQoL-6) score • Change in pain-free walking distance on a constant load treadmill test **Supportive secondary endpoints:** • ~~Follow-up change in maximum walking distance on a constant load treadmill test~~	See rationale above the table
Section 3.2.3 Exploratory endpoint	Footnote updated: [a]The activity tracker is only applied in a subset of patients (n=~~242~~*125*).	To accommodate recruitment difficulties and prioritise recruitment activities for the main study
Section 5 Trial population	Expected number of patients to complete the activity tracker evaluation: ~~222~~ *115* (~~242~~ *125* planned for randomisation, withdrawal rate of 8 % is anticipated).	To accommodate recruitment difficulties and prioritise recruitment activities for the main study
Section 7.1 Discontinuation of trial treatment	If a patient has discontinued treatment with trial product prematurely, the site should perform a premature EOT visit (V8A) ~~and Premature EOT follow-up visit (V9A)~~ as soon as possible after the decision to *permanently* discontinue treatment is taken, *followed by an EOT follow-up visit (V9A) 5 weeks after V8A.* See the flowchart, Section 1.2 for data to be collected at the time of treatment discontinuation ~~(Premature EOT visit~~ (V8A~~)~~ and ~~Premature EOT follow-up visit (~~V9A) and for any further evaluations that need to be completed. *Patients should continue with the originally scheduled site visits (including V8 and V9) after completing the Premature EOT follow-up visit (V9A).* Efforts must be made to have patients who prematurely discontinue trial product treatment to attend and complete all scheduled visit procedures *after completing the premature EOT* visits.	For clarification

Section # and name	Description of change	Rationale
	However, as a minimum, these patients must be asked to attend visit 8 *and 9* (…)	
Section 7.2 Patient discontinuation/withdrawal from the trial	If a patient withdraws consent, the investigator must ask the patient if he/she is willing, as soon as possible, to have assessment performed according to visit 8A ~~and visit 9A~~, *followed by an EOT follow-up visit (V9A) 5 weeks after V8A.*	For clarification
Section 8.1.1 Treadmill assessments	Minor editorial changes: The patient should be instructed *before performing the treadmill test to ensure that* ~~in the course of the treadmill test, ensuring~~ that (…). Patients should be encouraged to continue *for* as long as possible (…). The baseline treadmill test is to be performed in the beginning of the baseline visit and in the end of the baseline visit ~~in order~~ to evaluate	For clarification
Section 8.1.1 Treadmill assessments	*The treadmill assessments at visits 6, 8 and 9 can be performed at a later day than the other assessments and procedures at the given visit, provided that all assessments are completed within the visit window (visit windows are calculated from the randomisation date) (Section 1.2).*	To increase flexibility for the sites
Section 8.1.3 Physical activity tracker, patient training, dispensing and collection	To evaluate the ambulatory walking ability in the daily life of the patient, an activity tracker is applied in a subset of ~~242~~ *125* patients ~~(121 patients in each group)~~	Sample size for sub-study updated to accommodate recruitment difficulties and prioritise recruitment activities for the main study
Section 8.1.5.1 Pulse and blood pressure	~~Systolic blood pressure is to be recorded as the mean of the last 2 systolic blood pressure readings, and diastolic blood pressure as the mean of the last 2 diastolic blood pressure readings.~~ *The last 2 systolic and last 2 diastolic blood pressure measurements should be recorded in the eCRF. The eCRF will calculate the mean of the last 2 measurements.*	For clarification
Section 9.1 Statistical hypotheses	The hypothesis for the confirmatory endpoint, ratio to baseline in *maximum walking distance at week 57 and* pain-free walking distance at week 52 is the same as for the primary endpoint.	To align with the changes in testing hierarchy of the endpoints
Section 9.1 Statistical hypotheses	**Multiplicity adjustment:** The following hierarchical testing strategy will be applied to control the type-I error at an overall alpha level (two-sided) of 0.05 across the confirmatory endpoints:	To align with the changes in testing hierarchy of the endpoints.

Section # and name	Description of change	Rationale
	1. Superiority of semaglutide 1 mg vs. placebo on ratio to baseline (week 0) at week 52 in maximum walking distance 2. *Superiority of semaglutide 1 mg vs. placebo on ratio to baseline (week 0) at week 57 in maximum walking distance* 3. *Superiority of semaglutide 1 mg vs. placebo on change from baseline (week 0) to week 52 in VascuQoL-6 score.* 4. Superiority of semaglutide 1 mg vs. placebo on ratio to baseline (week 0) at week 52 in pain-free walking distance ~~5. Superiority of semaglutide 1 mg vs. placebo on change from baseline (week 0) to week 52 in VascuQoL-6 score.~~	
Section 9.2 Sample size determination	The confirmatory secondary endpoints are *ratio to baseline (week 0) at week 57 in maximum walking distance, change from baseline (week 0) to week 52 in VascuQoL-6 score and* ratio to baseline (week 0) at week 52 in pain-free walking distance ~~and change from baseline (week 0) to week 52 in VascuQoL-6 score~~. Superiority will be tested for all ~~three~~ *four* endpoints.	To align with the changes in testing hierarchy of the endpoints
Section 9.2 Sample size determination	**Secondary confirmatory endpoints** The same assumptions as for the primary endpoint apply for the *ratio to baseline (week 0) at week 57 in maximum walking distance and* ratio to baseline (week 0) at week 52 in pain-free walking distance.	To align with the changes in testing hierarchy of the endpoints
Section 9.2 Sample size determination	Table 9-1 updated to reflect changes in testing hierarchy.	To align with the changes in testing hierarchy of the endpoints
Section 9.4.3.1 Confirmatory secondary endpoints	The confirmatory secondary endpoints are: • Ratio to baseline (week 0) at week *57* ~~52~~ in ~~pain-free~~ *maximum* walking distance, and will be analysed similarly to the primary endpoint with regards to the estimands • Change from baseline (week 0) to week 52 in VascuQoL-6 score and will be analysed similarly to the primary endpoint with regards to estimands but will not be log-transformed. • *Ratio to baseline (week 0) at week 52 in pain-free walking distance, and will be analysed similarly to the primary endpoint with regards to the estimands*	To align with the changes in testing hierarchy of the endpoints

Section # and name	Description of change	Rationale
Section 9.4.3.2 Supportive secondary endpoints	The ratio to baseline in ~~maximum walking distance and~~ pain free walking distance at follow-up will be analysed similarly to the primary endpoint.	To align with the changes in testing hierarchy of the endpoints
Appendix 8 (Section 10.8) Country/region-specific requirements	Country-specific requirement regarding optional biobanking included for Taiwan.	No patients from Taiwan will participate in the optional biobank part of the trial

Table of contents

1 Protocol summary

1.1 Synopsis

Rationale

Lower extremity peripheral artery disease (PAD) is an atherosclerotic disease and is a major cause of disability in older men and women affecting more than 200 million people worldwide.[3, 4] Approximately 1/3 of all PAD patients have type 2 diabetes (T2D). The purpose of this trial is to demonstrate that semaglutide 1 mg once-weekly improves clinical outcomes including walking distance compared to placebo in patients with T2D and intermittent claudication due to PAD.

Objectives and endpoints

The primary objective is to demonstrate the effect of s.c. semaglutide 1 mg once-weekly on walking ability compared with placebo, both added to standard-of-care, in patients with T2D and PAD with intermittent claudication.

The primary estimand will be the median treatment ratio to baseline at week 52 in maximum walking distance for semaglutide 1 mg versus placebo, both as add-on to standard-of-care, in all randomised patients, regardless of change in background medication, rescue treatment (e.g. revascularisation or starting cilostazol/pentoxifylline), and adherence to randomised treatment.

Two secondary estimands for the primary objective will be the median treatment ratio to baseline (i) at week 57 in maximum walking distance and (ii) at week 52 in pain-free walking distance for semaglutide 1 mg versus placebo, both as add-on to standard-of-care, in all randomised patients, regardless of change in background medication and adherence to randomised treatment. The rationale for pain-free walking estimand is that the pain-free walking distance is of particular importance to the patient, who is reminded of their disease in the moment pain is experienced.

The key secondary objectives are to compare the effect of s.c. semaglutide 1 mg once-weekly versus placebo, both added to standard-of-care in patients with T2D and PAD with intermittent claudication with regards to Patient-reported symptoms and impacts of intermittent claudication (VascuQoL-6[5]).

Overall design

This is a 52-week, randomised, double-blind, placebo-controlled trial comparing s.c. semaglutide 1 mg versus placebo both added to standard-of-care and administered once-weekly in patients with T2D and PAD with intermittent claudication. Screening period is approximately 2 weeks before randomisation, and patients will be randomised in a 1:1 ratio to receive either s.c. semaglutide 1 mg or placebo as add-on to standard-of-care. The treatment duration is 52 weeks including an eight weeks dose escalation period. The follow-up period is 5 weeks.

Key inclusion criteria:

- Male or female, age above or equal to 18 years at the time of signing informed consent. For Japan and Taiwan: Male or female, age above or equal to 20 years at the time of signing informed consent, Appendix 8, Section 10.8.

- Diagnosed with type 2 diabetes mellitus ≥ 180 days prior to the day of screening.
- Symptomatic PAD with intermittent claudication corresponding to Fontaine stage IIa (Rutherford classification grade I, category 1 and 2) meeting all of the following:

a. Stable symptoms of PAD with intermittent claudication in Fontaine stage IIa (able to walk without stopping > 200 m/656 feet/2 blocks) for ≥ 90 days prior to the day of screening based on patient interview.
b. Screening flat treadmill test (3.2 km/h (2 mph)): Pain-free walking distance of ≥ 200 meters/656 feet.
c. Screening constant load treadmill test with fixed inclination of 12% and a fixed speed of 3.2 km/h (2 mph): Walking distance ≤ 600 meters/1968 feet.
d. Ankle-brachial-index (ABI) ≤ 0.90 or toe-brachial index (TBI) ≤ 0.70 (the leg with lowest index is chosen in case of bilateral disease).

Key exclusion criteria:

- Current or previous treatment with any GLP-1 receptor agonist (GLP-1-RA within 90 days prior to the day of screening.
- Walking ability limited by conditions other than PAD (e.g. aortic aneurism, dysregulated arrhythmia or hypertension, angina pectoris, heart failure, chronic obstructive or restrictive pulmonary disease, Parkinson's disease, severe peripheral neuropathy, amputations, wheel chair or walker dependency, osteoarthritis, morbid obesity, severe varicose veins, etc.).
- Planned orthopaedic surgery in the legs, or other major surgery known on the day of screening (surgery affecting walking ability).
- Vascular revascularisation procedure of any kind 180 days prior to the day of screening.
- Planned arterial revascularisation known on the day of screening.
- Myocardial infarction, stroke, hospitalisation for unstable angina pectoris or transient ischemic attack within 180 days prior to the day of screening.
- Heart failure presently classified as being in New York Heart Association (NYHA) class III−IV.

Number of patients

Approximately 1,143 patients will be screened to achieve 800 patients randomly assigned to trial product. Expected number of patients to complete the trial on or off trial product is 736.

Treatment groups and duration

The total duration of trial participation for each patient is approximately 59 weeks, including a screening period of approximately 2 weeks, a treatment period of 52 weeks and a follow-up period of 5 weeks.

The investigational medicinal products (trial products) provided by Novo Nordisk are semaglutide, 1.34 mg/mL (investigational medicinal product (IMP), test product) and semaglutide placebo (IMP, reference therapy). The dosage form is a solution for subcutaneous injection packed in a 1.5 mL pre-filled PDS290 pen-injector.

When discontinuing trial product at the end of the treatment period, the patient should be transferred to a suitable marketed product at the discretion of the investigator. GLP-1 RAs are not allowed to be prescribed during the 5-week follow-up period.

Data monitoring committee

Not applicable.

1.2 Flowchart

	Screening	Baseline	Treatment					End of treatment	Follow-up	Premature EOT	Premature EOT follow-up
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**P7**	**V8**	**V9**	**V8A**	**V9A[a]**
Timing of visit (weeks)	**-2[b]**	**0**	**4**	**8**	**12**	**26**	**49**	**52**	**57**	**-**	**-**
Visit window (days)	**-7; +13[b]**	**±0**	**±4**	**±4**	**±4**	**±7**	**±7**	**±7**	**+7**	**±0**	**±0**
PATIENT-RELATED INFORMATION AND ASSESSMENTS											
Informed consent and demography[c]	X										
Eligibility criteria	X										
Randomisation		X									
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X
Information on regular exercise[d]		X									
Medical history/Concomitant illness	X										
Diabetes history	X										
Tobacco and nicotine products use[e]		X				X		X		X	
Childbearing potential	X										
EFFICACY											
Treadmill assessments[f]											
Pain-free walk distance-flat treadmill	X										
Pain-free walking distance-inclined treadmill		X[g]				X		X	X	X	X
Max. walking distance-inclined treadmill	X	X[g]				X		X	X	X	X
Lipids		X			X			X		X	
Toe-brachial index (TBI)	X					X		X	X	X	X
Ankle-brachial index (ABI)	X					X		X	X	X	X
PK sampling						X		X			
HbA1c	X[h]	X			X	X		X		X	
Body weight		X			X	X		X	X	X	X
Height		X									
Patient-reported outcome (PRO)											
Patient global impression of severity (PGI-S)[i]		X				X		X		X	
Patient global impression of change (PGI-C)[i]						X		X		X	

	Screening	Baseline	Treatment					End of treatment	Follow-up	Premature EOT	Premature EOT follow-up
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**P7**	**V8**	**V9**	**V8A**	**V9A[a]**
Timing of visit (weeks)	**-2[b]**	**0**	**4**	**8**	**12**	**26**	**49**	**52**	**57**	**-**	**-**
Visit window (days)	**-7; +13[b]**	**±0**	**±4**	**±4**	**±4**	**±7**	**±7**	**±7**	**+7**	**±0**	**±0**
VascuQoL-6 questionnaire (VascuQoL-6)		X				X		X		X	
Walking impairment questionnaire (WIQ)		X				X		X		X	
Short Form 36 (SF-36)		X				X		X		X	
SAFETY											
Pregnancy test[j]	X					X		X	X	X	X
Adverse event (AE)		X	X	X	X	X	X	X	X	X	X
Severe hypoglycaemic episodes		X	X	X	X	X	X	X	X	X	X
Laboratory assessments											
Biochemistry	X	X			X	X		X	X	X	X
Haematology		X			X	X		X	X	X	X
Physical examination	X	X						X		X	
Eye examination[k]	X							X		X	
Vital signs	X	X			X	X		X	X	X	X
OTHER ASSESSMENTS											
Biosamples for future analysis		X			X			X		X	
TRIAL MATERIALS											
IWRS session	X	X	X	X	X	X		X		X	
Hand out Directions for Use		X									
Dispensing visit		X	X	X	X	X					
Training in trial product, pen-handling		X									
Drug accountability		X	X	X	X	X		X		X	
REMINDERS											
Activity tracker[l]											
Phone reminder to use activity tracker							X				
Dispense activity tracker	X					X					
Hand out ID card	X										

Notes:

a) EOT follow-up visit (V9A) to be performed 5 weeks after V8A.

b) Visit 1 should be at least 2 weeks prior to visit 2 in the subset of patients included in the activity tracker sub-study.

c) Demography: date of birth (month and year), sex, ethnicity, and race (according to local regulations).

d) Information from patient.

e) Tobacco use/smoking is defined as smoking at least one cigarette or equivalent daily.

f) The treadmill assessments at visits 6, 8 and 9 can be performed at a later day than the other assessments and procedures at the given visit, provided that all assessments are completed within the visit window (visit windows are calculated from the randomisation date).

g) Inclined treadmill assessment must be done twice at V2, see details in Section 8.1.1.

h) Sample can be omitted if HbA_{1c} criterion is based on historical data obtained within 90 days prior to screening.

i) Related to both walking ability and quality of life.

j) Only applicable for women of childbearing potential; For Czech Republic a pregnancy test is also performed at weeks 4, 8 and 12. Please see Section 10.8 (Appendix 8) for country specific requirements.

k) Fundus photography/dilated fundoscopy should be performed:

- within 90 days prior to screening or within the period between screening and randomisation, see details in Section 8.2.2
- at V8 and V8A or within +/- 2 weeks of those visits

l) Activity tracker used for measuring step count during Weeks -2 and -1 as well as Weeks 51 and 52. Only selected sites participate in this substudy.

Abbreviations: EOT: End-of-Treatment; Hb: haemoglobin; HbA_{1c}: glycosylated haemoglobin; IWRS: interactive web response system; Max: maximum; w: week.

2 Introduction

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

2.1 Trial rationale

Semaglutide (trade name Ozempic) is a GLP-1 receptor agonist (GLP-1-RA) indicated to improve glycaemic control in patients with type 2 diabetes (T2D) as an adjunct to diet and exercise.[6] In the large clinical development programme for subcutaneous (s.c.) semaglutide for once weekly (OW) administration in T2D, semaglutide was superior in terms of glycaemic control and weight loss vs. all comparators (placebo or other approved T2D treatments).[6] In addition, the cardiovascular effects of semaglutide were assessed in a phase 3a cardiovascular outcomes trial (NN9535-3744, SUSTAIN 6). In this trial, treatment with semaglutide demonstrated a statistically significant 26% reduction in major adverse cardiovascular events (MACE) comprising death from cardiovascular causes, non-fatal myocardial infarction, and non-fatal stroke when compared to placebo in patients with T2D at high risk of cardiovascular events.[7]

The mode of action for the reduction of cardiovascular events is believed mainly to be due to an anti-atherosclerotic effect of semaglutide. This hypothesis is supported by animal studies, where semaglutide attenuated the development of atherosclerosis by preventing aortic plaque progression and reducing plaque inflammation.[8] Furthermore, a post-hoc analysis of data from the LEADER trial (EX2211-3748), investigating the effect of liraglutide (first generation GLP-1 receptor agonist) in patients with T2D and high risk of cardiovascular events, suggested a reduction in amputations in connection with foot ulcers when treated with liraglutide compared to placebo.[9]

Lower extremity peripheral artery disease (PAD) is an atherosclerotic manifestation and is a major cause of disability in older men and women affecting more than 200 million people worldwide.[3, 4] T2D is together with smoking the two leading causes of PAD, and both critical limb ischemia and amputations are more common in PAD patients with T2D compared to PAD patients without T2D. Approximately 1/3 of all PAD patients have T2D. Major risk factors are obesity, older age, smoking, and diabetes. PAD is diagnosed based on symptoms, ankle-brachial index (ABI) < 0.90 and often supplemented by relevant imaging. People with PAD have increased risk of cardiovascular mortality and morbidity, faster rates of functional decline and mobility loss due to amputations, which represent a significant socioeconomic burden.[10, 11]

The purpose of this trial is to demonstrate that semaglutide 1 mg once-weekly improves clinical outcomes including walking distance compared to placebo in patients with T2D and intermittent claudication due to PAD.

