ORIGINAL ARTICLE

Oral Semaglutide and Cardiovascular Outcomes in High-Risk Type 2 Diabetes

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ABSTRACT

BACKGROUND

The cardiovascular safety of oral semaglutide, a glucagon-like peptide 1 receptor agonist, has been established in persons with type 2 diabetes and high cardiovascular risk. An assessment of the cardiovascular efficacy of oral semaglutide in persons with type 2 diabetes and atherosclerotic cardiovascular disease, chronic kidney disease, or both is needed.

METHODS

In this double-blind, placebo-controlled, event-driven, superiority trial, we randomly assigned participants who were 50 years of age or older, had type 2 diabetes with a glycated hemoglobin level of 6.5 to 10.0%, and had known atherosclerotic cardiovascular disease, chronic kidney disease, or both to receive either once-daily oral semaglutide (maximal dose, 14 mg) or placebo, in addition to standard care. The primary outcome was major adverse cardiovascular events (a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke), assessed in a time-to-first-event analysis. The confirmatory secondary outcomes included major kidney disease events (a five-point composite outcome).

RESULTS

Among the 9650 participants who had undergone randomization, the mean (±SD) follow-up was 47.5±10.9 months, and the median follow-up was 49.5 months. A primary-outcome event occurred in 579 of the 4825 participants (12.0%; incidence, 3.1 events per 100 person-years) in the oral semaglutide group, as compared with 668 of the 4825 participants (13.8%; incidence, 3.7 events per 100 person-years) in the placebo group (hazard ratio, 0.86; 95% confidence interval, 0.77 to 0.96; P=0.006). The results for the confirmatory secondary outcomes did not differ significantly between the two groups. The incidence of serious adverse events was 47.9% in the oral semaglutide group and 50.3% in the placebo group; the incidence of gastrointestinal disorders was 5.0% and 4.4%, respectively.

CONCLUSIONS

Among persons with type 2 diabetes and atherosclerotic cardiovascular disease, chronic kidney disease, or both, the use of oral semaglutide was associated with a significantly lower risk of major adverse cardiovascular events than placebo, without an increase in the incidence of serious adverse events. (Funded by Novo Nordisk; SOUL ClinicalTrials.gov number, NCT03914326.)

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This article was published on March 29, 2025, at NEJM.org.

DOI: 10.1056/NEJMoa2501006

Approximately 828 million adults worldwide are affected by diabetes,[1] with type 2 diabetes accounting for more than 90% of cases.[2] Type 2 diabetes is associated with a high risk of cardiovascular disease.[3,4] Trials designed to assess cardiovascular outcomes in persons with type 2 diabetes have shown that certain glucagon-like peptide 1 (GLP-1) receptor agonists and certain sodium–glucose cotransporter 2 (SGLT2) inhibitors reduce the risk of major adverse cardiovascular events.[5-7]

Semaglutide is a long-acting GLP-1 receptor agonist. For the injectable formulation of semaglutide, cardiovascular efficacy has been established in persons with type 2 diabetes and cardiovascular disease or a high risk of cardiovascular disease, as well as in those with type 2 diabetes and chronic kidney disease.[5,8,9] For the oral formulation of semaglutide, cardiovascular safety has been established in persons with type 2 diabetes and high cardiovascular risk,[10] but an assessment of cardiovascular efficacy is needed. The Semaglutide Cardiovascular Outcomes Trial (SOUL) was designed to assess the cardiovascular efficacy of oral semaglutide in persons with type 2 diabetes and established atherosclerotic cardiovascular disease, chronic kidney disease, or both.

Methods

Trial Design and Oversight

We conducted an international, double-blind, randomized, placebo-controlled, event-driven, superiority phase 3b trial. The trial design has been described previously[11] and is summarized in Figure S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org.

The trial was overseen by an academic-led steering committee (a list of members is provided in the Supplementary Appendix) in partnership with the trial sponsor, Novo Nordisk, which managed trial operations. The trial steering committee provided overall leadership, oversaw the design and conduct of the trial and the analysis of the data, and was responsible for reporting the results. Data analysis was conducted by the sponsor, and the analyses of the primary and confirmatory secondary outcomes were independently verified by Statogen Consulting. All the authors had access to summary results from the analyzed data set, contributed to the writing of the manuscript, and made the decision to submit the manuscript for publication. Medical writing and editorial support was funded by the sponsor. All the authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol, available at NEJM.org.

Trial Participants

Persons were eligible for inclusion in the trial if they were 50 years of age or older and had type 2 diabetes, a glycated hemoglobin level of 6.5 to 10.0%, and at least one of the following conditions: coronary artery disease, cerebrovascular disease, symptomatic peripheral artery disease, or chronic kidney disease (defined by an estimated glomerular filtration rate [eGFR] of <60 ml per minute per 1.73 m^2).[11] Persons who had end-stage kidney disease or had received long-term kidney-replacement therapy were excluded. The full inclusion and exclusion criteria are provided in the Supplementary Appendix. All the participants provided written informed consent.

Trial Procedures

After completion of a screening visit, participants were randomly assigned in a 1:1 ratio to receive once-daily oral semaglutide or matching placebo, in addition to standard care. The dose-escalation regimen for oral semaglutide is described in Figure S1; the dose was started at 3 mg and was escalated to 7 mg and then 14 mg. The 14-mg dose was to be maintained until the end of treatment, with dose reductions, extensions of dose-escalation intervals, and treatment pauses allowed if needed to mitigate treatment-associated adverse events. Treatment was to be continued until the end of the trial, when the target number of primary-outcome events had occurred. Standard care consisted of glucose-lowering and cardiovascular risk–reducing therapies administered in accordance with local guidelines.

Participants were instructed to take the semaglutide or placebo tablet in the morning, in a fasting state, with up to 120 ml of water and to wait at least 30 minutes before taking food, drink, or other oral medications. Trial visits occurred at 4, 8, and 13 weeks after randomization and approximately every 13 weeks thereafter. Details regarding the visit schedule and assessments have been described previously.[11] The trial observation period was defined as the time from randomization until the end-of-trial visit or the participant's death,

the date of last contact, or the date of participant withdrawal.

TRIAL OUTCOMES

The primary outcome was major adverse cardiovascular events (a three-point composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke), assessed in an analysis of the time from randomization to the first event. The confirmatory secondary outcomes were three time-to-first-event outcomes tested in hierarchical order: major kidney disease events (a five-point composite of death from cardiovascular causes, death from kidney-related causes, a persistent reduction from baseline in the eGFR of ≥50% as measured with the Chronic Kidney Disease Epidemiology Collaboration method,[12] a persistent eGFR of <15 ml per minute per 1.73 m^2, or the initiation of long-term kidney-replacement therapy with either dialysis or transplantation); death from cardiovascular causes; and major adverse limb events (a two-point composite of hospitalization for acute limb ischemia or hospitalization for chronic limb ischemia).

Supportive secondary outcomes included time-to-first-event outcomes such as heart failure events (a three-point composite of death from cardiovascular causes, an urgent visit for heart failure, or hospitalization for heart failure), death from any cause, fatal or nonfatal myocardial infarction, fatal or nonfatal stroke, and severe hypoglycemic episodes. Measures of metabolism and inflammation were assessed; the change from baseline to week 104 for each of these measures was a prespecified secondary outcome. Adverse events and serious adverse events were reported. Details regarding the efficacy and safety outcomes are provided in the Supplementary Appendix. Potential cardiovascular and kidney-related outcome events and selected adverse events were assessed by means of central adjudication, which was performed with the use of standard outcome definitions by an external adjudication committee whose members were unaware of the randomized group assignments.[13]

STATISTICAL ANALYSIS

For this event-driven trial, we estimated that a sample of 9642 participants would provide the trial with 90% power to detect a 17% lower risk of a primary-outcome event in the oral semaglutide group than in the placebo group at an overall one-sided significance level of 0.025. The sample-size estimate was based on the following assumptions: a primary-outcome event occurring in 3.5% of the participants per year in the placebo group, a trial duration of 5 years 5 weeks, and withdrawal or loss to follow-up occurring in 1% of the participants in each group.[11] One interim analysis for superiority was prespecified to occur when two thirds of the total planned number of primary-outcome events had accrued. The target number of primary-outcome events was at least 1225.

Efficacy analyses were performed in the intention-to-treat population, which included all the individual participants who had undergone randomization, regardless of adherence to oral semaglutide or placebo or changes to background medications. Data from the participants who withdrew from the trial, died, or were lost to follow-up were censored at the time of withdrawal, death, or last contact, respectively.

For the time-to-first-event outcomes, hazard ratios and 95% confidence intervals were calculated with the use of a Cox proportional-hazards model with randomized group assignment as a fixed factor. For the primary outcome, the hazard ratio, 95% confidence interval, and P value were adjusted on the basis of the group sequential design with the use of likelihood-ratio ordering.[14] If superiority with respect to the primary outcome was established for oral semaglutide, the confirmatory secondary outcomes were to be evaluated in hierarchical order; a significant effect of oral semaglutide had to be shown at each step before the next outcome could be tested for significance. To account for the results from the prespecified interim analysis and to preserve the studywise one-sided type 1 error at 2.5%, the nominal significance level was calculated with the Lan–DeMets alpha-spending function for the primary and confirmatory secondary outcomes.[15] Although the statistical analysis plan specified that one-sided P values would be used for hypothesis testing, two-sided P values are reported here.

To investigate the effect of the assumption of independent censoring of data for participants who were withdrawn or lost to follow-up, a two-way tipping-point analysis and analyses with multiple imputation of event times for participants who were withdrawn or lost to follow-up were performed as sensitivity analyses. Consistency of

the treatment effect with respect to the primary outcome was explored in analyses of subgroups defined according to information obtained at baseline (age, sex, race, ethnic group, region, body-mass index, glycated hemoglobin level, medical history, eGFR, and medication use). The trial was not powered to compare the treatment effect across subgroups. Confidence intervals for supportive secondary outcomes were not adjusted for multiplicity and therefore cannot be used for hypothesis testing. Details regarding the interim analysis and the analyses of secondary outcomes are provided in the Supplementary Appendix. All statistical analyses were performed with SAS software, version 9.4 TS1M5 (SAS Institute).

RESULTS

PARTICIPANTS

From June 2019 through March 2021, a total of 9650 persons underwent randomization at 444 sites in 33 countries, with 4825 participants randomly assigned to each trial group (Table 1). The mean (±SD) age of the participants was 66.1±7.6 years, and 28.9% were women. Most participants had a history of cardiovascular disease (coronary artery disease in 70.7%, heart failure in 23.1%, cerebrovascular disease in 21.2%, and peripheral artery disease in 15.7%), and 42.4% had a history of chronic kidney disease. In both trial groups, 26.9% of the participants were receiving SGLT2 inhibitors at baseline. A full description of participant characteristics and medications used at baseline is provided in Table S1, and the representativeness of the trial population is summarized in Table S2.

The disposition of the participants is shown in Figure S2. The mean follow-up was 47.5±10.9 months, the median follow-up was 49.5 months (interquartile range, 44.0 to 54.9), and 9495 participants (98.4%) completed the trial, having died or attended the end-of-trial visit. Vital status was available for 99.5% of the participants. Participants received oral semaglutide or placebo for 87.4% of the total possible duration (86.5% in the oral semaglutide group and 88.4% in the placebo group). Treatment with an open-label GLP-1 receptor agonist during the trial (a protocol violation) was initiated in 172 participants (3.6%) in the oral semaglutide group and in 253 participants (5.2%) in the placebo group. The distribution of participants who were receiving the 3-mg, 7-mg, and 14-mg doses of oral semaglutide or placebo over time is summarized in Figure S3A. Premature permanent discontinuation of oral semaglutide or placebo occurred in 1309 participants (27.1%) in the oral semaglutide group and in 1373 participants (28.5%) in the placebo group (Fig. S3B).

PRIMARY AND CONFIRMATORY SECONDARY OUTCOMES

A primary-outcome event occurred in 579 of the 4825 participants (12.0%; incidence, 3.1 events per 100 person-years) in the oral semaglutide group, as compared with 668 of the 4825 participants (13.8%; incidence, 3.7 events per 100 person-years) in the placebo group (hazard ratio, 0.86; 95% confidence interval [CI], 0.77 to 0.96; P=0.006), results that showed the superiority of oral semaglutide over placebo (Fig. 1A and Table 2). In a prespecified analysis of primary-outcome events occurring through week 156 (3 years), the absolute risk reduction (difference in risk between the oral semaglutide group and the placebo group) was 2.0 percentage points, and the number needed to treat to prevent one event in this population was 50 persons (95% CI, 31 to 125). The effect of oral semaglutide with respect to the primary outcome was consistent across prespecified sensitivity analyses (Table S3) and appeared to be consistent across most analyses of prespecified subgroups, including those defined according to age, sex, body-mass index, a history of cardiovascular or kidney disease, eGFR, and medication use at baseline (Fig. S4).

A total of 301 participants (6.2%) in the oral semaglutide group and 320 participants (6.6%) in the placebo group died from cardiovascular causes (hazard ratio, 0.93; 95% CI, 0.80 to 1.09) (Fig. 1B). Nonfatal myocardial infarction occurred in 191 participants (4.0%) in the oral semaglutide group and in 253 participants (5.2%) in the placebo group (hazard ratio, 0.74; 95% CI, 0.61 to 0.89) (Fig. 1C), and nonfatal stroke occurred in 144 (3.0%) and 161 (3.3%), respectively (hazard ratio, 0.88; 95% CI, 0.70 to 1.11) (Fig. 1D).

For the first confirmatory secondary outcome in the hierarchy (major kidney disease events), an event occurred in 403 participants (8.4%; incidence, 2.1 events per 100 person-years) in the oral semaglutide group, as compared with 435 participants (9.0%; incidence, 2.3 events per 100 person-years) in the placebo group (hazard ratio, 0.91; 95% CI, 0.80 to 1.05; P=0.19) (Fig. 1E).