2.2 Background

To prevent the complications associated with T2D, the goal of the therapy is to mitigate the multiple heterogeneous metabolic defects associated with the disease and to reduce the occurrence of complications and comorbidities, e.g. atherosclerotic disease.[12]

Semaglutide is a next-generation glucagon-like peptide-1 (GLP-1) receptor analogue with a high degree of homology to human GLP-1[13] and is approved in several countries under the trade name Ozempic® by Novo Nordisk.

Lower extremity arterial disease is the third leading cause of atherosclerotic cardiovascular morbidity, following coronary artery disease and stroke.[2] Manifestations of PAD include intermittent claudication (30-40 % of PAD patients) limiting functional capacity, fatigue, rest pain, impairment in quality-of-life, and ultimately, with progression of the disease, necrosis and amputations[3, 4], often below the knee.[5, 6] PAD is prevalent in up to 30% of patients with diabetes, and for each 1% increase in glycosylated haemoglobin (HbA_{1c}), the incidence of PAD increases 28%.[3, 7] Furthermore, higher rates of microvascular complications and major amputations are seen with increasing HbA_{1c}.[3, 7]

Intermittent claudication is the classical complaint in symptomatic PAD of the lower extremities and is associated with limited functional capacity reflected in impaired walking ability and health-related quality of life.

The combined findings in trials and known mechanisms of semaglutide suggest that the compound may be effective in the treatment of PAD with intermittent claudication in patients with T2D. Semaglutide might have both indirect (weight loss) and direct (vascular) effects in PAD with intermittent claudication. The potential weight loss induced by semaglutide 1 mg is expected to have a positive impact on functional capacity and health-related quality of life in itself. Other potential more direct mechanisms of semaglutide may include increased microvascular recruitment and improved blood flow by increasing nitrogenmonoxid formation, and decreasing vascular smooth cell proliferation, thereby also increasing functional capacity, and limiting calf pain.[12]

The trial will include patients with T2D and stable PAD with intermittent claudication, Fontaine stage IIa. This population is appropriate for a functional outcome intervention and will ensure that the primary objective of the trial can be met within a reasonable timeframe and sample size and without a substantial number of patients progressing to amputation or revascularisation during the course of the trial.

2.3 Benefit-risk assessment

Main benefits and risks are described in 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[14] or summary of product characteristics/prescribing information[6, 15] and any updates thereof.

2.3.1 Risk assessment

Table 2-1 Potential risks of clinical significance

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Trial treatment (semaglutide)		
Gastrointestinal disorders (GI)	Consistent with other GLP-1 RAs, the most frequent adverse events (AEs) with semaglutide are gastrointestinal (GI) (nausea, vomiting and diarrhoea). In general, these reactions are mild or moderate in severity, of short duration, and dose dependent. In patients treated with GLP-1 RAs, nausea, vomiting and diarrhoea may lead to significant dehydration. This should be considered when treating patients with impaired renal function as it may cause a deterioration of renal function.	Clinical trials have shown that a low starting dose and gradual dose escalation mitigates the risk of developing gastrointestinal symptoms. Patients with GI symptoms are recommended to drink plenty of fluids to avoid volume depletion.
Episodes of hypoglycaemia	There is a low risk of hypoglycaemic episodes when semaglutide is used as monotherapy. Patients treated with semaglutide in combination with sulfonylurea or insulin may have an increased risk of hypoglycaemia.	The risk of hypoglycaemia can be lowered by reducing the dose of sulfonylurea or insulin when initiating treatment with semaglutide.
Diabetic retinopathy complications	In a 2-year clinical trial with s.c. semaglutide (NN9535-3744, SUSTAIN 6) involving 3,297 patients with T2D, high cardiovascular (CV) risk, long duration of diabetes and poorly controlled blood glucose, event adjudication committee (EAC)-confirmed events of diabetic retinopathy complications occurred in more patients treated with s.c. semaglutide (3.0%) compared to placebo (1.8%). The absolute risk increase for diabetic retinopathy complications was larger among patients with a history of diabetic retinopathy at baseline. In the patients who did not have a documented history of diabetic retinopathy the number of events were similar for s.c. semaglutide and placebo. In the other clinical trials up to 1 year involving 4,807 patients with T2D, AEs related to diabetic retinopathy were reported in similar proportions of patients treated with	Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy, but other mechanisms cannot be excluded. Long-term glycaemic control decreases the risk of diabetic retinopathy. These patients should be monitored closely and treated according to clinical guidelines.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
	s.c. semaglutide (1.7%) and comparators (2.0%).	
Allergic reactions	As with all protein-based pharmaceuticals, treatment with semaglutide may evoke allergic reactions, including serious allergic reactions such as anaphylactic reactions and angioedema.	As a precaution, patients with known or suspected hypersensitivity to semaglutide or related products will not be enrolled in this trial. In addition, patients will be instructed to contact the site staff as soon as possible for further guidance if suspicion of a hypersensitivity reaction to the trial product occurs.
Acute pancreatitis	Acute pancreatitis has been observed with the use of GLP-1 RAs. In the completed phase 3 trials with semaglutide s.c. and oral semaglutide, both the event rate and the proportion of patients experiencing confirmed pancreatitis were similar with semaglutide and comparator. Few events were confirmed; the events occurred throughout the trial periods and the overall rates were similar to the rates reported in background populations.	Patients should be informed of the characteristic symptoms of acute pancreatitis and if pancreatitis is suspected, semaglutide should be discontinued. If confirmed, semaglutide should not be restarted.
Pancreatic cancer	Patients with T2D have an increased risk of certain types of cancer such as pancreatic cancer. There is currently no support from non-clinical studies, clinical trials or post-marketing data that GLP-1 based therapies increase the risk of pancreatic cancer. However, pancreatic cancer has been classified as a potential class risk for all marketed GLP-1 RAs by regulatory agencies. There is no indication of an increased relative risk in the semaglutide treatment groups vs. comparator, including placebo. The rates of EAC-confirmed events of pancreatic cancer were consistently low across trials.	Patients with presence or history of malignant neoplasm within 5 years prior to the day of screening will not be enrolled in this trial.
Medullary thyroid cancer	Thyroid C-cell tumours were seen in mouse and rat carcinogenicity studies after daily exposure to semaglutide for 2 years. The rodent C-cell tumours are caused by a non-genotoxic, specific GLP-1 receptor mediated mechanism to which rodents are particularly sensitive. No C-cell tumours were observed in monkeys after 52 weeks exposure up	To mitigate this risk, patients with a family or personal history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2 (MEN2) are excluded from clinical trials with semaglutide.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
	to 52-fold above the clinical plasma exposure at 14 mg/day. The GLP-1 receptor is not expressed in the normal human thyroid, and therefore the clinical relevance of the findings is considered to be low.	
Trial procedures		
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 enrollment in countries where the COVID-19 pandemic is evaluated to be sufficiently under control
Other		
Pregnancy and fertility	Studies in animals have shown reproductive toxicity. There are limited data from the use of semaglutide in pregnant women.	Semaglutide should not be used during pregnancy. Women of childbearing potential are required to use highly effective contraceptive methods when participating in this trial Table 10-3. If a patient wishes to become pregnant, or pregnancy occurs, semaglutide should be discontinued (please refer to protocol Section 8.3.5 for further guidance). The effect of semaglutide on fertility in humans is unknown.

2.3.2 Benefit assessment

In clinical trials semaglutide has provided superior long-term glycaemic control in T2D and clinically relevant reductions in body weight as compared to commonly used marketed products and placebo. A statistically and clinically significant reduction in cardio vascular (CV) events has been demonstrated for semaglutide s.c. (SUSTAIN 6).[7]

During the present trial it is expected that all patients, including those randomised to placebo will benefit from participation through frequent contact with the trial site, where diabetes, PAD and CV diseases are monitored and treated following careful medical examinations. To ensure all patients, including those receiving placebo, have an adequate glycaemic control and CV risk factor management, investigators are encouraged to optimise treatment with anti-diabetic medications as

well as medications affecting CV risk factors throughout the trial. All patients in this trial will receive trial product and auxiliary supplies free of charge.

2.3.3 Overall benefit-risk conclusion

Data from the clinical development programme for semaglutide has not revealed any safety issues that would outweigh the benefits. The trial population will consist of T2D patients with established PAD and therefore an elevated risk of CV events. Assessment of diabetes and CV risk factors and appropriate attention to the standard of care treatment will be ensured throughout the trial. It is therefore concluded that the potential benefits from the trial will outweigh the potential risks for the semaglutide as well as the placebo treated patients.

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 and any updates thereof.[14]

3 Objectives and endpoints

3.1 Primary, secondary and exploratory objectives and estimands

3.1.1 Primary objective and estimands

The primary objective is to demonstrate the effect of s.c. semaglutide 1 mg once-weekly on walking ability compared with placebo, both added to standard-of-care, in patients with T2D and PAD with intermittent claudication.

The primary estimand will be the median treatment ratio to baseline at week 52 in maximum walking distance for semaglutide 1 mg versus placebo, both as add-on to standard-of-care, in all randomised patients, regardless of change in background medication, rescue treatment (e.g., revascularisation or starting cilostazol/pentoxifylline), and adherence to randomised treatment. A composite strategy is used to handle intercurrent events of death and physical inability to perform the treadmill test, these intercurrent events are incorporated into the outcome by ascribing them an extreme unfavourable rank.

Two secondary estimands for the primary objective will be the median treatment ratio to baseline (i) at week 57 in maximum walking distance and (ii) at week 52 in pain free walking distance for semaglutide 1 mg versus placebo, both as add-on to standard-of-care, in all randomised patients, regardless of change in background medication and adherence to randomised treatment. The rationale for pain-free walking estimand is that the pain-free walking distance is of particular importance to the patient, who is reminded of their disease in the moment pain is experienced.

The primary and secondary estimands for the primary objective are listed in Table 3-1 below.

Table 3-1 Primary and secondary estimands for the primary objective

Objective	Estimand category	Estimand
Primary objective: To demonstrate the effect of s.c. semaglutide 1 mg once-weekly on walking ability compared with placebo, both added to standard-of-care, in patients with T2D and PAD with intermittent claudication	**Primary**	**Treatment condition:** Semaglutide 1 mg or placebo, regardless of adherence to randomised treatment and initiation of rescue treatment **Variable/Endpoint:** Ratio to baseline in maximum walking distance at week 52 **Population of interest** All randomised **Intercurrent event strategy** Events of death or physical inability to perform the treadmill test are incorporated into the outcome by ascribing them an extreme unfavourable rank (composite) Interventions and medications related to worsening of PAD (rescue treatment): "regardless of initiation of rescue treatment" (treatment policy) **Population-level summary measure** Median ratio of semaglutide 1 mg vs placebo
	Secondary 1[a]	**Treatment condition:** Semaglutide 1 mg or placebo, had all patients adhered to randomised treatment and not received rescue treatment **Variable/Endpoint:** Ratio to baseline in maximum walking distance at week 52 **Population of interest** All randomised **Intercurrent event strategy**

Objective	Estimand category	Estimand
		Discontinuation of trial product: "had the patient not discontinued treatment" (hypothetical) Interventions and medications related to worsening of PAD (rescue treatment): "had rescue treatment not been available" (hypothetical) Events of death or physical inability to perform the treadmill test: "had the patient not died or been unable to perform the test" (hypothetical) **Population-level summary measure** Geometric mean ratio of semaglutide 1 mg vs placebo
	Secondary 2	**Treatment condition:** Semaglutide 1 mg or placebo, regardless of adherence to randomised treatment and initiation of rescue treatment **Variable/Endpoint:** Ratio to baseline in maximum walking distance at week 57 **Population of interest** All randomised **Intercurrent event strategy** Events of death or physical inability to perform the treadmill test are incorporated into the outcome by ascribing them an extreme unfavourable rank (composite) Interventions and medications related to worsening of PAD (rescue treatment): "regardless of initiation of rescue treatment" (treatment policy) **Population-level summary measure** Median ratio of semaglutide 1 mg vs placebo
	Secondary 3	**Treatment condition:** Semaglutide 1 mg or placebo, had all patients adhered to randomised treatment and not received rescue treatment **Variable/Endpoint:** Ratio to baseline in maximum walking distance at week 57 **Population of interest** All randomised **Intercurrent event strategy** Discontinuation of trial product: "had the patient not discontinued treatment" (hypothetical) Interventions and medications related to worsening of PAD (rescue treatment): "had rescue treatment not been available" (hypothetical) Events of death or physical inability to perform the treadmill test: "had the patient not died or been unable to perform the test" (hypothetical) **Population-level summary measure** Geometric mean ratio of semaglutide 1 mg vs placebo
	Secondary 4	**Treatment condition:** Semaglutide 1 mg or placebo, regardless of adherence to randomised treatment and initiation of rescue treatment **Variable/Endpoint:** Ratio to baseline in pain free walking distance at week 52 **Population of interest** All randomised **Intercurrent event strategy** Events of death or physical inability to perform the treadmill test are incorporated int/o the outcome by ascribing them an extreme unfavourable rank (composite) Interventions and medications related to worsening of PAD (rescue treatment): "regardless of initiation of rescue treatment" (treatment policy) **Population-level summary measure** Median ratio of semaglutide 1 mg vs placebo
	Secondary 5[a]	**Treatment condition:** Semaglutide 1 mg or placebo, had all patients adhered to randomised treatment and not received rescue treatment **Variable/Endpoint:**

Objective	Estimand category	Estimand
		Ratio to baseline in pain free walking distance at week 52 **Population of interest** All randomised **Intercurrent event strategy** Discontinuation of trial product: "had the patient not discontinued treatment" (hypothetical) Interventions and medication related to worsening of PAD (rescue treatment): "had rescue treatment not been available" (hypothetical) Events of death or physical inability to perform the treadmill test: "had the patient not died or been unable to perform the test" (hypothetical) **Population-level summary measure** Geometric mean ratio of semaglutide 1 mg vs placebo

Notes: [a] Not related to the confirmatory hypotheses.

3.1.2 Secondary objectives and estimands

The secondary objectives are to compare the effect of s.c. semaglutide 1 mg once-weekly versus placebo, both added to standard-of-care in patients with T2D and PAD with intermittent claudication with regards to:

- Patient-reported symptoms and impacts of intermittent claudication (VascuQoL-6[5])
- Body weight
- HbA_{1c}
- Lipids
- Blood pressure
- Non-invasive blood pressure indices (ankle-brachial index (ABI), toe-brachial index (TBI))
- Safety
- Patient-reported walking ability (WIQ[16])
- Patient-reported health-related quality of life (SF-36[17])

The estimands related to the confirmatory secondary endpoint are described in Table 3-2.

Table 3-2 Estimands for the confirmatory secondary endpoint

Objective	Estimand category	Estimand
Secondary objective: To compare the effect of s.c. semaglutide 1 mg once-weekly versus placebo, both added to standard-of-care in patients with T2D and PAD with intermittent claudication with regards to disease specific patient reported outcome	**Secondary 1**	**Treatment condition:** Semaglutide 1 mg or placebo, regardless of adherence to randomised treatment and initiation of rescue treatment **Variable/Endpoint:** Change from baseline in VascuQoL-6 at week 52 **Population of interest** All randomised **Intercurrent event strategy** Events of death are incorporated into the outcome by ascribing them an extreme unfavourable rank (composite) Interventions and medications related to worsening of PAD (rescue treatment): "regardless of initiation of rescue treatment" (treatment policy) **Population-level summary measure** Median difference between semaglutide 1 mg vs placebo
	Secondary 2[a]	**Treatment condition:** Semaglutide 1 mg or placebo, had all patients adhered to randomised treatment and not received rescue treatment **Variable/Endpoint:**

Objective	Estimand category	Estimand
		Change from baseline in VascuQoL-6 at week 52 **Population of interest** All randomised **Intercurrent event strategy** Discontinuation of trial product: "had the patient not discontinued treatment" (hypothetical) Interventions and medication related to worsening of PAD (rescue treatment): "had rescue treatment not been available" (hypothetical) Events of death: "had the patient not died" (hypothetical) **Population-level summary measure** Mean difference between semaglutide 1 mg vs placebo

[a] Not related to the confirmatory hypotheses

3.1.3 Exploratory objective

The exploratory objective is to compare the effects of s.c. semaglutide 1 mg once-weekly versus placebo, both added to standard-of-care in patients with T2D and PAD with intermittent claudication with regards to

- Daily activity levels (wrist worn activity tracker)

3.2 Primary, secondary and exploratory endpoint

3.2.1 Primary endpoint

Endpoint title	Time frame	Unit
Change in maximum walking distance on a constant load treadmill test	From baseline (week 0) to end of treatment (week 52)	Ratio to baseline (no unit)

3.2.2 Secondary endpoints

3.2.2.1 Confirmatory secondary endpoint

Endpoint title	Time frame	Unit
Follow-up change in maximum walking distance on a constant load treadmill test	From baseline (week 0) to end of follow-up (week 57)	Ratio to baseline (no unit)
Change in Vascular Quality of Life Questionnaire-6 (VascuQoL-6) score	From baseline (week 0) to end of treatment (week 52)	Score (no unit, range: 6 to 24)
Change in pain-free walking distance on a constant load treadmill test	From baseline (week 0) to end of treatment (week 52)	Ratio to baseline (no unit)

3.2.2.2 Supportive secondary endpoints

Endpoint title	Time frame	Unit
Follow-up change in pain-free walking distance on a constant load treadmill test	From baseline (week 0) to end of follow-up (week 57)	Ratio to baseline (no unit)
Change in $_{HbA1c}$	From baseline (week 0) to end of treatment (week 52)	%-point
Change in body weight	From baseline (week 0) to end of treatment (week 52)	Kilogram
Change in systolic blood pressure	From baseline (week 0) to end of treatment (week 52)	mmHg
Change in total cholesterol	From baseline (week 0) to end of treatment (week 52)	Ratio to baseline (no unit)
Change in Low-density lipoprotein (LDL)-cholesterol	From baseline (week 0) to end of treatment (week 52)	Ratio to baseline (no unit)
Change in High density lipoprotein (HDL)-cholesterol	From baseline (week 0) to end of treatment (week 52)	Ratio to baseline (no unit)
Change in triglycerides	From baseline (week 0) to end of treatment (week 52)	Ratio to baseline (no unit)
Change in ABI	From screening (week -2) to end of treatment (week 52)	Ratio (no unit)
Change in TBI	From screening (week -2) to end of treatment (week 52)	Ratio (no unit)
Change in Walking Impairment Questionnaire (WIQ) global score	From baseline (week 0) to end of treatment (week 52)	%-point
Change in Short Form 36 (SF-36) physical functioning domain	From baseline (week 0) to end of treatment (week 52)	Score, no unit (range: 19.03 to 57.60)

3.2.3 Exploratory endpoint

Endpoint title	Time frame	Unit
Change in mean daily number of steps[a]	From baseline (week 0) to end of treatment (week 52)	Steps

Notes: [a]The activity tracker is only applied in a subset of patients (n=125). For the step count measured by activity tracker, measurements will be made at baseline (weeks -2 to -1) and at end of treatment (weeks 51 to 52).

4 Trial design

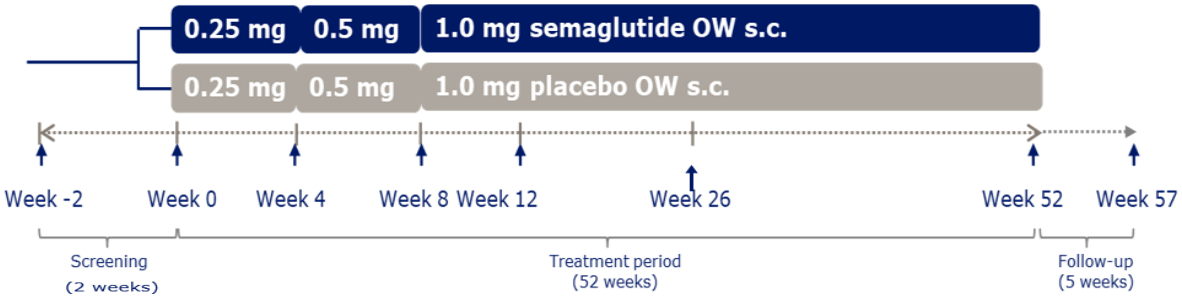
4.1 Overall design

This is a 52-week, randomised, double-blind, placebo-controlled trial comparing s.c. semaglutide 1 mg versus placebo both added to standard-of-care and administered once-weekly in patients with T2D and PAD with intermittent claudication. Screening period is approximately 2 weeks before randomisation, and patients will be randomised in a 1:1 ratio to receive either s.c. semaglutide 1 mg or placebo as add-on to standard-of-care. The treatment duration is 52 weeks including an eight weeks dose escalation period. The follow-up period is 5 weeks. A schematic illustration of the trial design is shown in Figure 4-1.

In addition to the main study, an evaluation of daily activity level will be performed in a subset of patients using a wrist-worn activity tracker to quantify the level of activity in selected time periods of the study.

An external event adjudication committee (EAC) will perform ongoing adjudication of predefined CV events and other selected AEs in an independent and blinded manner.

Figure 4-1 Schematic trial design with the estimated duration of the trial periods including screening and follow-up periods. Randomisation 1:1



Notes: Arrows indicate site visits. Visit window for screening is -7; +13 days. Note that in the subset of patients included in the activity tracker sub-study, the screening (visit 1) should be at least 2 weeks prior to randomisation (visit 2).
Abbreviations: OW = once-weekly; s.c. = subcutaneous.

4.2 Scientific rationale for trial design

To minimise bias, the trial is randomised, double-blinded and placebo-controlled. Blinded treatment with semaglutide 1 mg or placebo offers a robust method for assessment of the effects of semaglutide 1 mg. A broad spectrum of concomitant anti-hyperglycaemic medication, as well as treatments for co-morbidities and CV risk factors can be introduced or adjusted throughout the trial based on individual requirements and at investigator's discretion. This is in accordance with a pragmatic approach to compare two treatment regimens: one where semaglutide 1 mg is available and another where it is not.

To support the patient during the dose escalation period site visits will occur more frequently during the first months of the trial. To maximise retention and compliance, and to optimise treatment, e.g. regarding glycaemic control, the patient is in contact with the investigator at regular visits

throughout the trial. A multinational design has been chosen to ensure a sufficient screening pool of patients and to reflect the anticipated patient population.

At screening all patients must demonstrate a pain-free walking distance (initial claudication distance) of more than 200 meters on a flat treadmill with a fixed speed (3.2 km/h, 2 mph) to confirm their Fontaine IIa stage. To make the trial population more homogeneous, an upper limit in maximum walking distance of 600 meters on a constant-load treadmill test with fixed speed (3.2 km/h, 2 mph) and fixed inclination (12%) must be demonstrated at screening in accordance with guidelines.[15-17] At baseline, a constant-load treadmill test with fixed speed (3.2 km/h, 2 mph) and fixed inclination (12%) and assessment of Patient Reported Outcomes (PROs) will be performed.

A treatment duration of 52 weeks was chosen to allow sufficient time to observe a potential treatment effect in relation to walking ability considering the hypothesised mechanisms of actions of semaglutide-induced weight loss and anti-atherosclerotic effects.

The trial will include a population of patients with T2D and PAD Fontaine stage IIa which is an appropriate risk target population for a functional improvement intervention and will ensure that the primary objective of the trial can be evaluated within a reasonable timeframe and sample size.

4.2.1 Patient input into design

There have been no patient involvement or suggestions to this trial.

4.3 Justification for dose

The target maintenance dose of 1 mg per week has been shown to have a positive benefit risk profile in T2D and is approved in a number of countries globally. Furthermore, a reduction in MACE has been observed with this dose in the SUSTAIN 6 trial.[7] The maximum approved dose was chosen to optimise the potential for effects in relation to walking ability.

4.4 Treatment of patients

4.4.1 Standard-of-care

The effect of s.c. semaglutide 1 mg will be assessed as an add-on to standard-of-care. This is in accordance with a pragmatic approach to compare two treatment regimens: one where semaglutide 1 mg is available and another where it is not.

To ensure that all patients, including those receiving placebo, have an adequate glycaemic control and management of their PAD, investigators are encouraged to optimise treatment throughout the trial in accordance with treatment guidelines including guidelines from the European Society of Cardiology (ESC)[18] and the American Heart association (AHA).[19] Anti-diabetic medications and medications affecting relevant cardiovascular risk factors are to be added and/or background treatment to be optimised. Initiating treatment with any other GLP-1 RAs is not permitted during the entire trial.

Counselling of lifestyle modifications including recommendations on exercise and smoking cessation are to be provided as per guidelines.

Recommendations for standard-of-care will be provided in guidance documents.

4.5 End of trial definition

A patient is considered to have completed the trial if he/she has completed all phases of the trial including the last follow-up visit (week 57). If a randomised patient has died during trial, `date of trial completion` is the date of death.

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

Number of patients to be investigated

Planned number of patients to be screened meaning the number of patients providing informed consent: 1,143 (screening failure rate of 30 % is anticipated).

Planned number of patients to be randomised: 800.

Expected number of patients to complete the trial on or off trial product: 736 (withdrawal rate of 8% is anticipated).

Expected number of patients to complete the activity tracker evaluation: 115 (125 planned for randomisation, withdrawal rate of 8 % is anticipated).

5.1 Inclusion criteria

Patients 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.
   For Japan and Taiwan: Male or female, age above or equal to 20 years at the time of signing informed consent, Appendix 8, Section 10.8.
3. Diagnosed with type 2 diabetes mellitus ≥ 180 days prior to the day of screening.
4. Symptomatic PAD with intermittent claudication corresponding to Fontaine stage IIa (Rutherford classification grade I, category 1 and 2) meeting all of the following:
   a) Stable symptoms of PAD with intermittent claudication in Fontaine stage IIa (able to walk without stopping > 200 m/656 feet/2 blocks) for ≥ 90 days prior to the day of screening based on patient interview.
   b) Screening flat treadmill test (3.2 km/h (2 mph)): Pain-free walking distance of ≥ 200 meters/656 feet.
   c) Screening constant load treadmill test with fixed inclination of 12% and a fixed speed of 3.2 km/h (2 mph): Walking distance ≤ 600 meters/1968 feet.
   d) Ankle-brachial-index (ABI) ≤ 0.90 or toe-brachial index (TBI) ≤ 0.70 (the leg with lowest index is chosen in case of bilateral disease).
5. For patients receiving PAD standard of care non-drug (e.g. exercise) or drug therapy (e.g. statin, cilostazol or pentoxifylline), treatment must have been stable for at least 90 days prior to the day of screening, as judged by investigator.
6. HbA_{1c} ≤10% (≤86 mmol/mol) based on latest available measurements prior to randomisation (visit 2). Laboratory results for inclusion can be based on medical records (no more than 90 days old at screening) *or* central laboratory measurement obtained at the screening visit.[a]

[a] If based on central laboratory, both National Glycohemoglobin Standardization Program (NGSP) and International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) need to be within limit.

5.2 Exclusion criteria

All exclusion criteria are based on the patient´s medical records, except for exclusion criterion #3, which is based on pregnancy test. Furthermore, exclusion criterion #12 (renal impairment) may be based on assessment of eGFR by the central laboratory.

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

1. Known or suspected hypersensitivity to trial product(s) or related products.
2. Previous participation in this trial. Participation is defined as randomisation.
3. 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 (see Appendix 4, Section 10.4 for further guidance). For country specific requirements see Appendix 8, Section 10.8.
4. Participation in any clinical trial of an approved or non-approved investigational medicinal product within 90 days before screening*.
5. Current or previous treatment with any GLP-1 receptor agonist within 90 days prior to the day of screening.
6. Walking ability limited by conditions other than PAD (e.g. aortic aneurism, dysregulated arrhythmia or hypertension, angina pectoris, heart failure, chronic obstructive or restrictive pulmonary disease, Parkinson's disease, severe peripheral neuropathy, amputations, wheel chair or walker dependency, osteoarthritis, morbid obesity, severe varicose veins, etc.).
   India: For country-specific requirements, please refer to Appendix 8 (Section 10.8)
7. Planned orthopaedic surgery in the legs, or other major surgery known on the day of screening (surgery affecting walking ability).
8. Vascular revascularisation procedure of any kind 180 days prior to the day of screening.
9. Planned arterial revascularisation known on the day of screening.
10. Myocardial infarction, stroke, hospitalisation for unstable angina pectoris or transient ischemic attack (TIA) within 180 days prior to the day of screening.
11. Heart failure presently classified as being in New York Heart Association (NYHA) class III−IV.
    India: For country-specific requirements, please refer to Appendix 8 (Section 10.8)
12. Renal impairment based on latest available measurements/evaluation prior to randomisation (visit 2). Renal impairment can be diagnosed based on an estimated Glomerular Filtration Rate (eGFR) value of eGFR< 30ml/min/1.73 m^2 (measured within last six months) as defined by KDIGO 2012[2] *or* chronic or intermittent haemodialysis or peritoneal dialysis.
13. Presence or history of malignant neoplasm within 5 years prior to the day of screening. Basal and squamous cell skin cancer and any carcinoma *in-situ* are allowed.
14. Personal or first-degree relative(s) history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma.
15. Uncontrolled and potentially unstable diabetic retinopathy or maculopathy.[b] Verified by a fundus examination performed within the past 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.
16. Any disorder, which in the investigator's opinion might jeopardise patient´s safety or compliance with the protocol.

[b] "Uncontrolled and potentially unstable" indicate retinopathy that has recently progressed to a level that requires intervention or is approaching intervention but has yet to be brought under control. In this case the patient is not eligible for participation in the trial.

17. For Hungary only: Presence or history of pancreatitis (acute or chronic).

*Simultaneous participation in a trial with the primary objective of evaluating an approved or non-approved investigational medicinal product for prevention or treatment of COVID-19 disease or COVID-19 postinfectious conditions is allowed if the last dose of the investigational medicinal product has been received more than 30 days before screening. For Japan and China: Co-participation in COVID-19 trials are not allowed, see country/region-specific requirements (Appendix 8, Section 10.8).

Rationale for trial population

The trial will include patients who are representative of the intended target population of patients with T2D and PAD with intermittent claudication. Thus, it is intended to enrol a population of adult patients with T2D and PAD in Fontaine stage IIa, corresponding to Rutherford classification grade 1, categories 1 and 2, as these are considered an appropriate target population for a pharmacological treatment to improve walking distance. Since there is no upper limit in the maximum walking distance for a population with PAD and intermittent claudication in Fontaine stage IIa, a maximum walking distance less than 600 meters on a constant-load treadmill test with a fixed speed (3.2 km/h; 2 mph) and fixed inclination (12%), has been set in this trial to make the trial population more homogeneous[20] and to ensure a certain degree of disease severity, making it likely that an improvement can be shown over a 52 week period of time.

Requirements with regards to meeting either the ABI or TBI threshold are in place to ensure that walking distance is limited due to PAD instead of other conditions. ABI and TBI should be measured and documented for both legs throughout the trial.

5.3 Lifestyle considerations

5.3.1 Physical activity

As exercise is part of standard of care in PAD, patients will be encouraged to exercise according to guidelines. No assistance with exercise nor restrictions are applied.

5.4 Screen failures

Screen failures are defined as patients 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 patients 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).

If patients withdraw their consent prior to randomisation or do not return for randomisation a screen failure session must be made in the interactive web response system (IWRS). The reason for failure will in all cases be captured in the electronic case report forms (eCRF).

Rescreening

Due to the long recruitment period, rescreening is allowed once for the following eligibility criteria:

- inclusion criteria #1-#6, except 4b), #4c) and #4d).
- exclusion criteria #3, #4, #5, #8, #10, #15 and #16.

Reasons for rescreening must be documented. Rescreening should only be performed if the investigator considers it likely the subject would be eligible based on the new screening. Previously randomised subjects cannot be rescreened.

Note that in case of rescreening, screening results for inclusion criteria #4b) and #4c) (treadmill test) and criterion #4d) (ABI/TBI) and can be reused, if it is within 90 days from last screening. Hence, if rescreening is performed more than 90 days after initial screening visit, the screening treadmill tests are to be performed again and ABI/TBI to be re-assessed, even though the test fulfilled inclusion criteria #4 at the initial screening visit.

Subjects who are rescreened are required to sign a new informed consent form and provided with a new subject ID. In case of rescreening, a new screening session must be made in the IWRS.

In case of technical issues (e.g. haemolysed, lost samples or broken equipment), re-sampling/re-assessment is allowed for the affected parameters/assessments and is not considered rescreening.

5.5 Run-in criteria and/or randomisation criteria and/or dosing day criteria

Not applicable.

6 Treatments

6.1 Preparation/handling/storage/accountability

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

Information on in-use conditions and in-use time will be available on the trial product label and in the trial materials manual (TMM).

Each trial site will be supplied with sufficient trial products for the trial on an on-going basis controlled by the IWRS. Trial product will be distributed to the trial sites according to screening and randomisation.

The following requirements must be followed:

- 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 patient 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 patient in what to return at next visit.
- Drug accountability should be performed in the IWRS by registering pen-injectors as returned either as used/partly used, unused or as lost.
- Destruction of trial products can be performed on an ongoing basis and will be done according to local procedures after accountability is finalised by the site and reconciled by the monitor.
- All returned, un-used, expired or damaged trial products (for technical complaint samples, see Appendix 5, Section 10.5) must be stored separately from non-allocated trial products. No temperature monitoring is required.
- Non-allocated trial products including expired or damaged products must be accounted as unused, at the latest at closure of the site.

6.2 Treatments administered

The investigational medicinal products (trial products) provided by Novo Nordisk are listed in Table 6-1. The trial products are packed blinded and are visually identical. For dose escalation, please refer to overall design, Section 4.1.

The investigator must document that directions for use are given to the patient verbally and in writing as a Direction for Use (DFU) document, at the first dispensing visit.

Investigational medicinal products (IMP)

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

Trial product name:	Semaglutide, 1.34 mg/mL (IMP, test product)	Semaglutide placebo (IMP, reference therapy)
Dosage form	Solution for injection	Solution for injection
Route of administration	Subcutaneous	Subcutaneous
Dosing instructions	Once-weekly	Once-weekly
Packaging	1.5 mL pre-filled PDS290 pen-injector	1.5 mL pre-filled PDS290 pen-injector

All baseline assessments must be done prior to administration of the first dose of trial product.