Table 1. Characteristics of the Participants at Baseline.*

Characteristic	Oral Semaglutide (N=4825)	Placebo (N=4825)
Age — yr	66.1±7.6	66.1±7.5
Female sex — no. (%)	1376 (28.5)	1414 (29.3)
Race or ethnic group — no. (%)†		
White	3327 (69.0)	3321 (68.8)
Black	124 (2.6)	128 (2.7)
Asian	1134 (23.5)	1121 (23.2)
American Indian or Alaska Native	7 (0.1)	12 (0.2)
Native Hawaiian or Pacific Islander	4 (<0.1)	5 (0.1)
Other	185 (3.8)	192 (4.0)
Not reported	44 (0.9)	46 (1.0)
Hispanic or Latino ethnic group — no. (%)†	674 (14.0)	706 (14.6)
Body weight — kg	87.5±19.1	88.3±19.6
Body-mass index‡	31.0±5.7	31.2±5.9
Glycated hemoglobin level — mmol/mol	63.6±12.6	63.5±12.3
Glycated hemoglobin level — %	8.0±1.2	8.0±1.1
Median duration of diabetes (IQR) — yr	14.7 (9.0–20.8)	14.6 (8.9–20.8)
History of cardiovascular or kidney disease — no. (%)§		
Cardiovascular disease only	2730 (56.6)	2738 (56.7)
Chronic kidney disease only	632 (13.1)	609 (12.6)
Both cardiovascular and chronic kidney disease	1303 (27.0)	1317 (27.3)
Hypertension — no. (%)	4378 (90.7)	4381 (90.8)
Current smoking — no. (%)	545 (11.3)	584 (12.1)
Systolic blood pressure — mm Hg	134.6±16.3	134.7±16.4
Diastolic blood pressure — mm Hg	76.6±10.1	76.7±10.1
Pulse — beats/min	72.8±11.1	72.9±11.4
Median high-sensitivity C-reactive protein level (IQR) — mg/liter	2.0 (0.9–4.3)	2.0 (0.9–4.5)
eGFR — ml/min/1.73 m^2¶	74.0±22.6	73.6±22.6

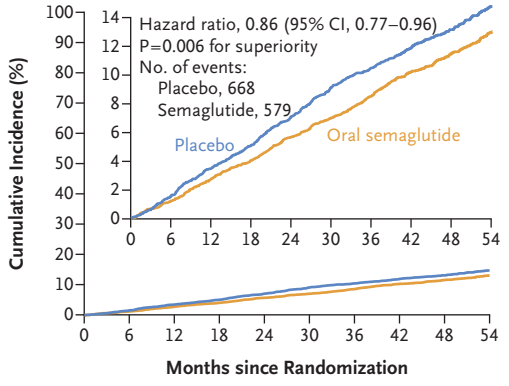
* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. A full description of participant characteristics and medications used at baseline is provided in Table S1. The abbreviation eGFR denotes estimated glomerular filtration rate, and IQR interquartile range.
† Race and ethnic group were reported by the participant.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ For 3.3% of the participants, whether only one criterion or two criteria were fulfilled was unknown. Chronic kidney disease was defined by an eGFR of less than 60 ml per minute per 1.73 m^2; the most recent eGFR available in the medical record was used if it had been obtained within the previous 6 months.
¶ The eGFR was measured at randomization with the use of the Chronic Kidney Disease Epidemiology Collaboration method.[12]

Among the five components of this composite outcome, death from cardiovascular causes accounted for 71.2% of the events, whereas 28.8% were kidney-related events. The remaining two confirmatory secondary outcomes in the hierarchy were not tested for significance: death from cardiovascular causes (hazard ratio, 0.93; 95% CI, 0.80 to 1.09) (Fig. 1B) and major adverse limb events (hazard ratio, 0.71; 95% CI, 0.52 to 0.96) (Fig. 1F).

SUPPORTIVE SECONDARY OUTCOMES

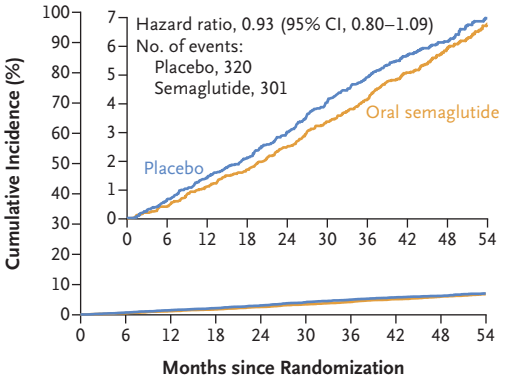
The results for additional efficacy outcomes are summarized in Table 2. The hazard ratio (oral

A Major Adverse Cardiovascular Events



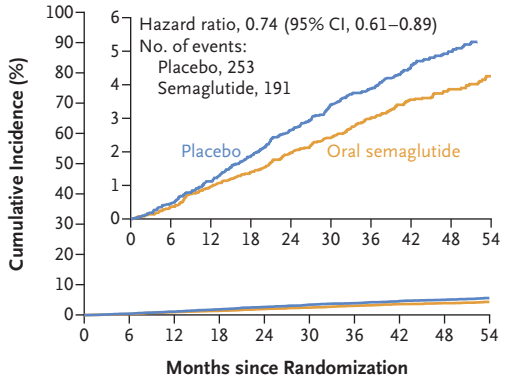
No. at Risk										
Placebo	4825	4718	4583	4455	4322	4194	4101	3727	2517	1346
Oral semaglutide	4825	4743	4635	4542	4438	4346	4239	3831	2555	1346

B Death from Cardiovascular Causes



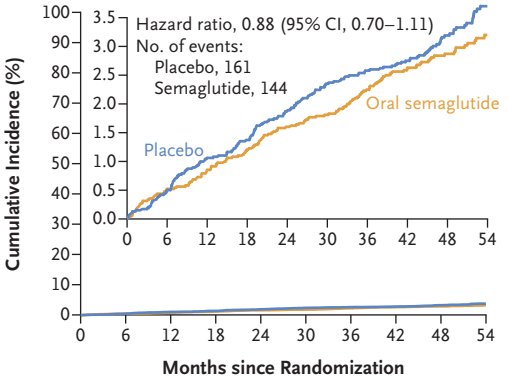
No. at Risk										
Placebo	4825	4760	4680	4594	4511	4427	4355	3991	2721	1460
Oral semaglutide	4825	4781	4712	4648	4583	4509	4436	4040	2727	1460

C Nonfatal Myocardial Infarction



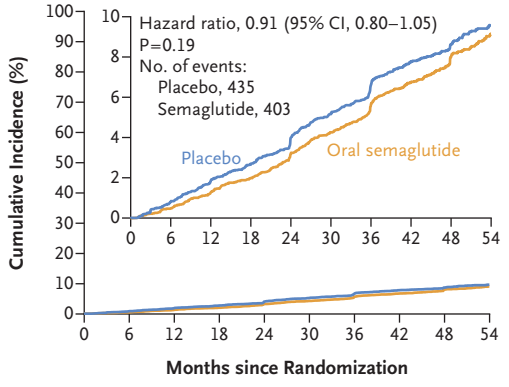
No. at Risk										
Placebo	4825	4739	4631	4511	4395	4284	4197	3821	2595	1390
Oral semaglutide	4825	4766	4672	4593	4505	4416	4322	3922	2638	1394

D Nonfatal Stroke



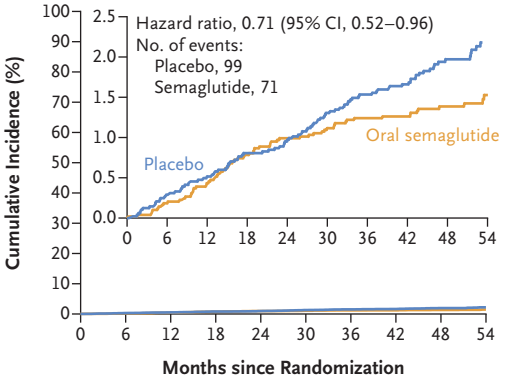
No. at Risk										
Placebo	4825	4739	4631	4533	4432	4330	4254	3890	2636	1412
Oral semaglutide	4825	4758	4675	4595	4513	4434	4346	3943	2640	1408

E Major Kidney Disease Events



No. at Risk										
Placebo	4825	4753	4661	4570	4469	4378	4282	3911	2658	1429
Oral semaglutide	4825	4778	4704	4636	4551	4469	4372	3973	2681	1430

F Major Adverse Limb Events



No. at Risk										
Placebo	4825	4746	4655	4459	4470	4376	4296	3940	2678	1436
Oral semaglutide	4825	4772	4691	4612	4540	4463	4388	3999	2696	1439

Figure 1 (facing page). Time-to-First-Event Efficacy Outcomes.

Cumulative-incidence plots are shown for the primary outcome: major adverse cardiovascular events (Panel A), a three-point composite of death from cardiovascular causes (Panel B), nonfatal myocardial infarction (Panel C), or nonfatal stroke (Panel D). Cumulative-incidence plots are also shown for the confirmatory secondary outcomes, which were tested in hierarchical order: major kidney disease events (Panel E), death from cardiovascular causes (Panel B), and major adverse limb events (Panel F). The major kidney disease events outcome is a five-point composite of death from cardiovascular causes, death from kidney-related causes, a persistent reduction from baseline in the estimated glomerular filtration rate (eGFR) of 50% or more as measured with the Chronic Kidney Disease Epidemiology Collaboration method, a persistent eGFR of less than 15 ml per minute per 1.73 m^2, or the initiation of long-term kidney-replacement therapy with either dialysis or transplantation. The major adverse limb events outcome is a two-point composite of hospitalization for acute limb ischemia or hospitalization for chronic limb ischemia. Two-sided P values are shown. Because the results for the first confirmatory secondary outcome were not significant, the results for the two subsequent confirmatory secondary outcomes in the testing hierarchy are reported as point estimates and 95% confidence intervals. The x axis is truncated at 54 months because of the limited number of participants in the trial after that time point. The insets show the same data on an enlarged y axis.

semaglutide vs. placebo) for heart failure events was 0.90 (95% CI, 0.79 to 1.03); for death from any cause, 0.91 (95% CI, 0.80 to 1.02); for fatal or nonfatal myocardial infarction, 0.73 (95% CI, 0.61 to 0.88); and for fatal or nonfatal stroke, 0.95 (95% CI, 0.76 to 1.17).

The change from baseline to week 104 in the mean glycated hemoglobin level was −0.71 percentage points with oral semaglutide and −0.15 percentage points with placebo (estimated difference, −0.56 percentage points; 95% CI, −0.61 to −0.52) (Fig. 2A); the trial population was also receiving standard care that could include glycemia treatment. The change from baseline to week 104 in the mean body weight was −4.22 kg with oral semaglutide and −1.27 kg with placebo (estimated difference, −2.95 kg; 95% CI, −3.18 to −2.73) (Fig. 2B). The high-sensitivity C-reactive protein level was lower in the oral semaglutide group than in the placebo group at baseline, and the difference persisted over time (geometric mean level at week 104, 1.56 vs. 2.01 mg per liter) (Fig. 2C).

A total of 88 episodes of severe hypoglycemia occurred in the oral semaglutide group, and 121 episodes occurred in the placebo group (mean ratio, 0.73; 95% CI, 0.50 to 1.07). These episodes occurred in 76 participants (1.6%) and 84 participants (1.7%), respectively; in an analysis of the time to the first episode, the hazard ratio was 0.90 (95% CI, 0.66 to 1.22).

SAFETY OUTCOMES

Serious adverse events were reported in 2312 participants (47.9%) in the oral semaglutide group and in 2427 participants (50.3%) in the placebo group (P=0.02). The most common serious adverse events were cardiac disorders (occurring in 861 [17.8%] and 954 [19.8%], respectively) and infections or infestations (occurring in 726 [15.0%] and 797 [16.5%]). Gastrointestinal disorders were more common with oral semaglutide than with placebo (occurring in 239 [5.0%] and 210 [4.4%], respectively). The difference between the trial groups in the incidence of gallbladder disorders, retinal disorders, or malignant neoplasms ranged from 0.4 to 0.8 percentage points (22 to 38 events). Acute pancreatitis occurred in 0.4% of the participants in both groups.

Adverse events that led to permanent discontinuation of oral semaglutide or placebo occurred in 749 participants (15.5%) in the oral semaglutide group and in 559 participants (11.6%) in the placebo group. Such events were mainly gastrointestinal disorders (in 310 [6.4%] and 98 [2.0%], respectively), as well as infections or infestations (in 63 [1.3%] and 96 [2.0%]). Additional adverse events that led to permanent discontinuation of the trial regimen were specified as other (in 6.6% and 7.9%) and as unintentional (in 2.9% and 4.0%). Death from noncardiovascular causes occurred in 227 participants (4.7%) receiving oral semaglutide and in 257 participants (5.3%) receiving placebo. A summary of safety events is shown in Table S4.

DISCUSSION

Oral semaglutide was associated with a significantly lower risk of major adverse cardiovascular events than placebo, with a hazard ratio of 0.86 (corresponding to a relative risk reduction of 14%), among persons with type 2 diabetes and atherosclerotic cardiovascular disease, chronic kidney disease, or both. These results show a cardiovas-

Table 2. Primary and Secondary Efficacy Outcomes.*

Outcome	Oral Semaglutide (N=4825)		Placebo (N=4825)		Hazard Ratio (95% CI)	P Value†
	no. of participants with event (%)	*no. of events per 100 person-yr*	*no. of participants with event (%)*	*no. of events per 100 person-yr*		
Primary outcome						
Major adverse cardiovascular events, three-point composite‡	579 (12.0)	3.1	668 (13.8)	3.7	0.86 (0.77–0.96)	0.006
Confirmatory secondary outcomes						
Major kidney disease events, five-point composite§	403 (8.4)	2.1	435 (9.0)	2.3	0.91 (0.80–1.05)	0.19
Death from cardiovascular causes	301 (6.2)	1.6	320 (6.6)	1.7	0.93 (0.80–1.09)	—
Major adverse limb events, two-point composite¶	71 (1.5)	0.4	99 (2.1)	0.5	0.71 (0.52–0.96)	—
Supportive secondary outcomes						
Major adverse cardiovascular events, five-point composite‖	670 (13.9)	3.6	777 (16.1)	4.3	0.84 (0.76–0.93)	—
Nonfatal myocardial infarction	191 (4.0)	1.0	253 (5.2)	1.4	0.74 (0.61–0.89)	—
Fatal or nonfatal myocardial infarction	200 (4.1)	1.1	268 (5.6)	1.4	0.73 (0.61–0.88)	—
Nonfatal stroke	144 (3.0)	0.8	161 (3.3)	0.9	0.88 (0.70–1.11)	—
Fatal or nonfatal stroke	164 (3.4)	0.9	171 (3.5)	0.9	0.95 (0.76–1.17)	—
Coronary revascularization	200 (4.1)	1.1	263 (5.5)	1.4	0.75 (0.62–0.90)	—
Hospitalization for unstable angina pectoris	74 (1.5)	0.4	80 (1.7)	0.4	0.92 (0.67–1.26)	—
Death from any cause	528 (10.9)	2.8	577 (12.0)	3.0	0.91 (0.80–1.02)	—
Death from noncardiovascular causes	227 (4.7)	1.2	257 (5.3)	1.4	0.87 (0.73–1.04)	—
Heart failure events, three-point composite**	405 (8.4)	2.1	443 (9.2)	2.4	0.90 (0.79–1.03)	—
Heart failure	146 (3.0)	0.8	167 (3.5)	0.9	0.86 (0.69–1.08)	—
Major kidney disease events, four-point composite††	112 (2.3)	0.6	129 (2.7)	0.7	0.86 (0.66–1.10)	—
Death from kidney-related causes	1 (<0.1)	<0.1	7 (0.1)	<0.1	0.14 (0.01–0.79)	—
Severe hypoglycemic episode	76 (1.6)	0.5	84 (1.7)	0.6	0.90 (0.66–1.22)	—

* Time-to-first-event outcomes are shown for the intention-to-treat population (all the individual participants who had undergone randomization) during the trial observation period. All the outcomes were analyzed with the use of a Cox proportional-hazards model with randomized group assignment as a categorical fixed factor. Confidence intervals for supportive secondary outcomes were not adjusted for multiplicity and therefore cannot be used for hypothesis testing. Data from participants without events of interest were censored at the end of their trial observation period.

† Two-sided P values are shown. After accounting for the results from the interim analysis, the nominal two-sided significance level for the primary outcome was 0.04561. The nominal two-sided significance level for the first confirmatory secondary outcome was 0.04433.

‡ As the primary outcome, the major adverse cardiovascular events outcome is a three-point composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.