Patients will be instructed to inject the trial product s.c. once-weekly at the same day of the week (to the extent possible) throughout the trial. Injections may be administered in the abdomen, thigh or upper arm, at any time of day irrespective of meals.

Dose escalation intervals are applied to lower the risk of gastrointestinal adverse events (AEs). Dose escalation of semaglutide/placebo will take place during the first 8 weeks after randomisation (Section 4.2). Patients should remain on the 1 mg dose level throughout the maintenance period; however, to prevent permanent premature 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 adverse events or due to other circumstances. Dose adjustments are at the discretion of the investigator (please refer to Section 6.6). If a dose is missed, the missed dose should be taken as soon as possible within 5 days after the missed dose. If more than 5 days have passed, the missed dose should be skipped, and the next dose should be administered on the regularly scheduled day.

Auxiliary supplies provided by Novo Nordisk:

- needles for the PDS290 pen-injector (maximum needle length 6 mm)
- directions for use for the prefilled PDS290 pen-injector

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

Shipment of trial product to patient'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 patient's home by courier service.

The process for sending trial product from the trial site or pharmacy to a patient's home is described in the "Trial site/pharmacy instruction for shipment of trial product to patients' homes" document. This 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 patient. 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 patients who will be involved in shipment of trial product to the patient's home will be adequately trained in this process.

6.2.1 Medical devices

Non-investigational medical device: PDS290 pen-injector and activity tracker.

Training in the PDS290 pen-injector

The patients must be trained according to the directions for use in handling the pen-injector when dispensed the first time and training must be repeated during the trial as needed. The investigator must document that directions for use are given verbally and in writing the first time trial product is dispensed and again during the trial as needed. Training is the responsibility of the investigator or delegate.

Activity tracker

Please refer to Section 8.1.3.

6.2.1.1 Non-investigational medical devices

Non-investigational medical devices are listed in Section 6.1 as auxiliary supplies.

6.3 Measures to minimise bias: Randomisation and blinding

This trial is double-blind. All patients 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, Section 1.2.

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

The trial products containing active drug and placebo are visually identical and will be packed in a manner that maintains blinding.

The IWRS is used for blind-breaking. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a patients' treatment is warranted. Patient 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 patients' treatment unless this could delay emergency treatment of the patient. If a patient'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 IWRS is not accessible at the time of blind break, the IWRS helpdesk should be contacted. Contact details are listed in

Attachment I. If the blind has been broken by an investigator, the patient may continue treatment with trial product if judged as safe by the investigator.

6.4 Treatment compliance

Drug treatment compliance

Throughout the trial, the investigator will remind the patients to follow the trial procedures and requirements to encourage patient compliance.

When patients self-administer trial product 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, apart from occasionally one or more missed doses, 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; counting returned trial product, visual inspection of pens
- Questioning of patients

Treatment start and stop dates will be recorded in the case report form (CRF).

6.5 Concomitant medication

Only medication other than the trial product that the patient is receiving at the time of randomisation or receives during the trial for the following reasons must be recorded in the eCRF:

- To treat diabetes or PAD
- To treat or prevent CV diseases (for example anti-hypertensives, lipid-lowering agents, anticoagulants, aspirin and other antiplatelet agents)
- In relation to an SAE, if relevant
- Administered in relation to a clinical trial for COVID-19 prevention or treatment
- Approved COVID-19 vaccine

The information collected for each concomitant medication includes trade name or generic name, indication; start date and stop date or continuation, and related AE number when applicable.

Initiating treatment with any other GLP-1 receptor agonists are not permitted during the entire trial. Other changes to background medications can take place during the trial. Risk of hypoglycaemic episodes is described in Section 2.3.1.

Medication in the relevant groups mentioned above that the patient is receiving at the time of the first visit or receives during the trial must be recorded along with:

- Trade name or generic name
- Indication
- Dates of administration including start and stop dates

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

6.5.1 Rescue therapy

The following rescue medication or rescue therapy (revascularisation) may be applied and should be reported on the concomitant medication form or on a specific event form, respectively.

- Medication: Starting on cilostazol or increasing dose of cilostazol with 20 % or more. Starting on pentoxifylline or increasing dose of pentoxifylline with 20 % or more.
- Revascularisation: Peripheral procedures including both endovascular / percutaneous procedures and open surgical revascularisation including hybrid procedures (e.g. combination of endovascular and open surgical revascularisation).

Patients that are started on rescue medication should continue to follow the protocol-specified visit schedule and stay on randomised treatment unless the investigator judges that it jeopardises safety. Rescue medications should be documented in medical records and reported in the case report form (CRF) as mentioned above.

6.6 Dose modification

Patients should remain on the 1 mg dose level throughout the maintenance period; however, to prevent permanent premature 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 adverse events or due to other circumstances. Dose adjustments are at the discretion of the investigator and modifications should be reported in the eCRF. Patients will be followed for the complete duration of the trial and extensive efforts will be made to collect outcome data for all randomised patients.

6.7 Treatment after end of trial

When discontinuing trial product at the end of the treatment period, the patient should be transferred to a suitable marketed product at the discretion of the investigator. GLP-1 RAs are not allowed to be prescribed during the 5-week follow-up period.

7 Discontinuation of trial treatment and patient discontinuation/withdrawal

Treatment of a patient 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 patients attend and complete all scheduled visit procedures, to collect the required data for the analysis of the primary (and confirmatory secondary) endpoint. Only patients who withdraw consent will be considered as withdrawn from the trial. Patients must be educated about the continued scientific importance of their data, even if they discontinue trial product.

7.1 Discontinuation of trial treatment

Discontinuation of treatment can be decided by both the investigator and the patient. The patient may be discontinued from trial product at any time during the trial at the discretion of the investigator for safety, compliance or administrative reasons. Treatment with trial product can be resumed if later deemed safe.

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

The trial product must be discontinued, if any of the following applies for the patient:

1. Pregnancy
2. Intention of becoming pregnant
3. Simultaneous use of an approved or non-approved investigational medicinal product in another clinical trial*
4. If acute pancreatitis is suspected, trial product should be discontinued; if confirmed, trial product should not be restarted
5. Other safety concerns, at the discretion of the investigator

*Simultaneous participation in a trial with the primary objective of evaluating an approved or non-approved investigational medicinal product for prevention or treatment of COVID-19 disease or COVID-19 postinfectious conditions is allowed at the investigator discretion without discontinuing trial product. Note: Co-participation in COVID-19 trials are not allowed in China and Japan, see country/region-specific requirements in Appendix 8 (Section 10.8).

Ad 1 and 2: If a patient intends to become pregnant, trial product must be discontinued at least 5 weeks before the contraceptive method is stopped. If a patient becomes pregnant unintentionally, trial product must be discontinued immediately during pregnancy, and during breast feeding. The patient will continue the other trial procedures or will be followed-up via phone contacts.

Ad 3: With the exception of an approved or non-approved investigational product for prevention or treatment of COVID-19, patients should be advised not to participate in other clinical trials, while participating in this trial. If done, treatment with trial product should be discontinued. If participation in the other trial is stopped, treatment can be resumed if there are no safety concerns at the discretion of the investigator after discussing with a Novo Nordisk medical expert.

If a patient has discontinued treatment with trial product prematurely, the site should perform a premature EOT visit (V8A) as soon as possible after the decision to permanently discontinue treatment is taken, followed by an EOT follow-up visit (V9A) 5 weeks after V8A. See the flowchart, Section 1.2 for data to be collected at the time of treatment discontinuation (V8A and V9A) and for any further evaluations that need to be completed. Patients should continue with the originally scheduled site visits (including V8 and V9) after completing the Premature EOT follow-up visit (V9A).

Once dosing has been initiated, the investigator should evaluate the safety profile at an individual patient level on an ongoing basis, based on all available information. If a safety concern emerges, trial product discontinuation should be considered at the investigator´s discretion.

Efforts must be made to have patients who prematurely discontinue trial product treatment to attend and complete all scheduled visit procedures after completing the premature EOT visits (including visits 8 and 9), to collect the required data for the analysis of the primary (and confirmatory secondary) endpoint. Only patients who withdraw consent will be considered as withdrawn from the trial. Patients must be educated about the continued scientific importance of their data, even if they discontinue trial product.

If a patient is unwilling to attend any of the scheduled clinic visits, efforts should be made to have the remaining visits converted to phone contacts. However, as a minimum, these patients must be asked to attend visit 8 and 9, and information about the attempts to follow-up with the patient must be documented in the medical records.

To assess the potential disease modifying effect of semaglutide 1 mg, testing for key endpoints will be performed at the follow-up visit (week 57), 5 weeks after end-of-treatment. The 5-week follow up is chosen due to the half-life of semaglutide and is considered appropriate for end of systemic exposure.

When initiating new anti-diabetic treatment after the discontinuation of trial product, the half-life of semaglutide of approximately one week should be kept in mind.

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

7.1.1 Temporary discontinuation of trial treatment

Temporary treatment discontinuation is allowed at the discretion of the investigator and the reason for discontinuation must be recorded in the eCRF. Treatment with trial product should be resumed if the circumstances later allow (Section 6.2). Similarly, patients who discontinue trial product on their own initiative should be encouraged to resume the treatment (Section 6.2). At both instances dose escalation may be necessary (Section 6.2). Date and last trial product dose should be recorded in the eCRF. A treatment status session in the IWRS should be performed when a patient is on treatment pause or resumes treatment.

7.2 Patient discontinuation/withdrawal from the trial

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

If a patient withdraws consent, the investigator must ask the patient if he/she is willing, as soon as possible, to have assessment performed according to visit 8A, followed by an EOT follow-up visit (V9A) 5 weeks after V8A. See the flowchart (Section 1.2) for data to be collected.

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

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

If a patient 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 patient 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 patient's rights. Where the reasons are obtained, the primary reason for withdrawal must be specified in the end of trial form in the CRF.

For patients who are withdrawn, when the trial comes to an end, the investigator must scrutinise publicly available registries to determine vital status, unless prohibited by local regulations or specifically prohibited by the patient upon withdrawal of consent. Please also refer to Section 4.5 for further details.

7.2.1 Replacement of patients

Patients who discontinue trial product or withdraw from trial will not be replaced.

7.3 Lost to follow-up

A patient 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 patient fails to return to the site for a required visit:

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

- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the trial with a primary reason of `lost to follow-up'.

8 Trial assessments and procedures

- The following Sections describe the assessments and procedures, while their timing is summarised in the flowchart, Section 1.2.
- Informed consent must be obtained before any trial related activity, Section 10.1.3.
- All screening evaluations must be completed and reviewed to confirm that potential patients meet all inclusion criteria and none of the exclusion criteria.
- The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reason for screen failure, as applicable.
- Procedures conducted as part of the patient's routine clinical management (e.g. eye examination), and obtained before signing of the informed consent, may be utilised for screening or baseline purposes, provided the procedures meet the protocol-specified criteria.
- At screening, patients 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.
- Each patient should be asked to provide contact information for persons (preferably at least 3), e.g. relative, primary care provider or other, whom the investigator can contact in case of issues when trying to contact the patient during the trial. The sites are encouraged to maintain as current details as possible throughout the course of the trial. For country-specific requirements see Appendix 8, Section 10.8.
- The investigator should, if the patient agrees, inform the patient’s primary physician about the patient’s participation in the trial.
- Adherence to the trial design requirements, including those specified in the flowchart, is essential and required for trial conduct.
- It is the responsibility of the investigator to schedule visits including laboratory assessments and contacts as per protocol, see flowchart, Section 1.2, and to ensure they take place. For drug treatment compliance see Section 6.4.
- One phone contact is scheduled in the trial, see Section 1.2. During this, the investigator should remind the trial patient to use the activity tracker, if applicable.
- Review of completed PRO questionnaires and laboratory reports etc. must be documented either on the documents or in the patient's source documents. If clarification of entries or discrepancies in the PRO questionnaires are needed, the patient must be questioned, and a conclusion made in the patient's source documents. Care must be taken not to bias the patient.
- Investigator must ensure that data from the PRO questionnaires are transcribed to the eCRF.
- Future biomarker testing is planned and will not be included in the clinical trial report (CTR). Please refer to Section 8.8.
- 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 Treadmill assessments

Treadmill assessments should be performed only on treadmills meant for medical use after correct calibration. Relevant medical personnel should be readily available to take care of the patients. A study manual will be made available for all sites describing the treadmill assessments in detail.

The constant-load treadmill test is a standardised method for the functional assessment of patients with PAD. The constant-load test is performed at a single work rate of 2 mph (3.2 km/h) at an inclination of 12%.[21, 22] The results of a constant-load test are expressed in units of distance walked. The test requires a treadmill capable of setting the speed and inclination at the required values (speed 3.2 km/h, inclination of 12%). The technician instructing and supervising the treadmill test should preferably be unaware of HbA_{1c}, AEs, side effects, and laboratory parameters that could indicate the patient´s randomisation (semaglutide 1 mg or placebo).

The patient should be instructed before performing the treadmill test to ensure that he/she understands that there will be two important time points during the same test (see the following Sections). Patients should be encouraged to continue for as long as possible disregarding the pain. Treadmill testing is to be discontinued on the patient´s request or in the absence of claudication after a total walking duration of 20 minutes. Firstly, the patient should indicate when pain starts in either leg (pain-free walking distance) but continue on the treadmill without stopping. Hereafter, the patient should continue despite the pain until it is impossible for him to walk more (max walking distance).

The baseline treadmill test is to be performed in the beginning of the baseline visit and in the end of the baseline visit to evaluate the variability within a single patient. As a minimum the two assessments should be one hour apart. This duplicate assessment is only needed at baseline.

The treadmill assessments at visits 6, 8 and 9 can be performed at a later day than the other assessments and procedures at the given visit, provided that all assessments are completed within the visit window (visit windows are calculated from the randomisation date) (Section 1.2).

8.1.1.1 Pain-free walking distance-inclined treadmill

The patient is instructed to indicate (verbally or with a pre-defined sign) when pain starts in either leg and to continue on the treadmill without stopping at this stage. The distance walked is noted as the pain-free walking distance. It is important that the patient is carefully instructed that he/she should continue walking at this time point. The patient should also report if experiencing pain in non-index leg and the time should be noted. This measurement is performed at baseline, week 26, EOT visit and Follow-up visit, please refer to flowchart, Section 1.2.

8.1.1.2 Maximum walking distance-inclined treadmill

The patient continues on the treadmill after indicating onset of pain and should continue as long as possible until pain limits further activity. This distance is noted as the maximum walking distance. This measurement is performed both at screening, baseline, week 26, EOT visit, and Follow-up visit, please refer to flowchart, Section 1.2.

8.1.1.3 Pain-free walking distance-flat treadmill

At the screening visit, proper classification of Fontaine IIa claudication has to be confirmed on a flat treadmill mimicking a normal walking situation. If the patient is able to walk at least 200 m (656 feet)on a flat treadmill with a fixed speed of 3.2 km/h (2 mph) before onset of pain in either leg, the patient is potentially eligible. This test is only performed at screening and not at any other timepoint in the trial, please refer to flowchart, Section 1.2.

8.1.2 Patient Reported Outcome (PRO) questionnaires

PRO questionnaires will be assessed at baseline (V2), at 6 months visit (V6) and at end-of-treatment (Visit 8/8A). PRO questionnaires are to be performed prior to other visit-related activities. Patients should be given the opportunity to complete the questionnaires by themselves without interruption. Each of the questionnaires takes approximately 5-10 minutes to complete.

In this functional outcome trial, two disease-specific PRO questionnaires have been chosen for evaluation of the patient´s experience of symptoms and function:

- Vascular Quality of Life 6 items (VascuQoL-6)
- Walking Impairment Questionnaire (WIQ)

One generic PRO questionnaire has been selected to evaluate the patient´s health-related quality of life:

- Short Form 36 (SF-36)

Furthermore, the Patient Global Impression of Change /-Severity (PGI-C / PGI-S) will be correlated to the primary and secondary confirmatory endpoints to assess a clinical meaningful change.

The daily level of activity is furthermore investigated using activity tracker in a sub-population.

Questionnaires

A more comprehensive overall PAD-related Quality of Life and functional measurement is performed using the VascuQoL-6 questionnaire,[23] which with 6 questions covers social, emotional, functional as well as pain- and symptom-related aspects of the patient´s overall quality of life. This questionnaire was developed from the original 25 item questionnaire, which shows good evidence of construct validity and responsiveness and some evidence of content validity and internal consistency.[24]

The patient-based ambulatory walking ability will be measured using the (WIQ) for PAD patients[16] which assesses the ability to walk at various speeds and distances and the ability to climb stairs. Evidence for internal consistency, test re-test reliability and responsiveness exist.[25]

Overall health-related quality of life is evaluated using the Short Form 36 v2.0 acute (SF-36). SF-36 is a generic measure of health status that yields 2 summary scores for physical health and mental health and 8 domain scores.[17]

To establish what difference in walking distance that comprises a meaningful change for the patient, two questions have been developed in the Patient Global Impression of Severity (PGI-S) and Patient Global Impression of Change (PGI-C) system. A change from one response category to the next (1-

step change) in the PGI-S (4-point scale) comprises a threshold for clinically meaningful change and this will be used as anchor for evaluation of a meaningful within-patient change from baseline in walking distance.

8.1.3 Physical activity tracker, patient training, dispensing and collection

To evaluate the ambulatory walking ability in the daily life of the patient, an activity tracker is applied in a subset of 125 patients. Through a wrist-worn activity tracker, the daily activity level will be measured in a 2-week period both in the beginning of the trial, and in the end. This is a supplement to the treadmill testing and questionnaires, reflecting the potential influence on the real-life activity level of the patients.

Physical activity data will be collected using a small wrist worn physical activity tracker designed for documenting physical activity. Data will be collected and transferred to Novo Nordisk from the physical activity tracker without site or patient interaction by a small data hub placed at the patient's home. Data can also be transferred manually at study site as a back-up solution in case of hub transfer failure. The patient and the study site will be blinded to the physical activity data which are collected. During the course of the study, the study site will have access to data on patients wearing compliance and it is recommended that the study site encourages the patient e.g., via phone and/or email to wear the physical activity tracker, if not done so.

The site staff must instruct the patient according to following recommendations:

- The physical activity tracker should be worn on the non-dominant arm
- The physical activity tracker should be firmly attached to the wrist and the tracker should not be able to slide up and down when the arm moves
- The patient should wear the physical activity tracker as much as possible, preferably 24 hours per day during the two 2-week periods.
- The measurements from the physical activity tracker are summarised into daily measures representing different aspects of physical activity. The study site will have access to data on the patient’s wearing compliance.

The physical activity tracker should be returned to the site when the site has un-assigned the physical activity tracker, either at the next clinic visit or as agreed with the site.

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 (see Section 1.2).

8.1.5 Vital signs

8.1.5.1 Pulse and blood pressure

Pulse rate as well as diastolic and systolic blood pressure will be assessed. When done in connection with a treadmill test, pulse and blood pressure should be assessed before the treadmill test.

Blood pressure and pulse rate measurements should be preceded by at least 5 minutes of rest for the patient in a quiet setting without distractions (e.g., no use of television, cell phones). First time

blood pressure is assessed (V1) it should be performed at both arms. The arm with the highest blood measurement should be used for all future measurements. Blood pressure and pulse rate measurements will be assessed sitting with a completely automated device. Manual techniques must be used only if an automated device is not available.

Blood pressure and pulse rate to be measured as listed in flowchart, Section 1.2. Blood pressure will consist of 2 systolic and 2 diastolic blood pressure measurements with intervals of at least 1-2 minutes. An additional third blood pressure measurement must be performed if the first two readings on systolic or diastolic blood pressure differ by >10 mmHg. The last 2 systolic and last 2 diastolic blood pressure measurements should be recorded in the eCRF. The eCRF will calculate the mean of the last 2 measurements.

Pulse rate will be measured in connection to the blood pressure measurements. The pulse rate is to be recorded as the last 2 measurements. The eCRF will calculate the mean of the last 2 measurements.

8.1.5.2 Toe-brachial index (TBI) and Ankle-brachial index (ABI)

Measurements of the ankle-brachial index (ABI) and toe-brachial index (TBI) are the most common methods for assessing PAD. The measurements should be performed in the supine patient after at least 5 minutes of resting. The measurements can be performed by an automatic calibrated Sphygmomanometer or by Doppler method. If both methods are available, the Doppler method is preferred. The same method should be used throughout the trial for the individual patient. The brachial blood pressure is measured simultaneously with each toe or ankle pressure. Note that both ABI and TBI are calculated averages of two measurements in each location, hence, at each scheduled assessment two measurements must be performed at each location (i.e. both right and left ankle, arm and toe).

The ABI is calculated as a ratio of the higher ankle systolic pressure to the higher systolic pressure measured in both arms. The ankle pressure is preferably measured using a Doppler probe to obtain systolic pressures in the following locations: posterior tibial and anterior tibial artery systolic pressures. The higher of the tibial pressure is chosen for the numerator for each leg, and the higher of the left and right brachial systolic pressure is chosen for the denominator.[26]

The ankle pressure is measured using a blood pressure cuff chosen according to the limb size. The width of the cuff should contour at least 40% of the limb circumference. If a Doppler device is used, an 8-10 MHz Doppler probe should be used (standard vascular probe).

The TBI is calculated as a ratio of the toe systolic pressure to the higher systolic pressure measured in both arms.[27, 28] If toe pressure is measured by laser Doppler flowmetry (LDF) this should be with linear deflation pressure and a cuff that is at least 1.2 times wider than the toe (usually a 2.5 – 3.0 cm cuff for the great toe). Equipment for measurement of toe pressure should be standard equipment in all vascular surgical departments for TBI measurement. The Doppler probe is applied to the plantar surface of the distal portion of cleaned great toe (or in absence of it on the second toe), and the occlusive cuff is placed around the proximal portion of the toe.

The ABI and TBI should be measured and noted for both legs and toes throughout the trial.

8.1.6 HbA_{1C}

HbA_{1c} will be measured in a blood sample and be analysed at central lab according to the flowchart, Section 1.2. Note that the screening HbA_{1c} sample can be omitted if HbA_{1c} criterion is based on historical data obtained within 90 days prior to screening.

8.1.7 Body measurements

Height and weight will be measured and recorded as specified in the flowchart, Section 1.2.

The patient can wear indoor, daytime clothing with no shoes.

Body weight must be measured (with an empty bladder, without shoes and only wearing light clothing) on a calibrated digital scale and recorded in the eCRF in kilogram or pound [kg / lb], with one decimal. The body weight should be assessed on the same calibrated weighing scale equipment throughout the trial, if possible. The scale must be calibrated yearly as a minimum, unless the manufacturer certifies that calibration of the weighing scale is valid for the life-time of the scale.

Height is measured without shoes in centimetres or inches [cm / in] and recorded in the eCRF with one decimal.

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 patient experienced prior to the time point from which AEs are collected. Only relevant and significant medical history, including COVID-19, as judged by the investigator should be recorded in the eCRF at the screening visit (V1). Findings of specific medical history should be described in designated forms.

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

8.2.1 Physical examinations

A physical examination will include assessments of the:

- general appearance
- respiratory system
- cardiovascular system
- gastrointestinal system
- foot ulcers

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

8.2.2 Eye examination

Patients 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. Optical coherence tomography and visual acuity testing are not acceptable for evaluating retinopathy or maculopathy.

If the patient 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 patient has experienced worsening of visual function since the last examination. If the applicable eye examination was performed before the patient 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 in Section 1.2. 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.

8.2.3 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
- AEs leading to discontinuation of trial product
- AEs of COVID-19, irrespective of seriousness
- 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.
- Pregnancies
- Episodes of severe hypoglycaemia
- Selected types of AEs (SAEs and non-SAEs) requiring additional data collection and events for adjudication (Table 8-1).
- Technical complaints

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

Japan: For AE reporting requirements please see Appendix 8, Section 10.8.

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 patients and will be evaluated by an independent external event adjudication committee (EAC) in a blinded manner, please refer to Appendix 1, Section 10.1.6.2

The list of events for adjudication can be found in Table 8-1 and the reporting timelines in Figure 10-1. Refer to Appendix 3, Section 10.3 for further details on criteria for reporting of events for adjudication.

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
Medication error	X	
Misuse and abuse	X	
Death (all cause)		X
Acute coronary syndrome (ACS)	X (specific event form only in case of coronary revascularisation)	X
Events leading to coronary artery revascularisation (non-ACS) *Note: The underlying condition should be reported as the AE diagnosis*	X	
Stroke or transient ischemic attack (TIA)	X (specific event form only in case of carotid revascularisation)	X
Events leading to carotid artery revascularisation (non-TIA/-stroke related) *Note: The underlying condition should be reported as the AE diagnosis*	X	
Acute or chronic limb ischemia requiring hospitalisation	X (specific event form only in case of limb revascularisation)	X
Events leading to peripheral artery revascularisation (not related to acute or chronic limb ischemia) *Note: The underlying condition should be reported as the AE diagnosis*	X	

A detailed description of the events mentioned in the above table can be found in Appendix 3, Section 10.3.3.

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 electronic data capture (EDC) system.
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 EDC system 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 EDC system 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.

Episodes of severe hypoglycaemia

Episodes of severe hypoglycaemia require additional data collection on a severe hypoglycaemic episode form regardless of seriousness. As opposed to AEs requiring additional data collection (Table 8-1), non-serious, severe hypoglycaemic episodes do not require an AE form to be filled in.

If the severe hypoglycaemic episode fulfils the criteria for an SAE then, in addition to the severe hypoglycaemic episodes form, an AE form and a safety information form must be filled in, please refer to Appendix 3, Section 10.3.5. For more information on episodes of severe hypoglycaemia, please refer to Appendix 7, Section 10.7.

8.3.1 Time period and frequency for collecting AE and SAE information

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 the follow-up 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 10.3.4. 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 within 24 hours of it being available.

Investigators are not obligated to actively seek for AE or SAE in former trial patients. However, if the investigator learns of any SAE, including a death, at any time after a patient 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 10.3.5.

Care should be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient 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 patient at subsequent visits/contacts. All SAEs should be followed until final outcome of the event or the patient 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 patients 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, institutional review board (IRB)/independent ethics committee (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 patients will be collected after first exposure to trial product and until pregnancy outcome.

If a female patient becomes pregnant, the investigator should inform Novo Nordisk within 14 calendar days of learning of the pregnancy and should follow the procedures outlined in Appendix 4, Section 10.4.

8.3.6 Cardiovascular and death events

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

8.3.7 Technical complaints

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

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

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

8.4 Treatment of overdose

There is no specific antidote for overdose with semaglutide. In the event of an overdose, appropriate supportive treatment should be initiated according to the patient´s clinical signs and symptoms. Overdoses of up to 4 mg in a single dose have been reported in clinical trials. The most commonly adverse reaction was nausea. All patients recovered without complications.

A prolonged period of observation and treatment for these symptoms may be necessary, taking into account the long half-life of semaglutide of approximately one week.

Accidental overdose must be reported as a medication error. Intentional overdose must be reported as misuse and abuse, please refer to Section 8.3 and Appendix 3, Section 10.3 for further details.

In the event of an overdose, the investigator should closely monitor the patient for overdose-related AE/SAE.

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

For more information on overdose, also consult the current version of the semaglutide investigator's brochure.[14]

8.5 Pharmacokinetics

- Single blood samples for measuring plasma concentration of semaglutide will be drawn on visits specified in the flowchart.
- The dosing information should be transcribed into the CRF for the date of the last dose of trial product prior to the PK assessment, as outlined in the flowchart.
- The exact timing of obtaining the PK sample must be recorded on the laboratory form.
- The purpose of measuring plasma semaglutide levels is to conduct exposure-response, and to evaluate adherence to the treatment.
- 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.
- PK samples will not be taken in China.

8.6 Pharmacodynamics

Not applicable

8.7 Genetics

Not applicable

8.8 Biomarkers

Collection of samples for biomarker research is part of this trial. Participation in the biobank component is optional. Patients 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 the flow chart, Section 1.2 and stored for future use.

Optional samples for biomarker research that should be collected from patients in the trial where possible are the following:

- serum
- plasma

The samples are collected for the purpose of allowing future analyses of circulating biomarkers, 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.

In addition, samples will be stored, and analysis may be performed on biomarker variants thought to play a role in PAD including, but not limited to serum and plasma analytes, or tissue biomarkers, to evaluate their association with observed clinical responses to semaglutide 1 mg.

These samples need to be frozen and should be sent to the central laboratory. 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 up to 15 years after end of trial at a central laboratory (see Appendix 6, Section 10.6).

8.9 Immunogenicity assessments

Not applicable.

9 Statistical considerations

9.1 Statistical hypotheses

For the primary endpoint, ratio to baseline in maximum walking distance at week 52, the following confirmatory one-sided hypothesis is planned to be tested. Let the median ratio to baseline for semaglutide 1 mg and placebo be defined as M_{sema} and $M_{placebo}$, respectively. Superiority for the maximum walking distance at week 52 will then be tested as:

$$H_0: M_{sema} \leq M_{placebo} \text{ against } H_a: M_{sema} > M_{plac}$$

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

The hypothesis for the confirmatory endpoint, ratio to baseline in maximum walking distance at week 57 and pain-free walking distance at week 52 is the same as for the primary endpoint. Likewise, the hypothesis for the confirmatory endpoint, change from baseline in Vascu-Qol-6 score at week 52, is the same as for the primary endpoint, except that M denotes median change from baseline.

Multiplicity adjustment

The following hierarchical testing strategy will be applied to control the type-I error at an overall alpha level (two-sided) of 0.05 across the confirmatory endpoints:

1. Superiority of semaglutide 1 mg vs. placebo on ratio to baseline (week 0) at week 52 in maximum walking distance
2. Superiority of semaglutide 1 mg vs. placebo on ratio to baseline (week 0) at week 57 in maximum walking distance
3. Superiority of semaglutide 1 mg vs. placebo on change from baseline (week 0) to week 52 in VascuQoL-6 score.
4. Superiority of semaglutide 1 mg vs. placebo on ratio to baseline (week 0) at week 52 in pain-free walking distance.

9.2 Sample size determination

The primary endpoint is ratio to baseline (week 0) at week 52 in maximum walking distance on a constant-load treadmill test. The confirmatory secondary endpoints are ratio to baseline (week 0) at week 57 in maximum walking distance, change from baseline (week 0) to week 52 in VascuQoL-6 score and ratio to baseline (week 0) at week 52 in pain-free walking distance. Superiority will be tested for all four endpoints. The type-I error rate will be controlled in the strong sense across the primary and the confirmatory secondary hypotheses at an overall alpha level (two-sided) of 0.05 as described above.

The trial is designed to have 89% power to be able to detect a 20% improvement in maximum walking distance at week 52 compared to baseline for semaglutide 1 mg relative to placebo, hence confirm superiority for the primary endpoint. This effect size is expected to be clinically relevant (evaluated by the PGI-S) and is considered achievable due to the potential mode-of-action of semaglutide as described in the introduction (Section 2.2).

Primary endpoint

The power has been calculated using stochastic simulation. First, a complete dataset has been simulated using a normal distribution for the log-transformed primary endpoint.

Treatment ratio (semaglutide 1 mg versus placebo) is assumed to be 1.2, the coefficient of variation to be 0.8 and a 1:1 randomisation. There is some uncertainty over the coefficient of variation but based on results from the cilostazol trials (by dividing the standard deviation with the mean)[29-31] an assumption of a coefficient of variation of 0.8 seems plausible.

Missing observations due to death (2% in total corresponding to 8 deaths in each treatment group), inability to perform the treadmill test (3% in total corresponding to 12 cases in each treatment group), and due to other reasons (3% in total corresponding to 12 cases in each treatment group), have been introduced in the complete dataset assuming equal distribution between treatment groups.

First, log-transformed endpoints that are missing due to other reasons than death or inability to perform the walking test are imputed by sampling from a normal distribution corresponding to the theoretical distribution in the placebo group. Second, the resulting imputed dataset is analysed using Wilcoxon rank-sum-test, where ranks are assigned as follows: Patients with non-missing observations are assigned ranks according to the observed endpoint. Patients with missing observation due to death or physical inability to perform the treadmill test are assigned ranks as described in Section 9.4.2. Third, the imputed standardized Wilcoxon test statistics are combined using Rubin's rule to obtain a p-value.

Repeating the simulation 5,000 times, each with 50 imputations, 800 patients must be randomised to obtain 89% power for confirming superiority for the primary endpoint.

Secondary confirmatory endpoints

The same assumptions as for the primary endpoint apply for the ratio to baseline (week 0) at week 57 in maximum walking distance and ratio to baseline (week 0) at week 52 in pain-free walking distance. This is also assumed achievable due to the mode of actions of semaglutide. Therefore, with 800 randomised patients there is a marginal power of 89% for confirming superiority for this secondary confirmatory endpoint.

For change from baseline (week 0) to week 52 in VascuQoL-6 score, the power for confirming superiority is calculated similar to the power for the primary endpoint. Stochastic simulation based on an assumption of a treatment difference of 2 points and a standard deviation of 5 are assumed based on earlier trials.[32]

Missing observations (8%) in total have been introduced in the simulated complete dataset in the same way as for the primary endpoint. The resulting imputed dataset is analysed using a Wilcoxon rank-sum-test with ranks assigned using the same algorithm for the primary endpoint and combined using Rubin's rule to obtain a p-value. Repeating the simulation 5,000 times, each with 50 imputations, with 800 randomised patients, the power is >99% for confirming superiority of VascuQoL-6 score.

Overall power

The joint (effective) power is calculated under the assumption of independence of endpoints by multiplying the respective marginal powers successively. Since some of these endpoints/tests are positively correlated, the assumption of independence is viewed as conservative.

With the above assumptions, 89% power for confirming superiority for the primary endpoint will require a total of 800 randomised patients (400 patients randomised in each treatment group), when comparing semaglutide 1 mg to placebo. Table 9-1 summarises the assumptions for the sample size calculation and provides an overview of the marginal and joint power for each hypothesis.

Table 9-1 Assumptions used in sample size calculation and power for meeting individual hypotheses as well as joint power

Endpoint	Hypothesis	Assumptions	Randomised patients	Marginal power	Joint power
Maximum walking distance	Superiority	Treatment ratio = 1.2 Coefficient of variation = 0.8	800	89%	89%
VascuQoL-6 score	Superiority	Treatment difference = 2-points Standard deviation = 5	800	> 99%	~89%
Pain-free walking distance	Superiority	Treatment ratio = 1.2 Coefficient of variation = 0.8	800	89%	~79%

Abbreviations: VascuQoL-6: Vascular Quality of Life-6

Each scenario assumes 2% (8 per treatment group) dead; 3% unable to perform walking test (walking test endpoints only, 12 per treatment group); 3% missing due to other reasons (12 per treatment group).

The sample size calculations above are sensitive to the assumptions made for the true treatment ratio for the primary endpoint. Table 9-2 illustrates this with six alternative set of assumptions.