§ As the first confirmatory secondary outcome, the major kidney disease events outcome is a five-point composite of death from cardiovascular causes, death from kidney-related causes, a persistent reduction from baseline in the eGFR of 50% or more as measured with the Chronic Kidney Disease Epidemiology Collaboration method, a persistent eGFR of less than 15 ml per minute per 1.73 m^2, or the initiation of long-term kidney-replacement therapy with either dialysis or transplantation.

¶ The major adverse limb events outcome is a two-point composite of hospitalization for acute limb ischemia or hospitalization for chronic limb ischemia.

‖ As a supportive secondary outcome, the major adverse cardiovascular events outcome is a five-point composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina.

** The heart failure events outcome is a three-point composite of death from cardiovascular causes, an urgent visit for heart failure, or hospitalization for heart failure.

†† As a supportive secondary outcome, the major kidney disease events outcome is a four-point composite of death from kidney-related causes, a persistent reduction from baseline in the eGFR of 50% or more as measured with the Chronic Kidney Disease Epidemiology Collaboration method, a persistent eGFR of less than 15 ml per minute per 1.73 m^2, or the initiation of long-term kidney-replacement therapy with either dialysis or transplantation.

cular benefit of oral semaglutide and are consistent with results reported for injectable semaglutide and other GLP-1 receptor agonists with established cardiovascular efficacy.[8,9]

Among the three components of the primary outcome, nonfatal myocardial infarction had the largest difference in risk between the oral semaglutide group and the placebo group. This finding contrasts with results from PIONEER 6, a noninferiority trial investigating the use of oral semaglutide in persons with type 2 diabetes and high cardiovascular risk, in which a reduction in the risk of death from cardiovascular causes was the dominant beneficial effect.[10] Of note, the mean duration of follow-up and the sample size in SOUL (47.5 months and 9650 participants, respectively) were approximately three times those in PIONEER 6 (15.8 months and 3183 participants). Overall, the reduction in the risk of a primary-outcome event in SOUL is in keeping with observations in other trials assessing cardiovascular outcomes associated with GLP-1 receptor agonists.[5,7]

The results for all three confirmatory secondary outcomes were directionally consistent with the results for the primary outcome, but a significant effect was not observed for the first outcome in the hierarchy (major kidney disease events), and thus statistical testing was stopped at the second step. Among the five components of the first confirmatory secondary outcome, death from cardiovascular causes accounted for 71.2% of the events. The results for this composite outcome in SOUL (hazard ratio, 0.91; 95% CI, 0.80 to 1.05; P=0.19) differed from those seen in FLOW (hazard ratio, 0.76; 95% CI, 0.66 to 0.88; P=0.0003), a trial investigating injectable semaglutide administered once weekly at a dose of 1.0 mg in persons with type 2 diabetes and chronic kidney disease.[9]

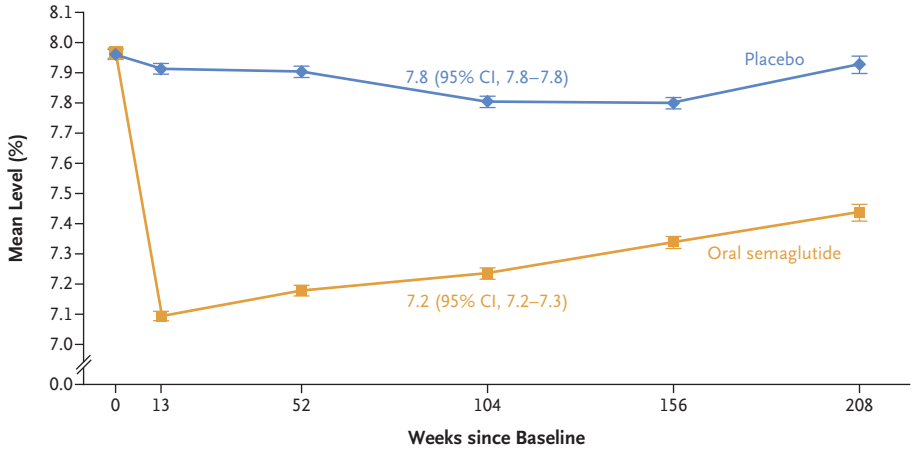
The difference between these two trials in the risk of major kidney disease events may be due to chance, or it could be related to population characteristics (baseline eGFR, 47.0 ml per minute per 1.73 m^2 in FLOW vs. 73.8 ml per minute per 1.73 m^2 in SOUL). In addition, the difference in bioavailability between subcutaneous semaglutide administered once weekly at a dose of 1 mg (89%) and oral semaglutide administered once daily at a dose of 14 mg (0.4 to 1%) may be a factor.[16,17] However, the option to have an efficacious oral GLP-1 receptor agonist is relevant to patients' preference for oral over injectable diabetes medication[18] and aims to alleviate concerns about injections among patients and clinicians.[19]

The overall safety profile of oral semaglutide in SOUL was consistent with that seen in previous trials of semaglutide,[20] and no new safety signals were observed. The incidence of serious adverse events was lower among participants receiving oral semaglutide than among those receiving placebo, a difference that was mostly due to the higher incidence of cardiac disorders and infections or infestations in the placebo group. The incidence of adverse events that led to discontinuation of oral semaglutide or placebo was higher among participants receiving oral semaglutide, a difference that was largely due to gastrointestinal symptoms. Gastrointestinal events are known to occur with GLP-1 receptor agonists, particularly during treatment initiation and dose escalation.[21]

The strengths of this trial include its large sample size and long follow-up duration. The effect of oral semaglutide with respect to cardiovascular outcomes appeared to be consistent across age-based subgroups and consistent with the effect observed in trials of injectable semaglutide, although direct comparisons cannot be made outside the context of a comparative-effectiveness trial. The effect of oral semaglutide with respect to the primary outcome appeared to be larger among participants with glycated hemoglobin levels higher than 8% than among those with lower glycated hemoglobin levels and also appeared to be larger among participants in certain regions (particularly Asia). It should be noted that the trial was not powered to compare the treatment effect across subgroups, and the effect appeared to be consistent across all other subgroups. Furthermore, the cardioprotective effect of oral semaglutide was seen in a population with high concomitant use of cardiovascular protective drugs, including SGLT2 inhibitors.

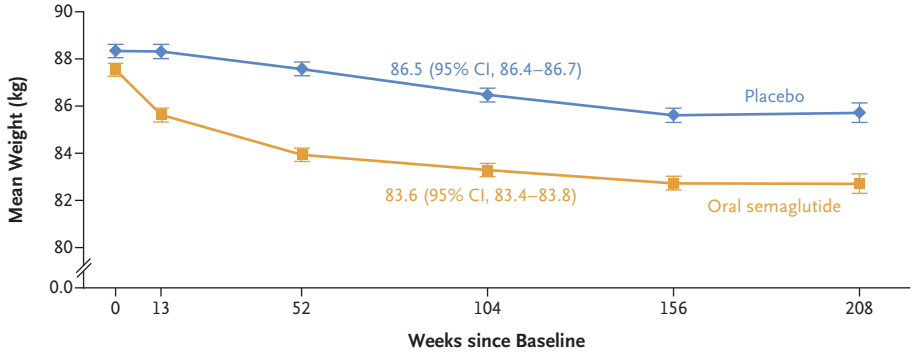
Among limitations of this trial was the inclusion criterion of a history of cardiovascular disease, chronic kidney disease, or both, which was designed to enrich the trial population for assessing the effect of oral semaglutide. Although this inclusion criterion resulted in a trial population that was not representative of the global population with type 2 diabetes, approximately 32% of persons with type 2 diabetes have cardiovascular disease,[22] and an estimated 25 to 40%

A Glycated Hemoglobin Level



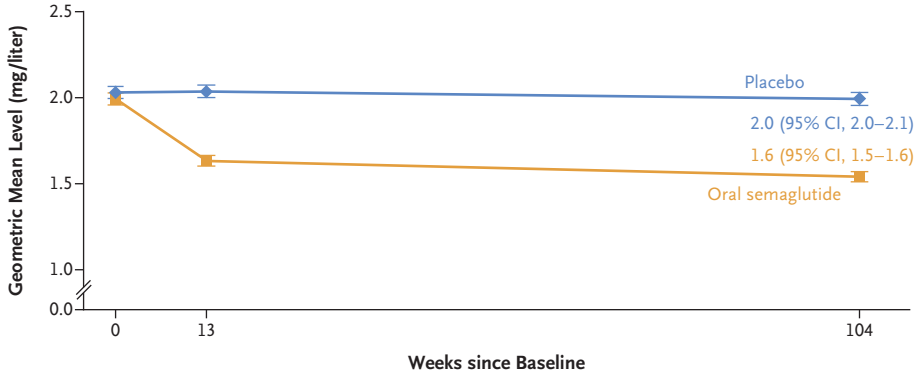
No. at Risk						
Placebo	4749	4497	4355	4065	3837	2057
Oral semaglutide	4736	4525	4386	4144	3985	2155

B Body Weight



No. at Risk						
Placebo	4820	4322	4350	4159	3897	2100
Oral semaglutide	4819	4336	4371	4255	4022	2183

C High-Sensitivity C-Reactive Protein Level



No. at Risk			
Placebo	4791	4546	4119
Oral semaglutide	4786	4583	4200

Figure 2 (facing page). Measures of Metabolism and Inflammation.

Shown are the observed mean glycated hemoglobin level (Panel A), mean body weight (Panel B), and geometric mean high-sensitivity C-reactive protein level (Panel C) for the intention-to-treat population (all the individual participants who had undergone randomization) during the trial observation period. The change from baseline to week 104 for each of these measures was a prespecified secondary outcome. I bars indicate standard errors.

have chronic kidney disease.[23] In addition, as seen in other trials assessing cardiovascular outcomes, the trial population was not fully representative of the overall global population in terms of demographic characteristics, particularly because only 28.9% of enrolled participants were women and only 2.6% identified as Black (Table S1); 9.5% of the participants enrolled in the United States identified as Black. Type 2 diabetes is more likely to affect Black persons than White persons, and the risk of cardiovascular disease and the associated mortality are higher among women than men.[24,25] Finally, the effects of oral semaglutide with respect to kidney-related outcomes could not be clarified.

In this randomized, placebo-controlled trial involving persons with type 2 diabetes and atherosclerotic cardiovascular disease, chronic kidney disease, or both, daily oral semaglutide was superior to placebo in reducing the risk of major adverse cardiovascular events.

Supported by Novo Nordisk.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank Sonia Vyskocilova, Ph.D., for providing medical writing support on earlier drafts of the manuscript, including the first draft, under the direction of the authors; Beverly La Ferla, M.Res., and Helen Marshall, B.A., of Ashfield MedComms (an Inizio company) for providing editorial support on earlier drafts; and Karoline Liisberg, M.Sc., of Novo Nordisk for providing statistical support.

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Supplementary Appendix

Supplement to: McGuire DK, Marx N, Mulvagh SL, et al. Oral semaglutide and cardiovascular outcomes in high-risk type 2 diabetes. N Engl J Med. DOI: 10.1056/NEJMoa2501006

This appendix has been provided by the authors to give readers additional information about the work.

SUPPLEMENTARY APPENDIX

Supplement to: Darren K. McGuire, Nikolaus Marx, Sharon L. Mulvagh, et al. ***Oral Semaglutide and Cardiovascular Outcomes in High-Risk Type 2 Diabetes***

This appendix has been provided by the authors to give readers additional information about the work.

TABLE OF CONTENTS

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Trial Organization and Oversight

The trial protocol was developed in partnership with the trial sponsor, Novo Nordisk (Søborg, Denmark), and the academic steering committee. A global expert panel of physician leaders in participating countries advised on regional operational challenges. National and institutional regulatory and ethical authorities approved the protocol, and all participants provided written informed consent. An independent data monitoring committee reviewed unblinded efficacy and safety data. The SAP was prepared by Novo Nordisk along with the academic steering committee (SAP finalized on 14 December 2022 as version 2). Novo Nordisk maintained the clinical database and performed the statistical analyses. Statogen Consulting (Research Triangle Park, NC, USA) had

received all relevant study tabulation data model (STDM) datasets and performed an independent review and statistical analysis of data pertaining to the primary and confirmatory outcomes. The academic authors had input into how data were analyzed and access to summary results from the analyzed datasets, as well as to the certification by Statogen Consulting validating the statistical analyses performed by the sponsor. This manuscript was reviewed and edited by all authors. The sponsor reviewed the manuscript and provided suggested revisions, but the final decision on content was reserved for the academic authors with no restrictions on the right to publish. All authors approved the final submission. All authors vouch for the completeness and accuracy of the data and all analyses and the fidelity to the trial protocol and statistical analysis plan (available online at NEJM.org).

Eligibility Criteria

Inclusion

- Male or female, aged 50 years or above at the time of signing informed consent
- Diagnosed with type 2 diabetes according to the criteria of American Diabetes Association[1]
- Glycated hemoglobin levels 6.5%–10.0% or 47–86 mmol/mol (both inclusive; latest available and no more than 30-day-old local laboratory assessment based on medical records or point of care measurement)
- At least one of the below conditions (a–d):
    a. Coronary artery disease, defined as at least one of the following:
        i. Prior myocardial infarction
        ii. Prior coronary revascularization procedure
        iii. ≥50% stenosis in ≥1 coronary artery documented by cardiac catheterization or computerized tomography coronary angiography
        iv. Coronary artery disease with ischemia documented by stress test with any imaging modality

b. Cerebrovascular disease defined as at least one of the following:
    i. Prior stroke
    ii. Prior carotid artery revascularization procedure
    iii. ≥50% stenosis in carotid artery documented by X-ray angiography, magnetic resonance angiography, computerized tomography angiography, or Doppler ultrasound
c. Symptomatic peripheral artery disease defined as at least one of the following:
    i. Intermittent claudication with an Ankle-brachial index below 0.85 at rest
    ii. Intermittent claudication with a ≥50% stenosis in peripheral artery (excluding carotid) documented by X-ray angiography, magnetic resonance angiography, computerized tomography angiography, or Doppler ultrasound
    iii. Prior peripheral artery (excluding carotid) revascularization procedure
    iv. Lower extremity amputation at or above ankle due to atherosclerotic disease (excluding e.g. trauma or osteomyelitis)
d. Chronic kidney disease defined as estimated glomerular filtration rate (eGFR) below 60 ml/min/1.73 m^2 (based on medical records using latest available and no more than 6-month-old assessment)

Exclusion

- Known or suspected hypersensitivity to trial product or related products
- Previous participation in this trial (defined as randomization)
- Pregnancy, breast-feeding, or intention to become pregnant, or being of child-bearing potential and not using a highly effective contraception
- Participation in any clinical trial of an approved or nonapproved investigational medicinal product within 30 days before screening

    - Simultaneous participation in a trial of investigational medicinal product for prevention or treatment of coronavirus disease (COVID-19) or postinfectious conditions was allowed, if the last dose has been received more than 30 days before screening

- Any of the following: myocardial infarction, stroke, hospitalization for unstable angina pectoris, or transient ischemic attack within the past 60 days prior to the day of screening
- Planned coronary, carotid, or peripheral artery revascularization known on the day of screening
- Heart failure presently classified as being in New York Heart Association Class IV
- Treatment with any glucagon-like peptide-1 receptor agonist within 30 days before screening
- History of major surgical procedures involving the stomach that may affect drug absorption
- Uncontrolled and potentially unstable diabetic retinopathy or maculopathy (documented by a retinal examination required within 90 days before screening or in the period between screening and randomization)
- Presence or history of malignant neoplasm within 5 years prior to screening. Basal and squamous cell skin cancer and any carcinoma in situ was allowed
- Personal or first-degree relative(s) history of multiple endocrine neoplasia 2 or medullary thyroid cancer
- End-stage kidney disease or long-term or intermittent hemodialysis or peritoneal dialysis
- History of major surgical procedures involving the stomach or small intestine potentially affecting absorption of drugs and/or nutrients, as judged by the investigator

Prespecified Trial Efficacy Outcomes

The primary outcome was major adverse cardiovascular events, a 3 -point composite, assessed in a time-to-first-event analysis of the first occurrence of any component:

- Death from cardiovascular cause
- Nonfatal myocardial infarction
- Nonfatal stroke

Confirmatory secondary outcomes were assessed in time-to-first-event analyses and tested in hierarchical order:

- Major kidney disease events, a 5-point composite of:
    - Death from cardiovascular cause
    - Death from kidney cause
    - Onset of persistent ≥50% reduction in eGFR (CKD-EPI) compared with baseline
    - Onset of persistent eGFR (CKD-EPI) below 15 ml/min/1.73 m^2
    - Initiation of long-term kidney replacement therapy (dialysis or kidney transplantation)
- Death from cardiovascular cause
- A major adverse limb event composite of:
    - Acute limb ischemia hospitalization
    - Chronic limb ischemia hospitalization

Supportive secondary outcomes were not controlled for multiplicity.