Table 9-2 Power with different assumptions for the treatment ratio for the primary endpoint

Treatment ratio	Coefficient of variation	Power obtained with 800 randomised patients
1.2	0.8	89%
1.2	1.0	77%
1.2	1.5	53%
1.3	0.8	>99%
1.3	1.0	98%
1.3	1.5	85%

Approximately 1,143 patients will be screened to achieve 800 patients (screening failure rate of 30 % is anticipated) randomly assigned to trial product.

9.3 Populations for analyses

Data selection for statistical analyses will be a two-step process, first selecting patients based on the analysis population and subsequently events/data for those patients based on the observation period,

see Table 9-3 and for definitions of analysis populations and observation periods, respectively. The following populations are defined:

Table 9-3 Analysis populations

Population	Description
Randomised	All patients randomised
Full analysis set (FAS)	All patients randomised. Patients will be analysed according to the randomised treatment
Safety analysis set (SAS)	All patients randomly assigned to trial treatment and who take at least 1 dose of trial product. Patients will be analysed according to the trial product received for the majority of the period they were on treatment

Table 9-4 Observation periods

Observation period	Description
In-trial	This observation period is defined as the period from the date of randomisation to the first of the following dates, both inclusive: • Date of the end-of-trial visit (V9) • Date of death • Date when patient withdrew informed consent • Date of last contact for patients lost to follow-up
On-treatment	This observation period includes assessments and events for the time period where patients are exposed to the investigational medicinal products, regardless of whether the patients have received rescue treatment or not, as well as baseline assessments. The observation period starts at the date of first dose of trial product and ends at the follow-up visit for endpoints related to adverse events, and at last treatment day + 7 days for other endpoints. More details regarding the on-treatment end date can be found in the Statistical Analysis Plan (SAP).
On-treament without rescue treatment	This observation period includes assessments and events for the time period where patients were exposed to trial product and before rescue treatment. Thus, this observation period is a subset of the on-treatment period, excluding observations at and following rescue treatment

In general patients should not be excluded from an analysis set and observations should not be excluded from an observation period, if they fulfil the criteria. If patients or observations are excluded, the reasons for their exclusion must be documented before database lock and described in the clinical trial report. Any decision to exclude either a patient or single observation from the statistical analysis is the joint responsibility of the members of the Novo Nordisk study group.

9.4 Statistical analyses

The statistical analysis plan (SAP) will be finalised prior to first patient first visit (FPFV), and it will include a more technical and detailed description of the statistical analyses described in this Section. This Section is a summary of the planned statistical analyses of the most important endpoints including primary and confirmatory secondary endpoints.

9.4.1 General considerations

Where applicable, the comparison presented from a statistical analysis will be semaglutide 1.0 mg 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.

Unless otherwise mentioned, baseline assessment is defined as the latest available measurement from the randomisation visit (V2) or the screening visit (V1). Thus, if a V2 assessment is missing then the assessment from V1 will be used as the baseline assessment, if available. For the endpoint 'maximum walking distance', the baseline assessment is defined as the mean of the two assessments from the randomisation visit (V2). If only one of the assessments is available, this will be used as the baseline assessment, and if no assessments are available at V2 then the assessment at V1 will be used.

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

9.4.2 Primary endpoint

The primary endpoint is ratio to baseline (week 0) at week 52 in maximum walking distance on a constant-load treadmill.

According to the primary estimand (see Section 3.1.1), the primary analysis will be based on all randomised patients and the in-trial observation period and, as per the composite strategy for handling intercurrent events, patients with missing values at 52 weeks due to death or physical inability to perform the walking test, will be handled by ascribing them an extreme unfavourable rank.

Specifically, ranks for the primary endpoint will be assigned as follows:
1. Patients with missing values due to death are ordered by time of death (the earlier death, the worse rank)
2. Patients with missing values due to being physically unable to perform the test are ranked more favourably than all deaths, and ordered by the walking distance at baseline (a higher baseline value corresponds to a greater deterioration and so is assigned a worse rank)
3. Patients with observed values or missing values due to other reasons than death or inability to perform the walking test, are ranked more favourably than all deaths or patients unable to perform the walking test, and ordered according to their actual or imputed value, see below (the lower the walking distance relative to baseline, the worse rank)

The maximum walking distance will be log-transformed and the analysis will be based on difference between the log transformed value at week 52 and baseline.

Patients with missing values for the primary endpoint due to other reasons than death or inability to perform the walking test will have their values imputed using multiple imputation under a missing at random (MAR) assumption.

Imputation will be performed separately within groups defined by randomised treatment and treatment status at week 52, for a total of four groups:

9.4.2.1.1.1 semaglutide/on-treatment;

9.4.2.1.1.2 semaglutide/off-treatment;

9.4.2.1.1.3 placebo/on-treatment;
9.4.2.1.1.4 placebo/off-treatment.

First, intermittent missing values are imputed Markov Chain Monte Carlo (MCMC) to obtain a monotone missing data pattern, generating 500 complete data sets. Second, sequential conditional linear regression will be used to impute monotone missing values, starting with the first visit after baseline and sequentially continuing to the last planned visit at week 52. The regression model used for imputation will include baseline and post-baseline values for the endpoint observed prior to the visit in question as covariates.

Table 9-5 summarises the handling of missing values for the primary analysis.

The 500 complete data sets will be analysed using a Wilcoxon rank-test. Rubin's rule will be used to combine the standardised Wilcoxon test statistics. The confirmatory statistical testing will be based on the p-value from the pooled standardised Wilcoxon test statistic.

Superiority is considered confirmed if the p-value is strictly below 0.05.

For estimation of effect in relation to the primary estimand, the Hodges-Lehmann estimator will be calculated on log-transformed data for each of the 500 complete data sets. Rubin's rule will be used to obtain inferences. Results will be back transformed to original scale, thus showing the median treatment ratio of the ratio to baseline in maximum walking distance and 95% confidence intervals.

Table 9-5 Handling of missing and observed values for the primary estimand/analysis

Assessment at week 52	Patients on randomised treatment at week 52?	Type description	Handling
Available	Yes	**Available on randomised treatment** Patients with a week 52 assessment and on randomised treatment	Use observed value
	No	**Available but discontinued** Patients who discontinued treatment prematurely but returned to have a week 52 assessment	Use observed value
Missing	Yes	**Physically unable to perform walking test on randomised treatment** Patients on randomised treatment but without a week 52 assessment due to inability to perform walking test	Incorporate into endpoint (composite strategy)
		Missing on randomised treatment Patients on randomised treatment but without a week 52 assessment for other reasons than inability to perform walking test	Impute in own treatment group based on 'Available on randomised treatment'
	No	**Physically unable to perform walking test and discontinued** Patients who discontinued randomised treatment prematurely, returned to have a week 52 assessment but were unable to perform walking test	Incorporate into endpoint (composite strategy)
		Death Patients without a week 52 assessment due to death	Incorporate into endpoint (composite strategy)
		Missing and discontinued Patients who discontinued randomised treatment prematurely and did not return to have an assessment at week 52.	Impute in own treatment group based on 'Available but discontinued'

The secondary estimand for the primary endpoint (see Section 3.1.1), will be based on all randomised patients and the on-treatment without rescue treatment observation period. The maximum walking distance will be log-transformed and the change from baseline to the 52 weeks will be analysed using a mixed model for repeated measurements (MMRM). The model will include measurements at both week 26 and 52 as dependent variables. The independent effects included in the model will be treatment and region as categorical fixed effects and baseline maximum walking distance (log-transformed) as a covariate, all nested within visit (week) as a factor. An unstructured covariance matrix for measurements within the same patient will be employed. From the MMRM model the treatment difference at week 52 will be estimated and the corresponding 95% confidence interval and p-value will be calculated. The estimated treatment difference and confidence intervals will be back transformed to original scale, and thus present the estimated treatment ratio with confidence interval.

Sensitivity analyses

As a sensitivity analysis for the primary estimand, a two-dimensional tipping point analysis will be performed. Missing data will be imputed according to the primary multiple imputation approach and fixed values δ_1 and δ_2 will be added to each imputed value in the semaglutide treatment group and placebo treatment group, respectively. The primary analysis will then be performed with these delta-adjusted imputations. This will be repeated for a grid of (δ_1, δ_2)-values, including scenarios where patients with missing values in the semaglutide group have worse outcomes than those in the placebo group. This sensitivity analysis evaluates the robustness of the superiority conclusion to deviations from the MAR assumption for missing data.

9.4.3 Secondary endpoints

9.4.3.1 Confirmatory secondary endpoints

The confirmatory secondary endpoints are:

- Ratio to baseline (week 0) at week 57 in maximum walking distance, and will be analysed similarly to the primary endpoint with regards to the estimands
- Change from baseline (week 0) to week 52 in VascuQoL-6 score and will be analysed similarly to the primary endpoint with regards to estimands but will not be log-transformed.
- Ratio to baseline (week 0) at week 52 in pain-free walking distance, and will be analysed similarly to the primary endpoint with regards to the estimands

The confirmatory tests will be based on the primary estimand (the composite strategy and treatment policy estimand).

9.4.3.2 Supportive secondary endpoints

The ratio to baseline in pain free walking distance at follow-up will be analysed similarly to the primary endpoint.

All other supportive secondary endpoints will be analysed using a model similar to the MMRM model described as the secondary estimand for the primary endpoint.

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 safety analyses

All safety analyses will be made on the safety analysis set.

The adverse events will be reported descriptively.

9.4.6 Other analyses

The 'Change of Patient Global Impression of Severity (PGI-S) category' will be used for an anchor-based analysis to determine the meaningful within-patient change in the maximum walking distance and VascuQoL-6. The within-patient standard deviation, estimated using the baseline maximum walking distance, will be used as a secondary and supportive measure of the meaningful within-patient change in the maximum walking distance.

For other analyses, please refer to the SAP.

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 PAD. 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 SUSTAIN 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 analysis

Not applicable

9.7 Data monitoring committee

Not applicable

9.8 Reporting of the main part of the trial

A database lock is planned shortly after last patient last visit (LPLV) of the trial. The results from the trial will thereafter be reported.

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[33] and applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guideline[34]
- 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. See Section 10.8 for country-specific requirements in Latvia.

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 patients.

Before a site is allowed to start screening patients, written notification from Novo Nordisk must be received.

The investigator will be responsible for:

- providing written summaries of the status of the trial annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC and/or regulatory authorities
- notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- providing oversight of the conduct of the trial at the site and adherence to requirements of ICH guidelines, the IRB/IEC, and all other applicable local regulations
- ensuring submission of the CTR synopsis to the IRB/IEC
- reporting any potential serious breaches to the sponsor immediately after discovery

10.1.2 Financial disclosure

Investigators and sub-investigators will provide Novo Nordisk with sufficient, accurate financial information as requested to allow Novo Nordisk to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the trial and one year after completion of the trial.

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 patient and answer all questions regarding the trial.
- The investigator must ensure the patient ample time to come to a decision whether or not to participate in the trial.
- Patients must be informed that their participation is voluntary.
- Patients must be informed about their privacy rights.
- Patients will be required to sign and date a statement of informed consent that meets the requirements of local regulations, ICH guidelines[34], Declaration of Helsinki[33] and the IRB/IEC or site.
- The informed consent form will contain a separate form that addresses long-term storage of human samples and or the use of samples for optional exploratory research.
- 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.
- Patients 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 form(s) must be provided to the patient.

10.1.4 Information to patients during trial

The site will be offered a communication package for the patient 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 patients. The written information will be translated and adjusted to local requirements and distributed to the patient at the discretion of the investigator. The patient may receive a "welcome to the trial letter" and a "thank you for your participation letter" after completion of the trial. Further, the patient may receive other written information during the trial.

All written information to patients 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

- Patients will be assigned a 6-digit unique identifier, a patient number. Any patient records or datasets that are transferred to Novo Nordisk will contain the identifier only. No direct identifiers from the patient are transferred to Novo Nordisk.
- The patient and any biological material obtained from the patient will be identified by patient number, visit number and trial ID. Appropriate measures such as encryption or leaving out certain identifiers will be enforced to protect the identity of patients as required by local, regional and national requirements.

- The patient 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 patient.
- The patient must be informed that his/her medical records may be examined by auditors or other authorised personnel appointed by Novo Nordisk, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.6 Committees structure

10.1.6.1 Novo Nordisk safety committee

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

10.1.6.2 Event adjudication committee

An independent external EAC is established to perform ongoing blinded adjudication of selected AEs and deaths (see Section 8.3).The purpose of the adjudication is to evaluate events in a consistent manner according to standardised criteria using independent external medical experts.

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.

10.1.7 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)[35], the Food and Drug Administration Amendment Act (FDAAA)[36], European Commission Requirements[1, 37, 38] and other relevant recommendations or regulations. If a patient 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 patient. 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 patient first visit (LPFV) + 54 weeks, corresponding to visit 8 (end of treatment). If the last patient is withdrawn early, the PCD is considered the date when the last patient would have completed visit 8. 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 patient data relating to the trial will be recorded on electronic CRFs unless transmitted electronically to Novo Nordisk or designee (e.g. laboratory and activity tracker data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The following will be provided as paper CRFs:

- Pregnancy forms

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

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

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

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

10.1.8.2 Monitoring

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

Trial monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorised site personnel are accurate, complete and verifiable from source documents; that the safety and rights of patients 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 patient's medical records and other source data, e.g. the PROs, to ensure consistency and/or identify omissions compared to the CRF.

10.1.8.3 Protocol compliance

Deviations from the protocol should be avoided. If deviations do occur, the investigator must inform the monitor without delay and the implications of the deviation must be reviewed and discussed.

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

10.1.9 Source documents

- All data entered in the eCRF must be verifiable in source documentation other than the CRF
- The original of the completed PROs must not be removed from the site, unless they form part of the CRF, and a copy is kept at the site.
- For Activity tracker, data in the service providers' database is considered source data.
- Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the site.
- Data reported on the paper CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents, or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records. Also, current medical records must be available.
- It must be possible to verify patient's medical history in source documents, such as patient'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 patient data will be provided in an electronic readable format to the investigator before access is revoked to the system supplied by Novo Nordisk. Site-specific CRFs and other patient 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.

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

10.1.11 Trial and site closure

Novo Nordisk reserves the right to close the site or terminate the trial at any time for any reason at the sole discretion of Novo Nordisk. If the trial is suspended or terminated, the investigator must inform the patients 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 patients 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 patients.

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 patient 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. 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 patients to a specific qualified physician who will be readily available to patients 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.

Novo Nordisk accepts liability in accordance with country specific requirements, see Appendix 8, Section 10.8.

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 patient 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.[39]

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 patients, 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 and Table 10-2 will be performed by the central laboratory. Information on central laboratory can be found in Attachment I.

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 will be destroyed no later than at finalisation of the CTR, except for biomarker samples, which will be stored as described in Appendix 6, Section 10.6.

For female patients of childbearing potential, local urine pregnancy tests must be performed at screening according to flowchart, Section 1.2. Serum testing is mandatory if required by local regulations or the IRB/IEC.

For haematology samples (differential count) where the test result is not normal, then a part of the sample may be kept for up to two years or according to local regulations.

Human biosamples for future research will be stored as described in Appendix 6, Section 10.6.

Table 10-1 Protocol-required efficacy laboratory assessments

Laboratory assessments	Parameters
Glucose metabolism	• HbA_{1c}
Lipids	• Cholesterol • High density lipoprotein (HDL) cholesterol • Low density lipoprotein (LDL) cholesterol • Triglycerides
Pharmacokinetics	• Plasma semaglutide

Notes: Laboratory results that could unblind the trial (e.g. PK data) will not be reported to the trial sites until the trial has been unblinded.

Table 10-2 Protocol-required safety laboratory assessments

Laboratory assessments	Parameters
Haematology	• Erythrocytes • Haematocrit • Haemoglobin • Leucocytes • Thrombocytes
Biochemistry[a]	• Albumin • Creatinine

Laboratory assessments	Parameters
	• Potassium • Sodium • Alanine aminotransferase (ALT) • Aspartate aminotransferase (AST) • Gamma glutamyltransferase (GGT) • Total bilirubin
Pregnancy Testing	• Highly sensitive serum or urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[b]

Notes:

[a] Details of required actions and follow-up assessments for increased liver parameters including any discontinuation criteria are given in Section 10.3 (Hy's Law) and Section 7.1.

[b] Local urine testing will be standard unless serum testing is required by local regulation or IRB/IEC.

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

10.3.1 Definition of AE

AE definition
An AE is any untoward medical occurrence in a clinical trial patient 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 unfavorable and unintended sign, including an abnormal laboratory finding, symptom or disease (new or exacerbated) temporally associated with the use of an IMP.

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

10.3.2 Definition of an SAE

An SAE is an AE that fulfils at least one of the following criteria:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient 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 patient 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 patient 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
- **Acute coronary syndrome:**

Conditions include all types of acute myocardial infarction and hospitalisation for unstable angina pectoris

- **Stroke or transient ischemic attack:**
  Episode of focal or global neurological dysfunction that could be caused by brain, spinal cord, or retinal vascular injury as a result of haemorrhage or ischaemia, with or without infarction
- **Acute or chronic limb ischemia requiring hospitalisation:**
  Acute limb ischemia is defined as a sudden decrease in limb perfusion threatening viability of the limb and leading to an urgent, unscheduled hospitalisation.
  Chronic limb ischemia is defined as a chronic condition with rest pain, non-healing ulcers or gangrene and leading to an urgent, unscheduled hospitalisation with need for intervention such as a revascularization procedure, amputation or pharmacological therapy.

Adverse events requiring additional data collection

- **Events leading to coronary artery revascularisation (ACS and non-ACS):**
  - ACS and non-ACS (e.g. stable angina pectoris) leading to catheter-based (percutaneous coronary intervention (PCI)) or a surgical procedure (coronary artery bypass surgery) designed to improve myocardial blood flow.
    - *Note*: The underlying condition should be reported as an AE diagnosis.