From randomization to end of trial:

- Time to first occurrence of an expanded major adverse cardiovascular events, a 5-point composite consisting of:
    - Death from cardiovascular cause

    - Nonfatal myocardial infarction
    - Nonfatal stroke
    - Coronary revascularization
    - Unstable angina requiring hospitalization
- Time to first occurrence of a composite heart failure outcome consisting of:
    - Death from cardiovascular cause
    - Heart failure requiring hospitalization
    - Urgent heart failure visit
- Time to first occurrence of a 4-point major kidney disease events composite consisting of:
    - Death from kidney cause
    - Onset of persistent ≥50% reduction in eGFR (CKD-EPI) compared with baseline
    - Onset of persistent eGFR (CKD-EPI) <15 ml/min/1.73 m^2
    - Initiation of long-term kidney replacement therapy (dialysis or kidney transplantation)
- Time to occurrence of all-cause death
- Time to first occurrence of nonfatal myocardial infarction
- Time to first occurrence of nonfatal stroke
- Time from randomization to first occurrence of heart failure requiring hospitalization or urgent heart failure visit
- Time to first occurrence of coronary revascularization
- Time to first occurrence of unstable angina requiring hospitalization
- Time to occurrence of death from kidney cause
- Time to first occurrence of onset of persistent ≥50% reduction in eGFR (CKD-EPI) compared with baseline
- Time to first occurrence of onset of persistent eGFR (CKD EPI) <15 ml/min/1.73 m^2

- Time to first occurrence of initiation of long-term kidney replacement therapy (dialysis or kidney transplantation)
- Time to first occurrence of a composite outcome consisting of:
    - All-cause death
    - Nonfatal myocardial infarction
    - Nonfatal stroke
- Time to first occurrence of acute limb ischemia requiring hospitalization
- Time to first occurrence of chronic limb ischemia requiring hospitalization
- Number of severe hypoglycemic episodes
- Time to first occurrence of a severe hypoglycemic episode

From randomization to end of treatment

- Annual rate of change in eGFR (CKD-EPI), ml/min/1.73 m^2 per year (total eGFR slope)

From randomization to 2 years (visit 12)

- Change in glycated hemoglobin level, percentage points
- Change in body weight, kg
- Change in high-sensitivity C-reactive protein, mg/l

Outcome Definitions – General Considerations

Definition of cardiovascular death[2]

Cardiovascular death includes death resulting from an acute MI, sudden cardiac death, death due to heart failure, death due to stroke, death due to cardiovascular procedures, death due to cardiovascular hemorrhage, death due to other cardiovascular causes, and death not attributable to one of the categories of cardiovascular death or to a non-cardiovascular cause (undetermined cause of death).

Definition of acute myocardial infarction[2,3]

The term myocardial infarction (MI) should be used when there is evidence of acute myocardial necrosis in a clinical setting consistent with myocardial ischemia. In general, the diagnosis of MI requires the combination of:

- Evidence of myocardial necrosis (either changes in cardiac biomarkers or postmortem pathological findings) ***AND***
- Supporting information derived from the clinical presentation, electrocardiographic changes, or the results of myocardial or coronary artery imaging.

The totality of the clinical, electrocardiographic, and cardiac biomarker information should be considered to determine whether or not an MI has occurred. Specifically, timing and trends in cardiac biomarkers and electrocardiographic information require careful analysis. The adjudication of MI should also take into account the clinical setting in which the event occurs. MI may be adjudicated for an event that has characteristics of an MI, but which does not meet the strict definition because biomarker or electrocardiographic results are not available.

Definition of stroke[2,4-6]

Stroke is defined as an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction. Persistence of

symptoms is an acceptable indicator of acute infarction. In the absence of brain imaging studies, new neurological symptoms lasting ≥24 hours should be considered a stroke event.

Subdural hematomas are intracranial hemorrhagic events and not strokes. Additionally, traumatic intracranial hemorrhages are not considered to be strokes.

Definition of a coronary revascularization[2]

A coronary revascularization event is a percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery designed to improve myocardial blood flow. The outcome of the revascularization is not relevant, and both successful and unsuccessful revascularization attempts should be confirmed as coronary revascularization procedures. The coronary revascularization outcome in SOUL only included coronary revascularization for acute coronary syndrome.

PCI is defined as the placement of an angioplasty guide wire, balloon, or other device (e.g., stent, atherectomy catheter, brachytherapy delivery device, or thrombectomy catheter) into a native coronary artery or coronary artery bypass graft for the purpose of mechanical coronary revascularization. In the assessment of the severity of coronary lesions with the use of intravascular ultrasound, coronary flow reserve, or fractional flow reserve, insertion of a guide wire will NOT be considered PCI.

CABG surgery is defined as a procedure performed to bypass partially or completely occluded coronary arteries with veins and/or arteries harvested from elsewhere in the body, thereby improving the blood supply to the coronary circulation supplying the myocardium.

Definition of unstable angina requiring hospitalization[2,3]

- Ischemic discomfort (angina, or symptoms thought to be equivalent) at rest, or in an accelerating pattern with frequent episodes associated with progressively decreased exercise capacity ***AND***
- An unscheduled hospitalization within 24 hours of the most recent symptoms ***AND***

- Ischemic electrocardiogram changes ***OR*** imaging evidence of myocardial ischemia ***OR*** angiographic evidence of new or worse ≥70% lesion (≥50% for left main lesion) and/or thrombus in an epicardial coronary artery that is believed to be responsible for the myocardial ischemic symptoms/signs ***OR*** the need for a coronary revascularization procedure (PCI or CABG) ***AND***
- Negative cardiac biomarkers and no evidence of acute MI.

Definition of death from kidney cause[7]

Death from kidney cause is defined as a non-cardiovascular death that is due to the direct consequences of severely impaired kidney function. A kidney-related death is the consequence of insufficient or no kidney replacement therapy where this would have been indicated, e.g., patients declining kidney replacement therapy, kidney replacement therapy not being available, kidney replacement therapy being considered futile by both physician and patient, or death occurring before kidney replacement therapy could be implemented when it was indicated or death due to complications of kidney replacement therapy.

Definition of initiation of long-term kidney replacement therapy (dialysis or transplantation)[8]

Long-term kidney replacement therapy is defined as any form of long-term dialysis (e.g., hemodialysis or peritoneal dialysis) or receiving a kidney transplant.

- Long-term is defined as at least 4 weeks of intermittent dialysis treatment. The 4-week criterion can be deviated from, if a competing risk arises (often death of the patient) that shortens the period the patient would otherwise have been on kidney replacement therapy.

Evidence of a reversible cause underlying the need for kidney replacement therapy must be absent.

Definition of heart failure[2,9]

A heart failure event includes hospitalizations and urgent outpatient visits for heart failure.

Heart failure hospitalization

The patient is admitted to the hospital (for at least 24 hours) with a primary diagnosis of heart failure with documented new or worsening symptoms due to heart failure on presentation and the patient has objective evidence of new or worsening heart failure (physical findings and/or laboratory evidence or invasive diagnostic evidence) and increase in or initiation of appropriate treatment.

Urgent heart failure visit

The patient has an urgent, unscheduled office/practice or emergency department visit for a primary diagnosis of heart failure, but not meeting the criteria for a heart failure hospitalization.

Supplementary Statistical Methods

SOUL was an event-driven trial, with trial closure planned upon reaching the targeted number (≥1225) of primary outcome events. One interim analysis for superiority regarding the primary outcome was prespecified to occur when two-thirds of the total planned number of primary outcome events had accrued. Interim testing evaluating the primary outcome for superiority was performed based on locked snapshot of the study database at the time point of an interim testing. Participants without a primary outcome event prior to the analysis cut-off date were censored with the censoring date defined as the first of in-trial end-date and analysis cut-off date. Interim testing was performed by a statistician independent of trial conduct and external to Novo Nordisk. The data monitoring committee evaluated the unblinded interim testing using the group sequential stopping boundaries as guidance. Stopping the trial for superiority was allowed if a stopping boundary was crossed and the data monitoring committee would make the decision to recommend early trial termination. The data monitoring committee performed this interim assessment on June 7, 2023, based on 841 primary outcome events accrued, and recommended a continuation of the trial without modification.

Final database lock occurred on September 19, 2024, at which time 1247 primary outcome events had been positively adjudicated. Alpha spend for the primary endpoint at the interim analysis was 0.00683 (one-sided). If superiority was established for the primary outcome, the superiority hypothesis was to be tested for each of the confirmatory secondary outcomes under multiplicity control via a stagewise hierarchical testing scheme using the below order:

1. Time from randomization to first occurrence of 5-point major kidney disease events composite event
2. Time from randomization to death from cardiovascular cause
3. Time from randomization to first occurrence of major adverse limb event

To account for the prespecified interim analysis, and to preserve the one-sided type 1 error at 2.5%, nominal significance levels for the primary and confirmatory secondary outcomes were

calculated with the Lan—DeMets alpha spending function,[10] approximating the O'Brien-Fleming's stopping boundaries accounting for the group sequential design (interim analysis). The one-sided alpha spending function is given by

$$g(t) = \min [\alpha * t^{0.7668}, \alpha]$$

where t is the proportion of information included in the analysis for the primary outcome and α is the overall one-sided alpha of 2.5%.

The P values (unadjusted) for the primary and confirmatory secondary outcomes were compared to the one-sided nominal significance level derived from the alpha spending function for the outcome. If the P value was below the limit, superiority had been shown. The testing procedure was stopped the first time an analysis failed to confirm superiority of the outcome in question using the one-sided nominal significance level.

The nominal significance level used for testing was based on the exact number of events available at interim and final analysis. Thus, for the primary and each of the confirmatory secondary outcomes, the nominal significance level was updated based on the exact number of accrued events.

In case of superiority for the primary outcome, the results were to be adjusted for the group sequential design using the likelihood ratio ordering. No adjustment of results for the confirmatory secondary outcomes due to the group sequential design was done.

Continuous supportive secondary outcomes (changes from baseline to week 104) were assessed by analysis of covariance, with 500 multiple imputations for missing values under a missing-at-random assumption. An imputation model (linear regression) is estimated separately for each treatment group including baseline value as a covariate and fitted to subjects having an observed data point at year 2. Participants without a baseline measurement were not a part of the model. The fitted model was used to impute values for all subjects with missing data at 2 years. Missing data were defined as data planned to be collected according to protocol but are not present in the database. Hence, data that are absent from the database due to death or administrative censoring were not considered missing and hence not imputed. Secondary outcomes were not adjusted for

multiplicity, hence CIs are reported. To evaluate the impact of the pre-specified multiple imputation scheme used, supplementary analyses were done using an alternative imputation scheme where all available data were used to impute missing values using a Missing At Random assumption while alive and last observation (measured or imputed) were carried forward for all visits missed due to prior death. These supplementary analyses provided similar results compared to the pre-specified analyses.

Nominal significance levels for primary and confirmatory secondary outcomes at the final analysis

Outcome	**One-sided**	**Two-sided**
3-point cardiovascular composite	0.02281	0.04561
5-point major kidney disease events composite	0.02216	0.04433
Death from cardiovascular cause	0.02245	0.04489
Major adverse limb event composite	0.02267	0.04534

Unadjusted results for the primary outcome

Outcome	**Hazard ratio (95% CI)**	**P value**
Primary 3-point cardiovascular composite*	0.85 (0.76–0.95)	0.0020

*Data not adjusted for the group sequential design.

Safety Data Collection and Adverse Event Reporting

An external event adjudication committee performed ongoing adjudication of predefined cardiovascular events and other selected adverse events in an independent and blinded manner.

The SOUL trial applied a targeted approach to collection of safety data focusing on serious adverse events, adverse events leading to discontinuation of trial product, and other selected adverse events.