- **Events leading to carotid artery revascularisation:**
  - Carotid artery stenosis leading to a surgical procedure (carotid artery endarterectomy incl. angioplasty and carotid artery stenting).
    - *Note*: The underlying condition should be reported as an AE diagnosis.

- **Events leading to peripheral artery revascularisation:**
  - Any type of limb ischemia leading to a catheter-based (incl. endovascular procedures) or a surgical procedure (surgical thrombectomy/thromboendarterectomy and/or peripheral bypass surgery or endovascular / surgical treatment of aortic aneurysm) designed to improve blood flow to the limb.
    - *Note*: The underlying condition should be reported as an AE diagnosis.

- **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 patient, such as:
    - Administration of wrong drug
      Note: Use of wrong dispensing unit number (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 a lower or higher dose than intended. The administered dose must deviate from the intended dose to an extent where clinical consequences for the trial patient were likely to happen as judged by the investigator, although they did not necessarily occur.
    - Treatment pauses are allowed in the trial, this should not 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. 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 patient identifiers, with the exception of the patient 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 patient, 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 patient 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 patient 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 patient has completed the follow-up period and is expected to recover.
- **Recovered/resolved with sequelae:** The patient 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 patient 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 patient died from a condition related to the reported AE. Outcomes of other reported AEs in a patient 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 patient 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 patient dies during participation in the trial or during a recognised follow-up period, the investigator should provide Novo Nordisk with a copy of autopsy report including histopathology.

New or updated information will be recorded in the CRF.

10.3.5 Reporting of SAEs

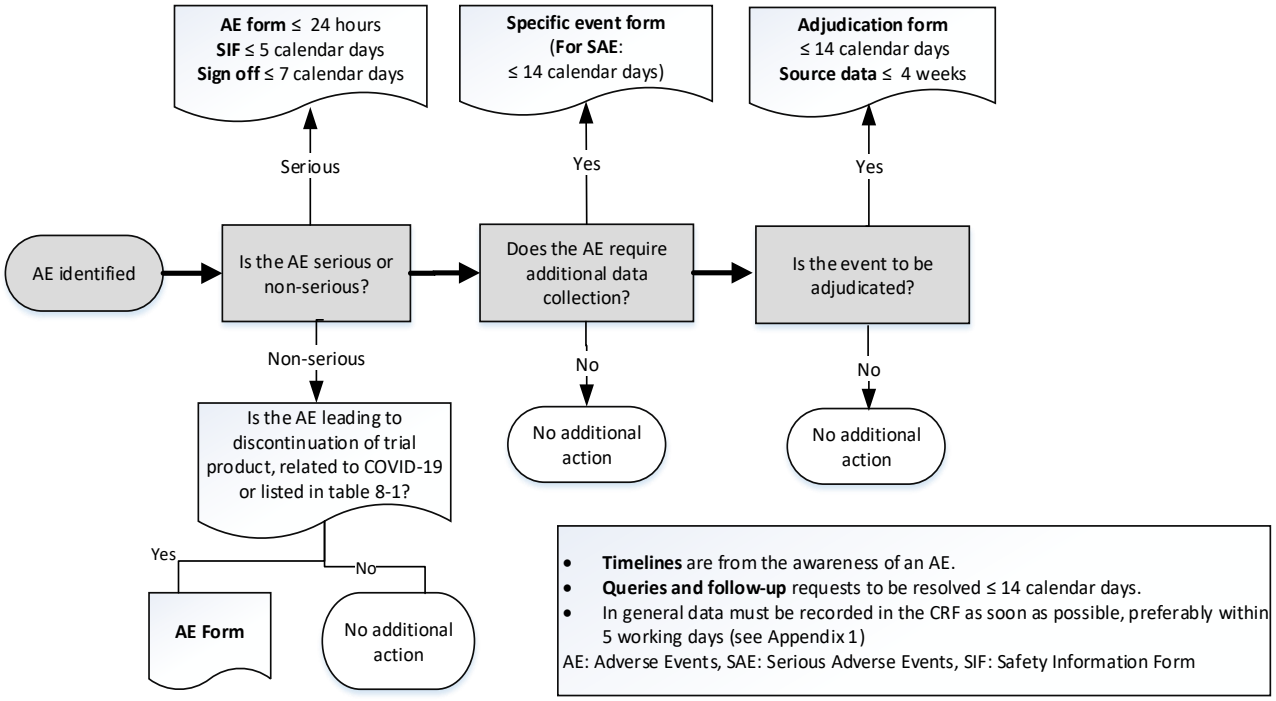
SAE reporting via electronic CRF

- Relevant forms (AE and safety information form) must be completed in the CRF.
- For reporting and sign-off timelines, see Figure 10-1 below.
- If the CRF is unavailable for more than 24 hours, then the site will use the paper AE form, and if the CRF 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 CRF 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 patient 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 (Table 10-3).

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

Contraception guidance

Male patients

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

Female patients

Female patients of childbearing potential are eligible to participate if they agree to use methods of contraception consistently and correctly as described in Table 10-3 below:

Table 10-3 Highly effective contraceptive methods

CONTRACEPTIVES[a] ALLOWED DURING THE TRIAL INCLUDE:

• **Highly effective methods[b,f] 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,f] 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]
  o oral
  o intravaginal
  o transdermal
  o injectable
  • 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 patient.

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, 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 5 weeks (corresponding to time needed to eliminate trial product) after the last dose of trial product. This period should be extended by 30 days in case of genotoxicity.

In certain cases, it is accepted to use double barrier methods (a condom combined with an occlusive cap (e.g. diaphragm) with/without the use of spermicide). This should only be allowed in females with:

1. known intolerance to the highly effective methods mentioned in Table 10-3 or where the use of any of the listed highly effective contraceptive measures are contraindicated in the individual patient, and/or
2. if the risk of initiating treatment with a specific highly effective method outweighs the benefit for the female.

Justification for accepting double barrier method should be at the discretion of the investigator taking into consideration his/her knowledge about the female's medical history, concomitant illness, concomitant medication and observed AEs. The justification must be stated in the medical records.

For country specific requirements, please see Appendix 8 (Section 10.8).

Pregnancy testing

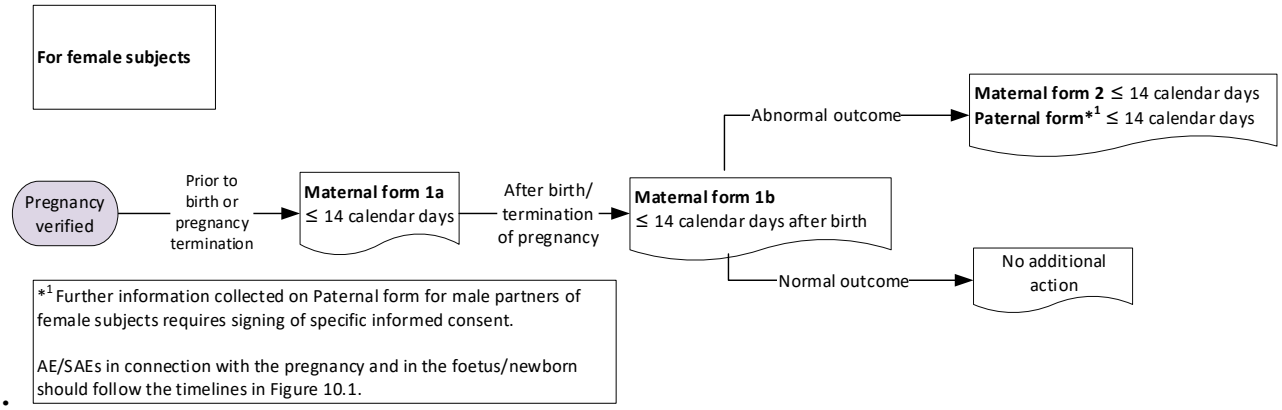
- WOCBP should only be included after a negative highly sensitive urine pregnancy test (refer to Appendix 2, Section 10.2).
- Additional urine pregnancy testing should be performed at end of treatment (V8) or at premature end of treatment (V8A) according to the flowchart.
- Pregnancy testing should be performed whenever a menstruation is missed or when pregnancy is otherwise suspected.
- Additional pregnancy testing should be performed during the treatment period, if required locally (Appendix 8, Section 10.8).

Collection of pregnancy information

Female patients who become pregnant

- Investigator will collect pregnancy information on any female patient 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 patient's pregnancy (see Figure 10-2).
- Patient will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on patient 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 patient'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 Appendix 3 (Section 10.3). While the investigator is not obligated to actively seek this information in former patients, 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 patient 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: 6. One technical complaint form must be completed for each affected DUN. 7. 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 CRF within: • 24 hours if related to an SAE • 5 days calendar for all other technical complaints If the CRF is unavailable, or when reporting a technical complaint on a trial product that is not yet allocated to patient, the information must be provided on a paper form to Customer Complaint Center, Novo Nordisk, within the same timelines as stated above. When the CRF becomes available again, the investigator must enter the information on the technical complaint form in the CRF.

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

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

10.5.3 Reporting of technical complaints

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

10.6 Appendix 6: Retention of human biosamples

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.

In countries where allowed, the trial will involve collection of human biosamples to be stored in a central archive (perhaps in another country) for future use as noted in Section 8.8.

The following samples will be stored:

- plasma
- serum

The samples will be stored at a secure central bio-repository after end of trial and until the research project terminates, but no longer than 15 years from end of trial after which they will be destroyed. Only Novo Nordisk staff and biorepository personnel will have access to the stored samples.

Patients may withdraw from the biobank component of the trial at any time, independent of participation in the trial. If a patient withdraws from the biobank component all stored biosamples obtained from their own body will be destroyed.

Confidentiality and personal data protection will be ensured during storage after the end of trial.

In the event that the collected biosamples will be used in the future, care will be taken to target analyses within the scope defined in Section 8.8.

For country specific requirements see Appendix 8 (Section 10.8).

10.7 Appendix 7: Severe hypoglycaemic episodes

Severe hypoglycaemia

Severe hypoglycaemia is an event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions. Plasma glucose (PG) concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.[40, 41]

10.8 Appendix 8: Country/region-specific requirements

Austria

- Section 5.2, Exclusion criterion #3 and Appendix 4 (Section 10.4): Contraceptive requirements as per EU CTFG guideline: http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf. Recommendations related to contraception and pregnancy testing in clinical trials", as listed in Table 10-3. This means that the use of double barrier methods is not applicable for Austria.

Belgium

- Section 5.2, Exclusion criterion #3 and Appendix 4 (Section 10.4): Use of methods of birth control for Belgium: E.g. Highly effective methods of birth control are defined as those, alone or in combination, that result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly; such as implants, injectables, combined oral contraceptives, some IUDs, true sexual abstinence (i.e. refraining from heterosexual intercourse during the entire period of risk associated with the trial treatments) or vasectomised partner.
- Appendix 1 (Section 10.1), Regulatory and ethical considerations: Indemnity statement: Novo Nordisk accepts liability in accordance with: Law concerning experiments on the human person of 07 May 2004 – Article 29: §1. Even if without fault, the sponsor is liable for the damage which the patient and/or his rightful claimants sustain, and which shows either a direct or an indirect connection with the trial.
- Section 8, Trial assessments and procedures no 7: Collection of contact information for persons other than the patient not relevant for Belgium.

Canada

- Appendix 1 (Section 10.1), Regulatory, ethical, and trial oversight considerations. Retention of clinical trial documentation: Part C, Division 5 of the Food and Drug Regulations [C.05.012] requires a 25-year retention period.

China

- Sections 5.1, Inclusion criteria and 5.2, Exclusion criteria: The criteria will be assessed at the investigator's discretion unless otherwise stated.
- Section 5.2, Exclusion criterion #4: Co-participation in COVID-19 trials are not allowed.
- Section 7.1, Discontinuation criterion #3: Co-participation in COVID-19 trials are not allowed.
- Section 8.5, Pharmacokinetics: PK samples will not be taken in China.
- Section 8.8, Biomarkers: No subjects from China will participate in the optional biobank part of the trial.
- Appendix 2 (Section 10.2), Clinical laboratory tests: The samples which tested at sites will be destroyed as biological waste according to local regulation, if applicable. The samples which tested at central lab will be destroyed as biological waste according to local regulation and lab manual. The laboratory samples for Chinese subjects will be destroyed no later than the finalization of the clinical trial report, or according to local regulatory requirement.

- Appendix 1 (Section 10.1), Regulatory, ethical, and trial oversight considerations: Any trial procedure conducted in China mainland should comply with "Regulations on management of Human Genetic Resources of People's Republic of China" and relative guideline. http://www.gov.cn/zhengce/content/2019-06/10/content_5398829.htm
- Appendix 1 (Section 10.1.7), Dissemination of clinical trial data. Information of the trial will be disclosed at clinicaltrials.gov, chinadrugtrials.org.cn and novonordisk-trials.com as China HA has requested to disclose trial information (phase 1-3) at chinadrugtrials.org.cn since 2013.
- Appendix 1 (Section 10.1.10), Retention of clinical trial documentation: About site specific data storage, sites have the equal right with sponsor. Long term preservation of Chinese Patients' Trial Data is Prohibited in any other entities.

Czech Republic

- Section 1.2: Pregnancy testing for women of childbearing potential will be done in line with the schedule below:

	Screening	**Baseline**	**Treatment**					**End of treatment**	**Follow-up**	**Premature EOT**	**Premature EOT follow-up**
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**P7**	**V8**	**V9**	**V8A**	**V9A**
Timing of visit (weeks)	**-2**	**0**	**4**	**8**	**12**	**26**	**49**	**52**	**57**	**-**	**-**
Visit window (days)	**-7; +13**	**±0**	**±4**	**±4**	**±4**	**±7**	**±7**	**±7**	**+7**	**±0**	**±0**
Safety											
Pregnancy test	X		X	X	X	X		X	X	X	X

-

- Section 1.2: Date of Birth: Patient's full Date of Birth is not allowed to be collected and must be shortened to Year of Birth.
- Section 5.2, Exclusion criterion #3 and Appendix 4 (Section 10.4): Contraceptive requirements as per EU CTFG guideline: http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf
- Appendix 4 (Section 10.4): In addition to the pregnancy testing described in the Flowchart (Section 1.2) and Appendix 4 (Section 10.4, for female subject of childbearing potential from Czech Republic, additional pregnancy testing will be done at week 4 (V3), week 8 (V4) and week 12 (V5). The additional pregnancy testing will not be reported in the CRF. In case of pregnancy, trial product will be discontinued, and the investigator should follow the procedures outlined in Appendix 4 (Section 10.4).

Denmark

- Section 5.2, Exclusion criterion #3 and Appendix 4 (Section 10.4): Contraceptive requirements as per EU CTFG guideline: http://www.hma.eu/fileadmin/dateien/Human_Medicines/01 About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf

Germany

- Section 1.2, Date of Birth: Patient's full Date of Birth is not allowed to be collected and must be shortened to Year of Birth.
- Section 5.2, Exclusion criterion #3: Contraceptive requirements as per CTFG guideline: http://www.hma.eu/fileadmin/dateien/Human_Medicines/01 About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf

Hungary

- Section 1.2, Date of Birth: Patient's full Date of Birth is not allowed to be collected and must be shortened to Year of Birth.
- Section 5.2, Exclusion criterion #17: Presence or history of pancreatitis (acute or chronic).

India

- Section 5.2, Exclusion criterion #6:
    - Digital x-ray of the foot should be performed according to local practice as part of the screening procedure in subjects who do not have recent imaging (within 90 days prior to the screening visit) to exclude foot deformities which can impact walking ability.
    - Conditions other than PAD which affects the walking ability includes anaemia or any other condition which in the investigator's opinion impacts the subjects walking ability.
- Section 5.2, Exclusion criterion #11: Echocardiography should be performed according to local practice as part of the screening procedure in subjects who do not have recent imaging (within 90 days prior to the screening visit).

Japan

- Section 5.1, Inclusion criterion #2: Male or female, age above or equal to 20 years at the time of signing informed consent.
- Section 5.2, Exclusion criterion #4: Co-participation in COVID-19 trials are not allowed.
- Section 6.2, Preparation/Handling/Storage/Accountability: The head of the trial site or the trial product storage manager assigned by the head of the trial site (a pharmacist in principle) is responsible for control and accountability of the trial products.
- Section 7.1, Discontinuation criterion #3: Co-participation in COVID-19 trials are not allowed.
- Section 8.3: For Japan, all AEs irrespective of seriousness should be collected from the day of randomisation and until the follow-up visit, at the time points specified in the flowchart. A non-severe non-serious hypoglycaemic episode should be reported as an AE. A severe non-serious hypoglycaemic episode should be reported as an AE and in addition a specific event form (severe hypoglycaemic episode) should be filled out.
- Appendix 1 (Section 10.1): Regulatory and ethical considerations: A name or a seal is accepted as a signature.

Latvia

- Section 10.1.1: Protocol, protocol amendments, informed consent form and investigator's brochure, must be also submitted, reviewed, and approved by the regulatory authorities before the trial is initiated.

Malaysia

- Appendix 6 (Section 10.6): No patients from Malaysia will participate in the optional biobank part of the trial.

Norway

- Section 5.2, Exclusion criterion #3 and Appendix 4 (Section 10.4): Contraceptive requirements as per EU CTFG guideline: http://www.hma.eu/fileadmin/dateien/Human_Medicines/01- About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf

Spain

- Section 5.2, Exclusion criterion #3 and Appendix 4 (Section 10.4): Contraceptive requirements as per EU CTFG guideline: http://www.hma.eu/fileadmin/dateien/Human_Medicines/01- About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf
- Appendix 1 (Section 10.1): Regulatory, ethical, and trial oversight considerations. Retention of clinical trial documentation: 25 years according to the new Spanish Royal Decree 1090/2015.