The following events were systematically collected from the day of randomization until the end-of-trial visit:

Overall safety profile:

- Serious adverse events:
    - Acute kidney failure
    - Hepatic disorders
    - Allergic reactions
    - Abuse and misuse
    - Rare events
    - Suspected transmission of an infectious agent
- Other events, irrespective of seriousness:
    - Adverse evets leading to permanent trial product discontinuation
    - All-cause death

Protocol-specified safety focus areas:

- Acute gallbladder disease
- Acute pancreatitis
- Diabetic retinopathy
- Malignant neoplasms

- Severe hypoglycemia
- Medication errors
- COVID-19

Other

- Vital signs
- Lab parameters
- Pregnancies

SUPPLEMENTARY TABLES

Table S1. Baseline characteristics (full)

	Oral semaglutide (n = 4825)	Placebo (n = 4825)
Age — years	66.1 (7.6)	66.1 (7.5)
Sex — n (%)		
Male	3449 (71.5)	3411 (70.7)
Female	1376 (28.5)	1414 (29.3)
Race — n (%)		
White	3327 (69.0)	3321 (68.8)
Black or African American	124 (2.6)	128 (2.7)
Asian	1134 (23.5)	1121 (23.2)
American Indian or Alaska Native	7 (0.1)	12 (0.2)
Native Hawaiian/Pacific Islander	4 (<0.1)	5 (0.1)
Other	185 (3.8)	192 (4.0)
Not reported	44 (0.9)	46 (1.0)
Ethnicity — n (%)		
Hispanic/Latino	674 (14.0)	706 (14.6)
Body weight — kg	87.5 (19.1)	88.3 (19.6)
Body mass index — kg/m^2	31.0 (5.7)	31.2 (5.9)
Glycated hemoglobin level — mmol/mol	63.6 (12.6)	63.5 (12.3)
Glycated hemoglobin level — %	8.0 (1.2)	8.0 (1.1)
Duration of diabetes — years, median (IQR)	14.7 (9.0–20.8)	14.6 (8.9–20.8)
History of cardiovascular disease — n (%)		
Coronary artery disease	3406 (70.6)	3415 (70.8)
Myocardial infarction	1944 (40.3)	1917 (39.7)
Coronary revascularization	2591 (53.7)	2607 (54.0)
Coronary artery stenosis ≥50%	2059 (42.7)	2043 (42.3)

Cerebrovascular disease		
Stroke	743 (15.4)	745 (15.4)
Ischemic	584 (12.1)	601 (12.5)
Hemorrhagic	40 (0.8)	46 (1.0)
Transient ischemic attack	203 (4.2)	224 (4.6)
Carotid artery stenosis ≥50%	329 (6.8)	324 (6.7)
Carotid arterial revascularization	139 (2.9)	147 (3.0)
Peripheral arterial disease	771 (16.0)	744 (15.4)
Heart failure	1105 (22.9)	1124 (23.3)
History of chronic kidney disease — n (%)*	2041 (42.3)	2051 (42.5)
Hypertension — n (%)	4378 (90.7)	4381 (90.8)
Current smoking — n (%)	545 (11.3)	584 (12.1)
Vital signs		
Systolic blood pressure —mm Hg	134.6 (16.3)	134.7 (16.4)
Diastolic blood pressure —mm Hg	76.6 (10.1)	76.7 (10.1)
Pulse — beats/min	72.8 (11.1)	72.9 (11.4)
Lipids — mmol/l, median (IQR)		
Total cholesterol	3.9 (3.3–4.6)	3.8 (3.3–4.6)
LDL cholesterol	1.9 (1.4–2.5)	1.8 (1.4–2.4)
HDL cholesterol	1.1 (0.9–1.3)	1.1 (0.9–1.3)
Triglycerides	1.8 (1.3–2.5)	1.8 (1.3–2.5)
High-sensitivity CRP — mg/l, median (IQR)	2.0 (0.9–4.3)	2.0 (0.9–4.5)
eGFR — ml/min/1.73 m^2 (CKD-EPI method[11])†	74.0 (22.6)	73.6 (22.6)
eGFR — ml/min/1.73 m^2, n (%)†		
End-stage kidney disease (<15)	7 (0.1)	4 (<0.1)
≥15 to <30	113 (2.3)	114 (2.4)
≥30 to <45	474 (9.8)	475 (9.8)
≥45 to <60	811 (16.8)	818 (17.0)

≥60 to <90	1845 (38.2)	1903 (39.4)
≥90	1531 (31.7)	1472 (30.5)
Cardiovascular-related medication at baseline — n (%)		
Lipid-lowering medication	4275 (88.6)	4297 (89.1)
Antiplatelet medication	3718 (77.1)	3727 (77.2)
Beta-blocker	3104 (64.3)	3097 (64.2)
Diuretic	2006 (41.6)	2058 (42.7)
ACE inhibitor	1990 (41.2)	1992 (41.3)
ARB	1814 (37.6)	1883 (39.0)
Calcium channel blocker	1762 (36.5)	1810 (37.5)
Anticoagulant medication	458 (9.5)	464 (9.6)
ARNI	17 (0.4)	18 (0.4)
Glucose-lowering medication at baseline — n (%)		
Metformin	3651 (75.7)	3675 (76.2)
Insulins	2476 (51.3)	2413 (50.0)
Sulfonylureas	1386 (28.7)	1434 (29.7)
SGLT2 inhibitors	1296 (26.9)	1300 (26.9)
DPP-4 inhibitors	1094 (22.7)	1141 (23.6)
Thiazolidinediones	225 (4.7)	188 (3.9)
α-glucosidase inhibitors	87 (1.8)	114 (2.4)
GLP-1 RAs and GIP GLP-1 RAs	0 (0.0)	2 (<0.1)
Other	70 (1.5)	53 (1.1)

Data are mean±SD unless otherwise stated. Concomitant therapies could be adjusted during the trial. Initiation of open-label treatment with a GLP-1 RA was prohibited.

*Chronic kidney disease was defined as eGFR <60 ml/min/1.73 m^2 based on medical records using the latest available ≤6 months old assessment.

†Measured at randomization.

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; CKD-EPI, The Chronic Kidney Disease Epidemiology Collaboration; CRP, C-reactive protein; DPP-4, dipeptidyl peptidase-4;

eGFR, estimated glomerular filtration rate; GIP, gastric inhibitory polypeptide; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; SD, standard deviation; SGLT2, sodium-glucose co-transporter-2.

Table S2. Representativeness of Study Participants

Category	
Disease problem, or condition under investigation	All participants in SOUL had T2D and either atherosclerotic cardiovascular disease, CKD, or both. T2D affected an estimated 828 million adults aged over 18 years in 2022, representing an increase of 630 million since 1990.[12] Approximately 32% of the global population with T2D also have CVD.[13] In the Framingham Heart Study, the lifetime (30-year) risk of CVD among women with diabetes was 54.8% and 78.8% among those with normal weight and obesity, respectively. For men with diabetes, the risk was 78.6% and 86.9%, respectively.[14] The prevalence of CKD among people with diabetes is at least 25%, with 40% estimated to develop CKD in their lifetime.[15] Thus, there is a large disease burden of cardiovascular and kidney-related comorbidities in people with T2D.
Sex and gender	T2D prevalence is increasing in both sexes.[16] In 2021, slightly more men (10.8%) than women (10.2%) were diagnosed with diabetes (difference of 17.7 million).[17] Men seem to have higher prevalence of stroke, myocardial infarction, angina pectoris, heart failure, and coronary artery disease than women; however, overall CVD rates are similar for both sexes (approximately 27%).[13] Women having a greater relative risk of CVD and associated mortality than men.[16] The prevalence of CKD stage 3–5 has been reported to be higher in women, while men have a higher prevalence of CKD stages 1–2 owing to albuminuria.[18]
Age	The prevalence of diabetes increases with age, from 2.2% in adults aged 20–24 years, to an estimated 24.0% in adults aged 75–79 years (2021 data).[17]
Race or ethnic group	T2D disproportionately affects Black, Asian, and Hispanic people compared with White individuals.[19-21]

Geography	Between 1990 and 2022, the largest increases in diabetes prevalence were in low-income and middle-income countries in south and southeast Asia, the Middle East and north Africa, and Latin America and the Caribbean.[12] The lowest prevalence in the world in 2022 was in western Europe and east Africa for both sexes, and in Japan and Canada for women.[12] The prevalence of diabetes is higher in urban than in rural areas (12.1% in urban and 8.3% in rural areas, respectively, in 2021).[17]
Other considerations	There was a high comorbidity burden in the SOUL trial, as participants with CVD and/or CKD were enriched in order to be able to show a treatment effect of oral semaglutide within a reasonable time frame. Thus, the prevalence of CVD and CKD in the trial population is higher than that of general population of people with T2D.
Overall representativeness of this trial	The SOUL trial does not duplicate a globally representative population with T2D and CVD/CKD, but it does offer broad representation of some subgroups for analysis. The trial included participants of both sexes (2790 females, 6860 males) and was conducted in 33 countries across five continents (2478 in Asia, 2887 in Europe, 1912 in North America, and 2373 in other areas). The proportion of female participants in SOUL (28.9%) is similar to other cardiovascular outcome trials with GLP-1 RAs (27.7–39.3%).[22-28] Participants in SOUL self-reported as White (6648), Black/African American (252), Asian (2255), other races (405), or did not provide race (90). In addition to reporting race, 1380 participants reported being of Hispanic or Latino ethnicity. Most of Black or African American participants in SOUL were enrolled in the USA (60.3%), followed by South Africa (22.6%) and Brazil (13.5%). Within the USA, the SOUL trial population included 9.5% of Black/African American participants and 7.1% of participants were of Hispanic or Latino ethnicity. In comparison, in the US census 2022, the proportion of

people identifying as Black was 13.7%, and 19.5% identified as Hispanic.[29] In South Africa, the SOUL trial population included 20.0% of Black and 48.4% Asian participants, compared with 81.4% and 2.7% in the general population, respectively.[30] In Brazil, Black participants comprised 12.0% of SOUL participants, compared with 10.2% in the general population.[31]

CKD, chronic kidney disease; CVD, cardiovascular disease; T2D, type 2 diabetes.

Table S3. Additional Analyses of the Primary Outcome

	Oral semaglutide (N = 4825)	Placebo (N = 4825)	Hazard Ratio (95% CI)
Sensitivity analyses			
Retrieved dropouts – permanent treatment discontinuation*	585	676	0.85 (0.76 to 0.95)
Retrieved dropouts – first treatment discontinuation†	584	675	0.85 (0.76 to 0.95)
Supplementary analyses			
Secondary estimand‡§	412	514	0.82 (0.72 to 0.93)
			Absolute Risk Difference (95% CI)
Absolute risk difference at week 156¶	408 (cumulative incidence 0.085)	503 (cumulative incidence 0.105)	–0.020 [–0.032 to –0.008]
			Numbers Needed to Treat (95% CI)
			50 (31 to 125)

*Sensitivity analysis of data from the in-trial period. Event times for subjects who were lost to follow up or withdrew consent were multiple imputed using event rates from retrieved dropouts in the same treatment arm. Retrieved dropouts were defined as subjects who permanently discontinued treatment but remained in trial. Event rates were estimated from observations after the on-treatment period using a piecewise exponential model with three time intervals. The time intervals were derived based on data to have the same number of events in each interval. The imputed data sets were analyzed using the same Cox regression model as for the primary analysis and results were combined using Rubin's rules. †Sensitivity analysis of data from the in-trial period. Event times for subjects who were lost to follow-up or who withdrew consent were multiple imputed using event rates from retrieved dropouts in the same treatment arm. Retrieved dropouts were defined as subjects who were off treatment for more than 5 weeks but remained in the trial. Event rates were estimated from observations after the first on-treatment period using a piecewise exponential model with three time intervals. The time intervals were derived based on data to have the same number of events in each interval. The imputed

data sets were analyzed using the same Cox regression model as for the primary analysis and results were combined using Rubin's rules.

‡Data from first on-treatment period, i.e. from date of first dose until first time where no dose has been administered within 5 weeks (35 days) or end of the in-trial period, whichever came first. Participants without events of interest were censored at the end of their first on-treatment period. Time from first dose of trial product to first EAC-confirmed major adverse cardiovascular event was analyzed using a Cox proportional hazards model with treatment as categorical fixed factor.

§The total number of participants for this analysis was 4814 in the oral semaglutide arm, and 4816 for the placebo arm.

¶Analysis of data from the in-trial period. Cumulative incidence estimates are based on time from randomization to first EAC-confirmed major adverse cardiovascular event with non-cardiovascular death modelled as competing risk using the Aalen-Johansen estimator. Subjects without events of interest were censored at the end of their in-trial observation period. The absolute risk difference was calculated as the difference between the cumulative incidence estimates for each treatment group at week 156.

CI, confidence interval; EAC, event adjudication committee.

Table S4. Adverse Events Summary

Event	Oral semaglutide (N = 4825)	Placebo (N = 4825)	
	Number of participants (%)		P value
Serious adverse events[*] — n (%)	2312 (47.9)	2427 (50.3)	0.02
Cardiac disorders	861 (17.8)	954 (19.8)	0.02
Infections and infestations	726 (15.0)	797 (16.5)	0.05
Nervous system disorders	382 (7.9)	387 (8.0)	0.88
Neoplasms benign, malignant, and unspecified	330 (6.8)	274 (5.7)	0.02
Renal and urinary disorders	249 (5.2)	287 (5.9)	0.10
Gastrointestinal disorders	239 (5.0)	210 (4.4)	0.18
Vascular disorders	237 (4.9)	222 (4.6)	0.50
Injury, poisoning and procedural complications	218 (4.5)	304 (6.3)	<0.001
General disorders and administration-site conditions	206 (4.3)	184 (3.8)	0.28
Respiratory, thoracic, and mediastinal disorders	185 (3.8)	217 (4.5)	0.11
Metabolism and nutrition disorders	182 (3.8)	219 (4.5)	0.07
Musculoskeletal and connective tissue disorders	161 (3.3)	169 (3.5)	0.70
Hepatobiliary disorders	115 (2.4)	101 (2.1)	0.37
Eye disorders	102 (2.1)	97 (2.0)	0.77
Adverse events leading to permanent discontinuation of trial product, regardless of severity[†] — n (%)	749 (15.5)	559 (11.6)	<0.001
Gastrointestinal disorders	310 (6.4)	98 (2.0)	<0.001
Neoplasms benign, malignant, and unspecified	79 (1.6)	61 (1.3)	0.15
Infections and infestations	63 (1.3)	96 (2.0)	0.01
Nervous system disorders	63 (1.3)	61 (1.3)	0.93
Cardiac disorders	59 (1.2)	74 (1.5)	0.22
Renal and urinary disorders	29 (0.6)	31 (0.6)	0.90

Metabolism and nutrition disorders	23 (0.5)	20 (0.4)	0.76
General disorders and administration-site conditions	22 (0.5)	20 (0.4)	0.88
Hepatobiliary disorders	17 (0.4)	19 (0.4)	0.87
Respiratory, thoracic and mediastinal disorders	16 (0.3)	16 (0.3)	1.00
Investigations	12 (0.2)	8 (0.2)	0.50
Vascular disorders	11 (0.2)	13 (0.3)	0.84
Injury, poisoning, and procedural complications	11 (0.2)	13 (0.3)	0.84
Psychiatric disorders	10 (0.2)	5 (0.1)	0.30
Prespecified safety focus areas — n (%)			
Acute gallbladder disease	136 (2.8)	104 (2.2)	0.04
Acute pancreatitis	18 (0.4)	21 (0.4)	0.75
Retinal disorders	1102 (22.8)	1080 (22.4)	0.61
Malignant neoplasms	332 (6.9)	294 (6.1)	0.13
Severe hypoglycemia	76 (1.6)	84 (1.7)	0.58
Medication errors	27 (0.6)	34 (0.7)	0.44
COVID-19			
All events	1076 (22.3)	1131 (23.4)	0.19
Serious events	255 (5.3)	317 (6.6)	0.008
Additional safety focus areas			
Acute kidney failure	148 (3.1)	168 (3.5)	0.28
Hepatic disorders	43 (0.9)	41 (0.8)	0.91
Allergic reaction	17 (0.4)	18 (0.4)	1.00
Abuse and misuse	5 (0.1)	4 (<0.1)	1.00

*A cut-off of ≥2% in the oral semaglutide arm was used for the reporting of serious adverse events.

†A cut-off of ≥0.2% in the oral semaglutide arm was used for the reporting of adverse events leading to permanent treatment discontinuation.

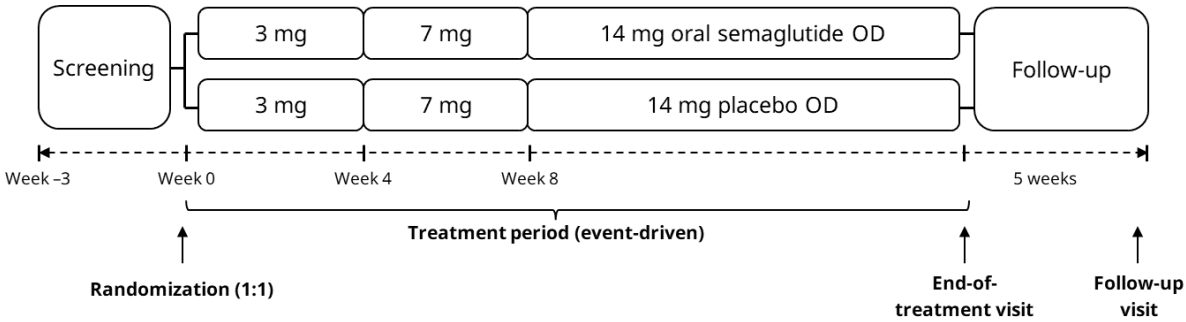
Events were classified according to the Medical Dictionary for Regulatory Activities (MedDRA), version 27.0, preferred terms. This trial involved targeted collection of safety data, in which the only adverse events systematically recorded and

reported were serious adverse events, adverse events leading to discontinuation of the trial product irrespective of seriousness, and adverse events of prespecified special interest irrespective of seriousness. Details of the adverse-event reporting are provided elsewhere in the Supplementary Appendix. Two-sided p-value from Fisher's exact test for test of no difference is shown, not adjusted for multiplicity.

MedDRA, Medical Dictionary for Regulatory Activities.

SUPPLEMENTARY FIGURES

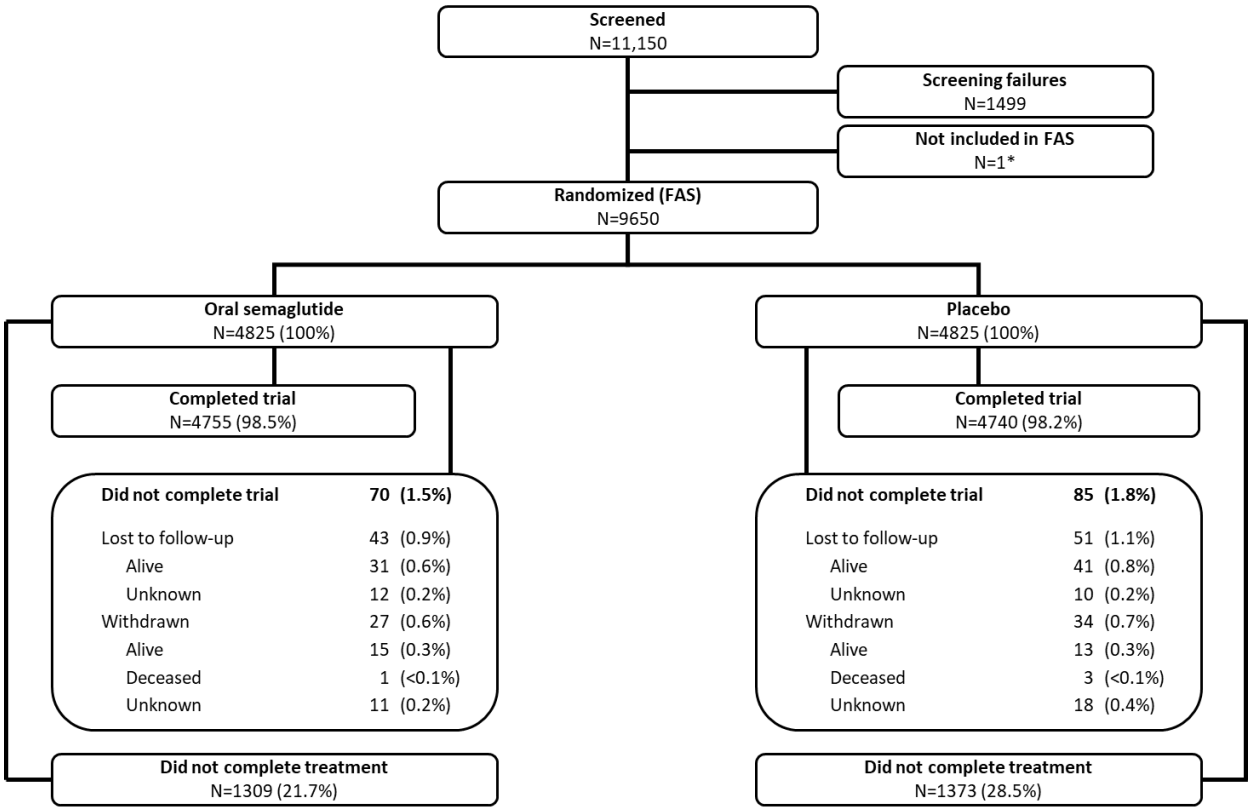
Figure S1. Summary of SOUL Trial Design



Oral semaglutide is formulated with semaglutide and the absorption enhancer sodium N-(8-[2-hydroxylbenzoyl] amino) caprylate (SNAC). Participants received once-daily 3 mg oral semaglutide/placebo for 4 weeks, followed by once-daily 7 mg oral semaglutide/placebo for 4 weeks, and thereafter once-daily 14 mg oral semaglutide/placebo. The 14 mg dose was to be maintained until the end of treatment; however, dose reductions, extensions of dose-escalation intervals, and treatment pauses were allowed if needed to mitigate treatment-associated adverse events.

OD, once daily.

Figure S2. Disposition of Participants in SOUL

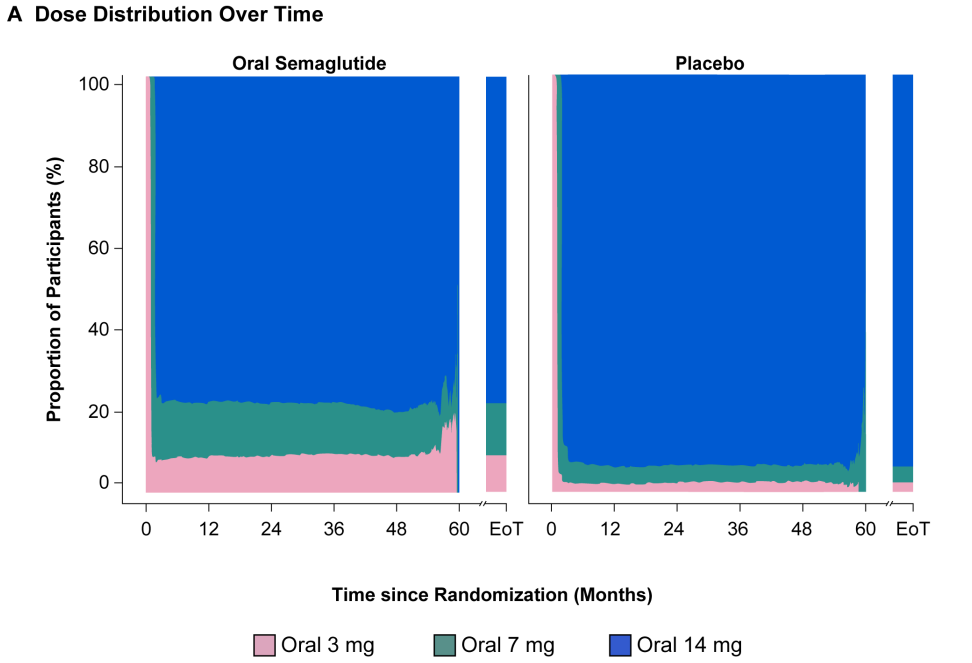


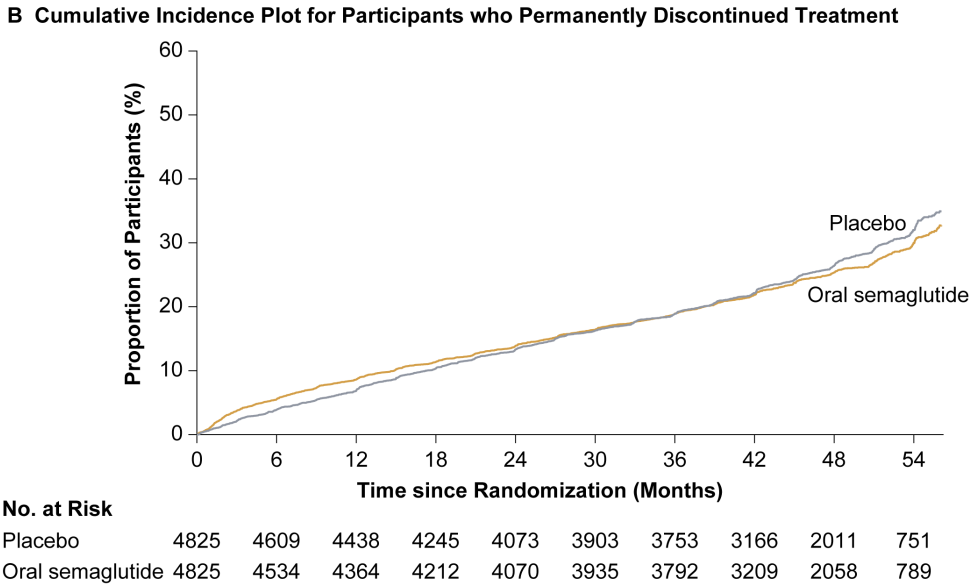
*Randomization was removed due to one participant being randomized more than once.

Participants who completed the trial were defined as those who attended the follow-up visit or died during the trial. Mean duration of exposure to treatment was 42.0±15.5 months overall (41.8±15.9 months for oral semaglutide and 42.1±15.1 months for placebo).

FAS, full analysis set.

Figure S3. A: Dose Distribution over Time. B: Proportion of Participants with Permanent Discontinuation for any Reason





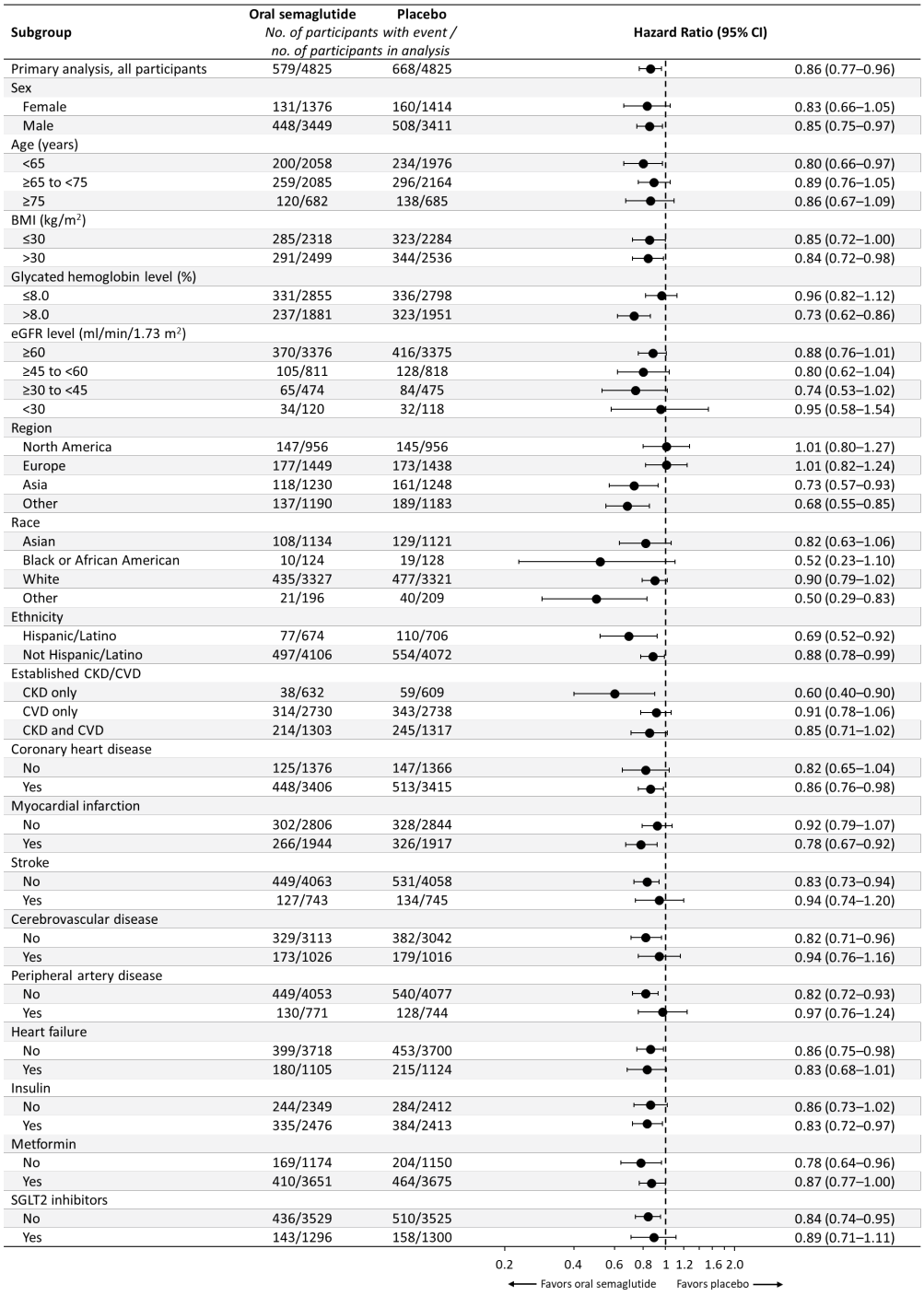
No. at Risk

Placebo	4825	4609	4438	4245	4073	3903	3753	3166	2011	751
Oral semaglutide	4825	4534	4364	4212	4070	3935	3792	3209	2058	789

Panel A: Proportions are based on number of participants receiving trial product. EoT: dose at the end of treatment visit for participants on treatment at that visit.

Panel B: Cumulative incidence estimates are based on the time from randomization to permanent treatment discontinuation, with death modelled as a competing risk. Participants who did not permanently discontinue treatment are censored at the time of their last dose. Permanent treatment discontinuations do not include treatment discontinuations starting the day before either completion, withdrawal, being lost to follow-up or the end of treatment visit. Participants never exposed to treatment are censored at day 1. The x-axis is truncated at 54 months due to the limited number of participants after 54 months.

Figure S4. Subgroup Analysis of the Primary Outcome



Subgroups were defined by values at baseline. CKD was defined as eGFR <60 ml/min/1.73 m^2.

For the primary analysis, the hazard ratios and CIs were adjusted for the group sequential design using the likelihood ratio ordering. For the subgroup analyses, estimated hazard ratios and corresponding CIs were estimated using a Cox proportional hazards model with interaction between treatment group and the relevant subgroup as fixed factor.

BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

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Protocol

Protocol for: McGuire DK, Marx N, Mulvagh SL, et al. Oral semaglutide and cardiovascular outcomes in high-risk type 2 diabetes. N Engl J Med. DOI: 10.1056/NEJMoa2501006

This trial protocol has been provided by the authors to give readers additional information about the work.

SUPPLEMENT TO

Cardiovascular Outcomes with Oral Semaglutide in People with High-Risk Type 2 Diabetes

This supplement contains the following items:

1. Original protocol
2. Final protocol
3. Summary of changes to the protocol
4. Original statistical analysis plan
5. Final statistical analysis plan
6. Summary of changes to the statistical analysis plan

1. Original protocol

Protocol

Protocol title: Semaglutide cardiovascular outcomes trial in patients with type 2 diabetes (SOUL)

Substance: Oral semaglutide

Universal Trial Number: U1111-1218-5368

EUdraCT Number: 2018-003141-42

Trial phase: 3b

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

Table of Contents

1 Synopsis

Rationale

To evaluate the hypothesis that oral semaglutide lowers the risk of cardiovascular events in patients with type 2 diabetes at high risk for cardiovascular disease.