Sweden

- Section 5.2, Exclusion criterion #3 and Appendix 4 (Section 10.4): Contraceptive requirements as per EU CTFG guideline: http://www.hma.eu/fileadmin/dateien/Human_Medicines/01- About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf. Recommendations related to contraception and pregnancy testing in clinical trials", as listed in Table 10-3.
- Section 6, Treatments: Refer to CSC for labelling requirements.

Taiwan

- Section 5.1, Inclusion criterion #2: Legal age is 20 years per local law. Thus, age limitation for adult trials shall be above or equal to 20 years in the entry criteria.
- Appendix 6 (Section 10.6): No patients from Taiwan will participate in the optional biobank part of the trial.

United States

- Section 5.2, Exclusion criterion #15: Funduscopy/fundus photography will be performed by the investigator or a local Ophthalmologist/Optometrist according to local practise.

10.8.1 Optional pre-screening

Applicable for Austria, Canada, Czech Republic, Denmark, Greece, India, Malaysia, Sweden, Thailand and United States.

In the countries mentioned above, the investigator may, after obtaining separate informed consent, perform pre-screening activities to identify potential study participants based on ABI and/or TBI (inclusion criterion #4d). Pre-screening is optional and participants must sign a separate informed consent form to participate. It is not necessary to obtain informed consent for the full study before pre-screening. The requirements for the informed consent process are the same as those outlined in Section 10.1.3.

Pre-screening assessments may include:

- Measurement of ABI and/or TBI.
- Review of medical history and concomitant medication, including the option to review medical records obtained from relevant sources such as primary care physicians and hospitals.

Pre-screening assessments are not defined as study-related procedures. Results of pre-screening will not be collected in the study database. Concerns related to any pre-screening assessment should not be reported as an AE.

It is encouraged that potential participants who are determined to be potentially eligible for the study should proceed to screening (visit 1) as soon as possible and preferably within 1 month of pre-screening. If the candidate is deemed potentially eligible for participation in the study, all assessments and information required for screening (visit 1) must be collected in accordance with the flowchart (Section 1.2).

The investigator must maintain a pre-screening log to record details of all candidates who were pre-screened and to track the outcome of the pre-screening.

Pre-screening assessments performed after signature of the separate informed consent for pre-screening can be reimbursed by Novo Nordisk A/S.

10.9 Appendix 9: Abbreviations

ABI	Ankle-brachial index
ACS	Acute coronary syndrome
AE	adverse event
AHA	American Heart association
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CFR	Code of Federal Regulations
COVID-19	Coronavirus disease 2019
CRF	case report form
CTFG	Clinical Trial Facilitation Group
CTR	clinical trial report
CV	Cardiovascular
DFU	directions for use
DPP-4 i	DPP-4 inhibitor
DUN	dispensing unit number
EAC	event adjudication committee
EAS	event adjudication system
EDC	Electronic data capture
eCRF	electronic case report form
EOT	end-of-treatment
ESC	European Society of Cardiology
FAS	full analysis set
FDA	U.S. Food and Drug Administration
FDAAA	FDA Amendments Act
FPFV	first patient first visit
FU	follow-up
GI	Gastrointestinal
GLP-1-RA	GLP-1 receptor agonist
GCP	Good Clinical Practice
HA	Health Authority
Hb	Haemoglobin
$HbA1_c$	glycated haemoglobin
hCG	human chorionic gonadotropin
HDL	High density lipoprotein
HRT	hormone replacement therapy
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	independent ethics committee
IFCC	International Federation of Clinical Chemistry and Laboratory Medicine
IMP	investigational medicinal product
IRB	institutional review board
IWRS	interactive web response system
KDIGO	Kidney Disease Improving Global Outcomes
LDF	laser Doppler flowmetry
LDL	Low-density lipoprotein
LPLV	last patient last visit
MACE	Major adverse cardiovascular event
Max	Maximum
MCMC	Markov Chain Monte Carlo
MEN2	multiple endocrine neoplasia type 2
MMRM	mixed model for repeated measurements
NGSP	National Glycohemoglobin Standardization Program
NYHA	New York Heart Association
OW	Once-weekly
PAD	peripheral artery disease
PCD	primary completion date

PGI-C	Patient global impression of change
PGI-S	Patient global impression of severity
PG	plasma glucose
PK	Pharmacokinetic
PRO	patient reported outcome
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
s.c.	Subcutaneous
SF-36	Short Form 36
SUSAR	suspected unexpected serious adverse reaction
T2D	type 2 diabetes
TBI	Toe-brachial index
TIA	transient ischemic attack
TMM	trial materials manual
V	Visit
VascuQoL-6	VascuQoL-6 questionnaire
W	Week
WIQ	Walking impairment questionnaire
WOCBP	woman of child bearing potential

10.10 Appendix 10: Protocol amendment history

The Protocol amendment summary of changes table for the current protocol version is located directly before the table of contents.

Protocol version 6.0 (06 June 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 offer optional pre-screening for potential study participants in selected countries, to determine eligibility for the study based on ankle-brachial-index (ABI) and/or toe-brachial index (TBI), either by measurement of ABI and/or TBI or by review of medical records.

Section # and name	Description of change	Rationale
Section 10.8: Country/Region-specific requirements – Optional pre-screening	*Section 10.8.1 Optional pre-screening* New subsection added with description of optional pre-screening to determine eligibility based on ABI and/or TBI in selected countries	To ease the screening process for sites and participants

Protocol version 5.0 (15 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 clarify trial-related procedures and to address local requirements in India.

Section # and name	Description of change	Rationale
Section 2.3 Benefit-risk assessment	Text added: *or any updates thereof*	For correctness

Section # and name	Description of change	Rationale
Section 2.3.1 Risk assessment, Table 2-1	Angioedema added under allergic reactions	To align with the investigator's brochure where the risk of angioedema has been included based on post-marketing reports and to align with the labelling of other marketed GLP-1 RAs
Section 5.1 Inclusion criterion 6	'~~85.8 mmol/mol~~' changed to '*86 mmol/mol*' Footnote added: *If based on central laboratory, both National Glycohemoglobin Standardization Program (NGSP) and International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) need to be within limit*	To align with industry standard for conversion between NGSP and IFCC To clarify process and prevent protocol deviations due to unclarity
Section 5.2 Exclusion criterion #6	Updated to include a reference to country-specific requirements for India	To accommodate local requirements in India
Section 5.2 Exclusion criterion #11	Updated to include a reference to country-specific requirements for India	To accommodate local requirements in India
Section 5.4 Screen failures	Text deleted: '~~, and any serious adverse event (SAE).~~'	To align with flowchart and clarify SAEs should not be reported for screen failures
Section 8.1.1 Treadmill assessments	Text changed from '~~specific protocol~~' to '*study manual*'	To clarify the wording of the study manual describing the treadmill assessments
Section 8.1.2 Patient Reported Outcome (PRO) questionnaires	Text changed from '~~Post-baseline assessments'~~ to '*PRO questionnaires*'	To ensure consistency in administering PROs prior to other visit-related activities
Section 8.1.5.1 Pulse and blood pressure	Text added: *First time blood pressure is assessed (V1) it should be performed at both arms*. The arm with the highest blood	To clarify process for blood pressure measurement

Section # and name	Description of change	Rationale
	measurement should be used *for all future measurements*. Text deleted: '~~the mean of~~' Text added: *The eCRF will calculate the mean of the last 2 measurements.*	To align with the eCRF where the mean pulse rate is calculated automatically after recording of the last 2 measurements
Section 10.8 (Appendix 8) Country/region-specific requirements	Requirements for India updated to include imaging as part of the screening procedure. Accordingly, echocardiography and digital x-ray of the foot should be performed according to local practice during screening.	To accommodate local requirements in India
Section 10.9 (Appendix 9) Abbreviations	Abbreviations added for NGSP and IFCC	For correctness

Protocol version 4.0 (27 May 2021)

This amendment is considered to be non-substantial for all countries 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.

Overall rationale for preparing protocol, version 4.0

To facilitate recruitment in the trial, selected inclusion and exclusion criteria have been amended and the potential of rescreening of subjects has been introduced.

Section # and name	Description of change	Rationale
Section 1.1 Synopsis and Section 5.1, Inclusion criterion #2.	Country-specific requirements for age added for Taiwan	To align with Section 10.8
Section 1.2 Flowchart	Visit window between screening (visit 1) and baseline (visit 2) revised from ~~±7 days~~ to *-7; +13 days.* Footnote added: *Visit 1 should be at least 2 weeks prior to visit 2 in*	To clarify process and prevent protocol deviations due to unclarity.

Section # and name	Description of change	Rationale
	the subset of patients included in the activity tracker substudy.	
Section 1.2 Flowchart	Footnote added: *Inclined treadmill assessment must be done twice at V2.*	To clarify process and prevent protocol deviations due to unclarity
Section 1.2 Flowchart	Footnote added: *Sample can be omitted if HbA_{1c} criterion is based on historical data obtained within 90 days prior to screening*	To clarify process and prevent protocol deviations due to unclarity
Section 2.3.1, Risk assessment; Table 2-1, Potential risks of clinical significance.	Risk of COVID-19 infection in relation to treatment omitted from table.	Any risks in relation to COVID-19 treatment will be presented in the IB for the investigators to follow.
Section 5.1 Inclusion criterion #6	Lower HbA_{1c} limit removed from criterion. Furthermore, it has been specified that criterion can be based on values obtained at screening or within 90 days prior to screening.	To facilitate recruitment. The primary objective of the trial is to assess the effect of semaglutide on PAD disease. Removing the lower limit of HbA_{1c}, and thereby allowing a better controlled T2D diabetes population, is considered not to impact trial objective or results.
Section 5.1 Inclusion criterion 4d)	Alignment of number of decimals of ABI and TBI included in criterion.	To align with worksheets and EDC where we are requesting rounding to two decimals
Section 5.2 Exclusion criteria	Text added: *Furthermore, exclusion criterion #12 (renal impairment) may be based on assessment of*	To clarify that criterion can be based on laboratory samples taken at screening visit (V1).

Section # and name	Description of change	Rationale
	eGFR by central laboratory.	
Section 5.2 Exclusion criterion #2	Previous participation changed from '~~signed informed consent~~' to *'randomisation'*	To enable rescreening.
Section 5.2, Exclusion criterion #4, Section 7.1, Treatment discontinuation criterion #3 and Appendix 8 (Section 10.8), country/region-specific requirements	Note added that *co-participation in COVID-19 trials are not allowed* in China and Japan	To comply with country/region-specific requirement
Section 5.2 Exclusion criterion 5	DDP-4 inhibitors omitted from criterion.	To facilitate recruitment. There are no data supporting a clear benefit of DPP-4i on CV risk. Given that the endpoints defined in this trial is related to atherosclerosis, the use of DPP-4i is assessed to have minimal effect on trial results.
Section 5.2 Exclusion criterion #12	Renal impairment ~~measured as~~ *based on latest available measurements/evaluation prior to randomisation (visit 2). Renal impairment can be diagnosed based on an* estimated Glomerular Filtration Rate (eGFR) value of eGFR< 30 mL/ min/1.73 m^2 (measured within last six months) as defined by KDIGO 2012[2] *or* chronic or intermittent haemodialysis or peritoneal dialysis.	To clarify that criteria should be evaluated based on the latest available assessment,
Section 5.4 Screen failure	Criteria for rescreening of subjects added	To facilitate recruitment

Section # and name	Description of change	Rationale
Section 6.5 Concomitant medication	DPP-4 inhibitors omitted from disallowed medication	To reflect SoC treatment
Section 8.1.2 Patient Reported Outcomes (PRO) questionnaires	Text added: *PRO questionnaires will be assessed at baseline (V2), at 6 months visit (V6) and at end-of-treatment (Visit 8/8A). Post-baseline assessments are to be performed prior to other visit-related activities.*	To clarify that post-baseline assessments is to be performed prior to other visit-related activities.
Section 8.1.5.2 ABI and TBI	Note added that calculation should be based on 2 measurements.	To clarify process and prevent protocol deviations due to unclarity.
Section 8.5 Pharmacokinetics	Text added: *PK samples will not be taken in China.*	To comply with protocol version 3.
Section 10.1.1 Regulatory and ethical considerations, and Section 10.8 (Appendix 8) Country/region-specific requirements	Text added: *Protocol, protocol amendments, informed consent form and investigator's brochure, must be also submitted, reviewed, and approved by the regulatory authorities before the trial is initiated.*	To comply with requirements in Latvia.
Section 10.6 (Appendix 6): Retention of human biosamples	Reference to Section 10.7 removed from paragraph regarding country-specific requirements	Reference added in error
Section 10.8 (Appendix 8) Country/region-specific requirements	Text added: *PK samples will not be taken in China. Co-participation in COVID-19 trials are not allowed.*	To comply with requirements in China.
Section 10.8 (Appendix 8), Country/region-specific requirements	Text added: *PK samples will not be taken in China. Co-participation in COVID-19 trials are not allowed.*	To comply with protocol version 3.

Protocol version 3.0 (18 November 2020)

This amendment is considered to be substantial for all countries 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. This amendment is not applicable in China.

Overall rationale for preparing protocol, version 3

Due to the COVID-19 pandemic the exclusion and discontinuation criteria have been amended to allow for simultaneous participation in trials with the primary objective of evaluating an approved or non-approved investigational medicinal product for prevention or treatment of COVID-19 disease or COVID-19 postinfectious conditions.

Additional blood sampling will be included for PK assessment. Plasma semaglutide concentrations will be used to describe the exposure-response analysis. PK samples will not be taken in China.

Section # and name	Description of change	Rationale
Section 1.1 Synopsis	Addition of "severe varicose veins" to Key exclusion criterion #2; IMP name corrected in Treatment group and duration	For clarification
Section 1.2 Flowchart	Correction of minor errors and addition of "Semaglutide plasma concentration" row	For clarification and to account for inclusion of PK samples
Section 5.2 Exclusion criteria	Addition to exclusion criterion #4 *Simultaneous participation in a trial with the primary objective of evaluating an approved or non-approved investigational medicinal product for prevention or treatment of COVID-19 disease or COVID-19 postinfectious conditions is allowed if the last dose of the investigational medicinal product has been received more	To allow for co-participation in COVID-19 trials

Section # and name	Description of change	Rationale
	than 30 days before screening.	
Section 5.2 Exclusion criteria	Addition of "severe varicose veins" to exclusion criterion #6	For clarification
Section 6.1 Preparation/handling/storage/accountability	Minor text revision	For clarification
Section 6.2 Treatments administered, Table 6-1	IMP name corrected	For clarification
Section 6.5 Concomitant medication	Text included for collection of COVID-19 concomitant medication	To specify that medication(s) in relation to a clinical trial for COVID-19 prevention or treatment as well as approved COVID-19 vaccine must be recorded
Section 7.1 Discontinuation of trial treatment	Text added to discontinuation criterion #3 and Ad 3 *Simultaneous participation in a trial with the primary objective of evaluating an approved or non-approved investigational medicinal product for prevention or treatment of COVID-19 disease or COVID-19 postinfectious conditions is allowed at the investigator discretion without discontinuing trial product.	To allow for co-participation in a COVID-19 trial
Section 8 Trial assessments and procedures	Text added to criterion #7 regarding country specific requirements	Collection of patient contact information not relevant for BE
Section 8.2 Safety assessments	Addition of COVID-19 in-text	To include COVID-19 to the concomitant illness/medical history

Section # and name	Description of change	Rationale
		that should be reported in the eCRF
Section 8.3 Adverse events and serious adverse events	Text regarding COVID-19 AEs included	To describe the procedure for collection of COVID-19 AEs
Section 8.5 Pharmacokinetics	Section added	To describe the procedure for collection of blood samples for PK assessment
Section 9.5 Pharmacokinetic modelling	Section added	To describe the exposure-response analysis, based on plasma semaglutide concentrations and the efficacy and safety results
Section 10.1.7 Dissemination of clinical trial data	Correction of trial duration (54 days corrected to 54 weeks)	For clarification
Section 10.2 Appendix 2, Table 10-1	Addition of PK sampling to efficacy laboratory assessments	To comply with additions to Sections 8.5 and 9.5
Section 10.3.5 Reporting of SAEs, Figure 10-1	Figure updated to include COVID-19 AEs	To describe the procedure for collection of COVID-19 AEs
Section 10.8 Appendix 8: Country/ region-specific requirements	Text added regarding country-specific requirements	Collection of contact information for persons other than the patient not relevant for Belgium
Section 10.9 Appendix 9: Abbreviations	Addition of COVID-19 and PK	For clarification

Protocol version 2.0 (28 September 2020)

This amendment is considered to be substantial for Hungary and Czech Republic 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.

Overall rationale for preparing protocol, version 2

The overall rationale for this local protocol amendment is to comply with requirements of the Czech health authorities to include more frequent pregnancy reporting for WOCBP, and to comply with requirements of the Hungarian health authorities to include presence or history of pancreatitis to the exclusion criteria.

Section # and name	Description of change	Rationale
Section 1.2, Flowchart	Footnote d) updated with reference to Appendix 8 for specific requirements for pregnancy testing for Czech Republic.	To comply with request from Czech health authorities.
Section 5.2, Exclusion criteria	Updated with an additional exclusion criterion (#17, for Hungary only): Presence or history of pancreatitis (acute or chronic).	To comply with request from Hungarian health authorities.
Section 10.8 (Appendix 8), Country/region-specific requirements	Requirement for additional pregnancy testing of WOCBP from Czech Republic at week 4, 8 and 12 added.	To comply with request from Czech health authorities.
Section 10.8 (Appendix 8), Country/region-specific requirements	Presence or history of pancreatitis has been added as an exclusion criterion, for Hungary only.	To comply with request from Hungarian health authorities.

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