Objectives and endpoints

The primary objective

To demonstrate that oral semaglutide lowers the risk of major adverse cardiovascular events compared to placebo, both added to standard of care in patients with type 2 diabetes and at high risk of cardiovascular events.

The key secondary objectives

To compare the effects of oral semaglutide versus placebo, both added to standard of care in patients with type 2 diabetes and at high risk of cardiovascular events with regards to:

- Chronic kidney disease
- Cardiovascular events
- Peripheral artery disease
- Glycaemic control and body weight
- Safety

The primary endpoint

The primary endpoint is time from randomisation to first occurrence of a major adverse cardiovascular event, a composite endpoint consisting of: cardiovascular death, non-fatal myocardial infarction or non-fatal stroke.

Key confirmatory secondary endpoints

Time from randomisation to first occurrence of:

- A composite chronic kidney disease endpoint consisting of: cardiovascular death, renal death, onset of persistent ≥ 50% reduction in estimated glomerular filtration rate (CKD-EPI) compared with baseline, onset of persistent eGFR (CKD-EPI) < 15 mL/min/1.73 m^2 or initiation of chronic renal replacement therapy (dialysis or kidney transplantation)
- cardiovascular death
- Major adverse limb events, a composite endpoint consisting of: acute limb ischemia hospitalisation or chronic limb ischemia hospitalisation

Estimand

The estimand for all objectives is the intention-to-treat estimand evaluating the effect of the randomised treatment intervention irrespective of adherence to treatment and changes to background medication.

Overall design

This is a randomised, double-blind, parallel-group, placebo-controlled trial comparing oral semaglutide versus placebo both administered once daily and added to standard of care in patients with type 2 diabetes at high risk of cardiovascular events. Patients will be randomised 1:1 to receive either oral semaglutide or placebo.

All inclusion criteria are based on the patients' medical records, except for inclusion criterion for HbA_{1c} (local laboratory or point-of-care device). The key inclusion criteria are:

- Male or female, age ≥50 years at the time of signing informed consent
- Diagnosed with type 2 diabetes mellitus
- HbA_{1c} 6.5% - 10.0% (47 - 86 mmol/mol) (both inclusive)[a]
- At least one of the below conditions (a-d):
  a) Coronary heart disease defined as at least one of the following:
     i. Prior myocardial infarction
     ii. Prior coronary revascularisation procedure
     iii. ≥50% stenosis in coronary artery documented by cardiac catheterisation, computerized tomography coronary angiography
     iv. Coronary heart disease with ischaemia documented by stress test with any imaging modality
  b) Cerebrovascular disease defined as at least one of the following:
     i. Prior stroke
     ii. Prior carotid artery revascularisation procedure
     iii. ≥50% stenosis in carotid artery documented by X-ray angiography, magnetic resonance angiography, computerized tomography angiography or Doppler ultrasound
  c) Symptomatic peripheral artery disease (PAD) defined as at least one of the following:
     i. Intermittent claudication with an Ankle-brachial index (ABI) < 0.85 at rest
     ii. Intermittent claudication with a ≥50% stenosis in peripheral artery (excluding carotid) documented by X-ray angiography, magnetic resonance angiography, computerized tomography angiography or Doppler ultrasound
     iii. Prior peripheral artery (excluding carotid) revascularization procedure
     iv. Lower extremity amputation at or above ankle due to atherosclerotic disease (excluding e.g. trauma or osteomyelitis)
  d) Chronic kidney disease defined as:
     i. eGFR < 60 mL/min/1.73 m^2 [b]

[a] Latest available and no more than 30 days old local laboratory assessment based on medical records or point of care measurement.

[b] Based on medical records using latest available and no more than 6 months old assessment.

The key exclusion criteria are:

- Any of the following: myocardial infarction, stroke, hospitalisation for unstable angina pectoris or transient ischaemic attack within the past 60 days prior to the day of screening
- Planned coronary, carotid or peripheral artery revascularisation known on the day of screening
- Heart failure presently classified as being in New York Heart Association Class IV
- Treatment with any glucagon-like peptide-1 receptor agonist within 30 days before screening

Number of patients

In this trial, 9,642 patients are planned to be randomly assigned to trial product.

Treatment groups and duration

The trial is event driven; therefore, end of trial will be scheduled according to projected trial closure. Trial duration is expected to be 61 months or more following randomisation of the first patient. Trial duration for each subject is expected to be approximately 3.5 to 5 years.

Trial products

Oral semaglutide 3 mg, 7 mg and 14 mg tablets
Placebo tablets

2 Flowchart

Trial Periods	Protocol Section	Screening	Randomisation	First year						Remaining period		End of treatment	Follow-up
Site visit (V)/Phone contact (P)		V1	V2	V3	V4	V5	V6	V7[a]	V8	V9/V10/V11/ V13/V14/V15 V17/V18/V19 V21/V22/V23	V12 V16 V20 V24	V-EOT[b]	P-FU
Timing of visit (weeks)		Up to -3 weeks	0	4	8	13	26	39	52	Every 13 weeks	Yearly	EOT	V-EOT +5 weeks
Visit window (days)				±3	±3	±3	±7	±7	±7	±7	±7	±7	+7
PATIENT-RELATED INFO/ASSESSMENTS													
Informed consent	Appendix 3	X											
Hand out ID card		X											
Inclusion/exclusion criteria	6.1; 6.2	X											
Tobacco use[c]			X								X		
Demography[d]		X											
Medical history/concomitant illness	9.4		X										
Concomitant medication	7.7		X	X	X	X	X	X	X	X	X	X	X
Ensure updated contact persons list	9	X	X	X	X	X	X	X	X	X	X		
Trial product dose	7.2			X	X	X	X	X	X	X	X	X	
Training in trial product and dosing instructions	7.1		X	(X)[e]	(X)[e]	(X)[e]	(X)[e]	(X)[e]	(X)[e]	(X)[e]	(X)[e]		
Hand out and instruct in BG meter[i]	7.1		(X)[i]	(X)[i]	(X)[i]	(X)[i]	(X)[i]	(X)[i]	(X)[i]	(X)[i]	(X)[i]	(X)[i]	
CLINICAL ASSESSMENTS													
Height	9.4.1		X										
Body weight			X			X			X		X	X[f]	
Waist circumference			X										
Physical examination			X									X	
Eye examination	9.4.4	X[g]							X[h]		X[h]	X[f]	
Vital signs	9.4.2		X			X			X		X	X[f]	
HbA_{1c} point of care	6.1;9.1.1	X		X	X	X	X	X	X	X	X	X	
Montreal cognitive assessment	9.1.4		X								X		

Trial Periods	Protocol Section	Screening	Randomisation	First year						Remaining period		End of treatment	Follow-up
Site visit (V)/Phone contact (P)		V1	V2	V3	V4	V5	V6	V7[a]	V8	V9/V10/V11/ V13/V14/V15 V17/V18/V19 V21/V22/V23	V12 V16 V20 V24	V-EOT[b]	P-FU
Timing of visit (weeks)		Up to -3 weeks	0	4	8	13	26	39	52	Every 13 weeks	Yearly	EOT	V-EOT +5 weeks
Visit window (days)				±3	±3	±3	±7	±7	±7	±7	±7	±7	+7
Patient surveys[j]	9.1.4		X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]
Adverse events	9.2		X	X	X	X	X	X	X	X	X	X	X
Severe hypoglycaemic episodes	9.2		X	X	X	X	X	X	X	X	X	X	X
Technical complaints	9.2.6		X	X	X	X	X	X	X	X	X	X	
Urine pregnancy test[k]	9.2.5	X										X	X[l]
CENTRAL LABORATORY ASSESSMENTS													
HbA_{1c}	Appendix 2		X			X			X		X	X[f]	
Creatinine			X			X			X		X	X[f]	
High sensitivity C-Reactive Protein			X			X					X[n]		
Liver parameters			X										
Lipids			X			X			X		X	X[f]	
Biosamples for future analysis (biobank, genetics)[m]			X										
Biosamples for future analysis (biobank, biomarkers)[m]			X			X					X[n]		
TRIAL MATERIAL													
IWRS session		X	X	X	X	X	X	X	X	X	X	X	
Dispensing visit			X	X	X	X	X	X	X	X	X		
Drug accountability	7.5		X	X	X	X	X	X	X	X	X	X	
End of trial	5.3												X

[a] After V6, all odd numbered visits (V7, V9, V11 etc.) can be conducted as a phone contact, however the patients must collect dispensed trial product.
[b] Will be scheduled according to trial completion.
[c] Tobacco use/smoking is defined as smoking at least one cigarette or equivalent daily.
[d] Demography: date of birth, sex, ethnicity and race (according to local regulation).
[e] As needed.

[f] If done within the past 5 weeks, assessment can be skipped.
[g] Must be performed within 90 days before screening or in the period between screening and randomisation, and results available at randomisation.
[h] Must be performed between 5 weeks before the visit and the day of visit (both included).
[i] Lancets, test strips and control solutions will be provided with the BG meter (if supplied) and during the trial as needed. Training will also be provided as needed.
[j] Only for a subset of the patients in selected countries. Patient expectations and experience survey will only be performed at Visit 2, Visit 12 and at end-of-treatment (V-EOT). Patient engagement assessment will be performed every half year, i.e. V2, V6, V8, V10, V12, V14, V16, V18, V20, V22, V24 and V-EOT. For US only visits to emergency room/urgent care unit will be recorded at every visit from V3.
[k] Only applicable for women of childbearing potential; urine HCG.
[l] Can be done at home.
[m] Only applicable for patients that have provided informed consent for biosamples for biomarkers and genetic analyses.
[n] Only applicable for the year two visit (V12).

3 Introduction

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

3.1 Trial rationale

The cardiovascular (CV) effect of oral semaglutide 14 mg once daily (OD) and s.c. semaglutide 0.5 and 1 mg once weekly were assessed in 2 CV outcomes trials (NN9924-4221, PIONEER 6 and NN9535-3744, SUSTAIN 6), each designed to rule out an 80% increased CV risk in patients with type 2 diabetes (T2D) at high risk for CV disease (CVD) in accordance with FDA guidance. PIONEER 6 demonstrated CV safety with a favourable point estimate. SUSTAIN 6 however demonstrated a statistically significant 26% risk reduction with s.c. semaglutide compared with placebo for the primary endpoint (time from randomisation to first occurrence of a major adverse cardiovascular event (MACE) consisting of: CV death, non-fatal myocardial infarction (MI) or non-fatal stroke).[1] Clinical pharmacology and clinical efficacy data indicate that the action of semaglutide is the same whether administrated via a subcutaneous injection or orally in a tablet. Hence, once semaglutide has entered systemic circulation, the properties and actions of the molecule are similar and independent of the route of administration. Accordingly it is hypothesised that oral semaglutide in the dose of 14 mg OD can reduce CV risk.

The current trial serves the purpose of confirming that oral semaglutide reduces the risk of MACE in patients with T2D and established CVD and/or chronic kidney disease (CKD).

3.2 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, including hyperglycaemia.[2] However, many patients with T2D do not achieve glycaemic control, so an unmet need for simple and convenient as well as safe and efficacious treatment options exists.[3, 4] In addition, CV disease is the predominant cause of death in patients with T2D, and diabetes increased the risk for coronary heart disease, stroke and CV death[5] with an about a two-fold excess, underscoring the need for therapies lowering the risk of CV events in patients with T2D.

Semaglutide is a next-generation glucagon-like peptide-1 (GLP-1) analogue with a high degree of homology to human GLP-1.[6] For oral administration, semaglutide has been co-formulated with an absorption enhancer (SNAC, 300 mg) in a tablet formulation. Non-clinical and clinical studies have established that oral semaglutide is safe and well tolerated and that it provides dose-dependent reductions in HbA_{1c} and body weight when used in compliance with the specified simple dosing conditions.[7] Detailed information for oral semaglutide is available in the current edition and any updates of the Investigator's Brochure (IB).[8]

The trial will include patients with T2D and high CV risk defined as having established CVD and/or CKD. A population at high risk for CV events is an appropriate target population for a risk reduction intervention and will ensure that the primary objective of the trial can be met within a reasonable timeframe and sample size.

3.3 Benefit-risk assessment

3.3.1 Risks

The sections below describe identified and potential risks associated with oral semaglutide treatment. For classification and further details of the risks, please refer to the current edition and any updates of the IB.[8] The identified/potential risks are based on findings in non-clinical studies and clinical trials with semaglutide (s.c. as well as oral) as well as other glucagon-like peptide-1 receptor agonists (GLP-1 RAs). For each of these risks, mitigating actions have been implemented to minimise the risks for patients enrolled in this trial.

Gastrointestinal adverse events

Consistent with the other GLP-1 RAs, the most frequent adverse events (AEs) with oral semaglutide are gastrointestinal AEs (nausea, vomiting, diarrhoea, dyspepsia and constipation). A low starting dose and gradual dose escalation with 4 weeks dose escalation increments have been implemented in the recent clinical trials with the intent to lower the risk of gastrointestinal AEs.

Impaired kidney function

In patients treated with GLP-1 RAs including oral semaglutide, gastrointestinal AEs such as nausea, vomiting and diarrhoea may lead to significant dehydration. This should be considered when treating patients with impaired renal function with GLP-1 RAs as it may cause a deterioration of renal function. Impaired renal function may increase the risk of metformin associated lactic acidosis.

Patients and providers should be advised to monitor hydration levels in order to avoid dehydration in connection with gastrointestinal AEs.

Hypoglycaemia

The risk of hypoglycaemic episodes associated with the use of GLP-1 RAs, including oral semaglutide, is low when used as monotherapy. Patients treated with semaglutide in combination with a sulfonylurea or insulin may have an increased risk of hypoglycaemia compared to patients treated with semaglutide as monotherapy or in combination with other anti-hyperglycaemic medications. The risk of hypoglycaemia can be lowered by reducing the dose of sulfonylurea or insulin when initiating treatment with oral semaglutide. It is also recommended that the investigator ensures that patients taking or initiating sulphonylurea or insulin perform adequately frequent blood glucose monitoring to ensure patient safety.

Allergic reactions

As expected for a protein-based drug, patients treated with oral semaglutide may develop localised or generalised immune and allergic reactions including urticaria, rash or pruritus. Severe allergic reactions such as anaphylactic reactions could potentially also pose a risk to patients treated with oral semaglutide. Data from the both the s.c. and the oral semaglutide development programmes indicate that the potential risk of allergic reactions is low.

Acute pancreatitis

Acute pancreatitis has been observed with the use of GLP-1 RA drug class. As a precaution, trial product should be discontinued in case of suspicion of acute pancreatitis in accordance with Section 8.1.

Acute gallstone disease (cholelithiasis)

Patients with T2D are often overweight or obese and have an inherent risk of developing gallstones (cholelithiasis). Events of cholelithiasis have been associated with the use of GLP-1 RAs including semaglutide. In the clinical development programme, events were mainly mild and non-serious and did not lead to an increased risk of complications such as cholecystitis or pancreatitis.

Diabetic retinopathy complications

The cardiovascular outcome trial in the s.c. semaglutide development programme (SUSTAIN 6) showed an increased risk of events related to diabetic retinopathy complications in patients treated with semaglutide compared to placebo, albeit the proportion of patients with an event of diabetic retinopathy complications was low. The imbalance was driven by patients with a history of diabetic retinopathy at baseline and patients who were treated with insulin. As a precaution, patients with a history of uncontrolled and potentially unstable diabetic retinopathy or maculopathy will be excluded from the trial, and eye examination will be performed according to flowchart (see Section 2).

Pancreatic cancer

There is currently no support from non-clinical studies, clinical trials or post-marketing data that GLP-1 RA-based therapies increase the risk of pancreatic cancer. However, pancreatic cancer has been classified as a potential class risk for all marketed GLP-1 RAs by regulatory agencies based on the unknown long-term effects on β-cell stimulation and α-cell suppression.

Medullary thyroid cancer (MTC) (based on non-clinical data)

Thyroid C-cell tumours were seen in the mice and rat carcinogenicity studies, after daily exposure to semaglutide for 2 years. No C-cell tumours were observed in monkeys after 52 weeks exposure of up to 40-fold higher doses than the clinical plasma exposure at 14 mg/day. The GLP-1 receptor is not expressed in the normal human thyroid[9]; and therefore, these findings are not likely to be

clinically relevant. 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.

Pregnancy and fertility

Studies in animals have shown reproductive toxicity. There are limited data from the use of semaglutide in pregnant women. Therefore, oral semaglutide should not be used during pregnancy. If a patient wishes to become pregnant, or pregnancy occurs, treatment with oral semaglutide should be discontinued immediately. Exclusion and discontinuation criteria related to pregnancy have been implemented in the trial.

3.3.2 Benefits

In clinical trials oral 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 statistical significant reduction in CV events has been demonstrated for semaglutide s.c. (SUSTAIN 6[1]) and this finding was supported by the results from the PIONEER 6 trial with oral semaglutide.

During this 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 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.

3.3.3 Risk and benefit 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 high 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 oral 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 oral semaglutide may be found in the Investigator's Brochure and any updates thereof.[8]

4 Objectives and endpoints

4.1 Primary, secondary and exploratory objective(s)

The primary objective
To demonstrate that oral semaglutide lowers the risk of major adverse cardiovascular events (MACE) compared to placebo, both added to standard of care in patients with T2D and at high risk of CV events.

The secondary objectives
To compare the effects of oral semaglutide versus placebo, both added to standard of care in patients with T2D and at high risk of CV events with regards to:

- CKD
- CV events
- Peripheral artery disease (PAD)
- Glycaemic control and body weight
- Safety

The exploratory objectives

To compare the effects of oral semaglutide versus placebo, both added to standard of care in patients with T2D and at high risk of CV events with regards to:

- Cognitive function
- Smoking

Estimand

The estimand for all objectives is the intention-to-treat estimand evaluating the effect of the randomised treatment intervention irrespective of adherence to treatment and changes to background medication.

4.2 Primary, secondary and exploratory endpoint(s)

4.2.1 Primary endpoint

Endpoint title	Time Frame	Unit
Time to first occurrence of MACE, a composite endpoint consisting of: • CV death • non-fatal myocardial infarction • non-fatal stroke	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Month(s)

[a] Trial is event driven.

4.2.2 Secondary endpoints

4.2.2.1 Confirmatory secondary endpoints

Endpoint title	Time Frame	Unit
Time to first occurrence of a composite endpoint consisting of: • CV death • renal death • onset of persistent ≥ 50% reduction in eGFR (CKD-EPI)[b] • onset of persistent eGFR (CKD-EPI) < 15 mL/min/1.73 m^2 • initiation of chronic renal replacement therapy (dialysis or kidney transplantation)	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Month(s)
Time to occurrence of CV death	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Month(s)
Time to first occurrence of major adverse limb events (MALE), a composite endpoint consisting of: • acute limb ischemia hospitalisation • chronic limb ischemia hospitalisation	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Month(s)

[a] Trial is event driven.
[b] Compared with baseline.
Abbreviations: eGFR, estimated glomerular filtration rate; CKD-EPI, chronic kidney disease – epidemiology collaboration

Definitions

Estimated glomerular filtration rate (eGFR) will be calculated using the – CKD-EPI formula.[10] A persistent change in eGFR is defined as having 2 consecutive samples meeting the criteria. The 2 samples must be at least 4 weeks apart.

4.2.2.2 Supportive secondary endpoints

Endpoint title	Time Frame	Unit
Time to first occurrence of an expanded MACE composite endpoint consisting of: • CV death • non-fatal myocardial infarction • non-fatal stroke • coronary revascularisation • unstable angina requiring hospitalisation	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Month(s)

Time to first occurrence of a composite heart failure endpoint consisting of: • CV death • heart failure requiring hospitalisation • urgent heart failure visit	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Month(s)
Time to first occurrence of a composite CKD endpoint consisting of: • renal death • onset of persistent ≥ 50% reduction in estimated glomerular filtration rate (eGFR) (CKD-EPI)[b] • onset of persistent eGFR (CKD-EPI) < 15 mL/min/1.73 m^2 • initiation of chronic renal replacement therapy (dialysis or kidney transplantation)	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Month(s)
Time to occurrence of all-cause death	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Month(s)
Time to first occurrence of non-fatal myocardial infarction (MI)	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Month(s)
Time to first occurrence of non-fatal stroke	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Month(s)
Time to first occurrence of heart failure requiring hospitalisation	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Month(s)
Time to first occurrence of urgent heart failure visit	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Month(s)
Time to first occurrence of coronary revascularisation	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Month(s)
Time to first occurrence of unstable angina requiring hospitalisation	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Month(s)
Time to occurrence of renal death	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Month(s)
Time to first occurrence of onset of persistent ≥ 50% reduction in eGFR (CKD-EPI)[b]	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Month(s)

Time to first occurrence of onset of persistent eGFR (CKD-EPI) < 15 mL/min/1.73 m^2	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Month(s)
Time to first occurrence of initiation of chronic renal replacement therapy (dialysis or kidney transplantation)	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Month(s)
Time to first occurrence of a composite endpoint consisting of: • all-cause death • non-fatal myocardial infarction • non-fatal stroke	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Month(s)
Time to first occurrence of acute limb ischemia	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Month(s)
Time to first occurrence of chronic limb ischemia	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Month(s)
Annual rate of change in eGFR (CKD-EPI) (total eGFR slope)	From randomisation (week 0) to end of treatment (up to 60 months or more[a])	ml/min/1.73 m^2 per year
Change in glycosylated haemoglobin (HbA_{1c})	From randomisation (week 0) to 2 years (visit 12)	%-points
Change in body weight	From randomisation (week 0) to 2 years (visit 12)	Kilogram
Number of severe hypoglycaemic episodes[11]	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Number of events
Time to first occurrence of a severe hypoglycaemic episode [11]	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Month(s)

[a] Trial is event driven.
[b] Compared with baseline.

4.2.2.3 Exploratory endpoints

Endpoint title	Time Frame	Unit
Change in Montreal Cognitive Assessment (MoCA) score	From randomisation (week 0) to 2 years (visit 12)	Score (0-30)
Change in Montreal Cognitive Assessment (MoCA) score	From randomisation (week 0) to 3 years (visit 16)	Score (0-30)
Current smoking	At year 2	Yes/no

5 Trial design

5.1 Overall design

This is a randomised, double-blind, parallel-group, placebo-controlled trial comparing oral semaglutide versus placebo OD added to standard of care in patients with T2D at high risk of CV events. Patients will be randomised 1:1 to receive either oral semaglutide or placebo.

The trial is event driven with trial closure being performed when the targeted number of primary endpoint events (1225) has been reached. The trial will employ a group sequential design and interim testing for efficacy will be performed by an independent external Data Monitoring Committee (DMC). With the assumed event rate and a recruitment period of approximately 18 months, expected trial duration for an individual patient is approximately 3.5 to 5 years including the follow-up period. The follow-up period is 5 weeks after end of treatment.

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. A schematic overview of the trial design is shown in Figure 5-1 below.

The trial is designed to evaluate CV outcomes and will apply a targeted approach to collection of safety data focusing on serious AEs (SAEs), AEs leading to discontinuation of trial product and other selected AEs. An adequate characterisation of the less serious and more common AEs are evaluated in the phase 3a trials conducted with oral semaglutide comprising more than 5,500 patients with T2D.

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

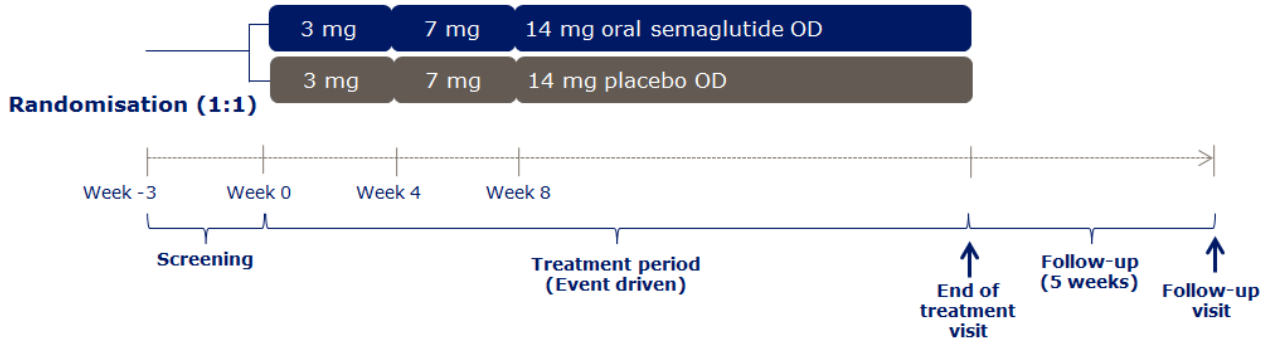


Figure 5-1 Trial design

5.2 Patient and trial completion

In this trial 9,642 patients are planned to be randomly assigned to trial product. The recruitment period is expected to be approximately 18 months.

Trial period completion for a patient is defined as when the randomised patient has:

- attended the final scheduled visit (follow-up visit (P-FU) according to the flowchart)

or

- died during trial.

The trial is event driven; therefore, end of treatment visit (V-EOT) and follow-up contact (P-FU) will be scheduled according to projected trial closure. When trial closure is initiated the investigators will be notified and instructed by Novo Nordisk regarding the visit schedules for their patients.

When the trial comes to an end, the investigator must make every effort to ascertain efficacy endpoint data and AEs with a focus on those related to the primary objective for all patients. This should be done by direct contact with the patient whenever possible. If a patient proves difficult to reach for the FU visit, all attempts to re-establish direct contact must be made as noted below. If establishing direct contact is not possible, AE status should be obtained from any available source including electronic medical records, the patients' primary physician or other health care professionals and, as a last resort, vital status (dead or alive) should be obtained. Publicly available data sources should also be searched. A search agency may be used to facilitate identifying updated contact details for a missing patient or provide vital status (dead or last alive date). The above suggestions should be followed unless prohibited by local regulation and may be modified according to practical aspects.

In a case where several attempts are required to establish direct contact to a patient, it may be necessary to exceed the visit window of a follow-up visit. In order for the data set to be as complete as possible, end of trial follow-up information can be collected until the randomisation codes are broken.

As a minimum the following contact attempts will be made and documented in the source documents:

- To patients: three phone calls and one written contact
- To primary physician and/or other health care professionals: calls until contact is established
- To relatives or other(s) on the contact persons list: three phone calls and one written contact
- Search/contact to public registries of deceased persons, if available and allowed by local regulation

5.3 End of trial definition

The end of the trial is defined as the date of the last visit (P-FU) of the last patient in the trial.

5.4 Scientific rationale for trial design

To minimise bias the trial is randomised, double-blinded and placebo-controlled. Blinded treatment with oral semaglutide or placebo offers a robust method for assessment of the effects of oral semaglutide. 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 oral semaglutide 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 every 13th week throughout the trial. A multinational design has been chosen to ensure a sufficient screening pool of patients and to reflect the anticipated patient population. The 5-week follow up is chosen due to the half-life of oral semaglutide and is considered appropriate for end of systemic exposure.

The trial will include a population of patients with T2D and established CV disease and/or CKD which is an appropriate high risk target population for a CV risk reduction intervention and will ensure that the primary objective of the trial can be evaluated within a reasonable timeframe and sample size.

5.5 Justification for dose

Three doses of oral semaglutide have been investigated in the phase 3a development programme: 3 mg, 7 mg and 14 mg. The selected doses are based on the data derived from the NN9924-3790 dose-finding trial. For further details regarding the results obtained in the phase 2 dose-finding trial (NN9924-3790), please refer to the current edition of the IB for oral administration of semaglutide (NN9924), or any updates thereto.

Similar to other cardiovascular outcomes trials, the maximum treatment dose (14 mg oral semaglutide) will be investigated and compared to placebo in the present trial.

6 Trial population

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

6.1 Inclusion criteria

All inclusion criteria are based on the patients' medical records, except for inclusion criterion for HbA_{1c} (local laboratory or point-of-care device). 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 ≥50 years at the time of signing informed consent.
3. Diagnosed with type 2 diabetes mellitus.
4. HbA_{1c} 6.5% - 10.0% (47 - 86 mmol/mol) (both inclusive).[a]
5. At least one of the below conditions (a-d):
   a) Coronary heart disease defined as at least one of the following:
      i. Prior myocardial infarction
      ii. Prior coronary revascularisation procedure
      iii. ≥50% stenosis in coronary artery documented by cardiac catheterisation or CT coronary angiography
      iv. Coronary heart disease with ischaemia documented by stress test with any imaging modality
   b) Cerebrovascular disease defined as at least one of the following:
      i. Prior stroke
      ii. Prior carotid artery revascularisation procedure
      iii. ≥50% stenosis in carotid artery documented by X-ray angiography, MR angiography, CT angiography or Doppler ultrasound
   c) Symptomatic peripheral artery disease (PAD) defined as at least one of the following:
      i. Intermittent claudication with an Ankle-brachial index (ABI) < 0.85 at rest
      ii. Intermittent claudication with a ≥50% stenosis in peripheral artery (excluding carotid) documented by X-ray angiography, MR angiography, CT angiography or Doppler ultrasound
      iii. Prior peripheral artery (excluding carotid) revascularization procedure
      iv. Lower extremity amputation at or above ankle due to atherosclerotic disease (excluding e.g. trauma or osteomyelitis)
   d) Chronic kidney disease defined as:
      i. eGFR < 60 mL/min/1.73 m^2 [b]

[a] Latest available and no more than 30 days old local laboratory assessment based on medical records or point of care measurement.

[b] Based on medical records using latest available and no more than 6 months old assessment.

6.2 Exclusion criteria

All exclusion criteria are based on the patients' medical records, except for exclusion criterion 3, urine pregnancy test. Patients are excluded from the trial if any of the following criteria apply:

1. Known or suspected hypersensitivity to trial product 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.
4. Participation in any clinical trial of an approved or non-approved investigational medicinal product within 30 days before screening.
5. Any disorder, which in the investigator's opinion might jeopardise patient's safety or compliance with the protocol.
6. Any of the following: myocardial infarction, stroke, hospitalisation for unstable angina pectoris or transient ischaemic attack (TIA) within the past 60 days prior to the day of screening
7. Planned coronary, carotid or peripheral artery revascularisation.
8. Heart failure presently classified as being in New York Heart Association (NYHA) Class IV.
9. Treatment with any GLP-1 receptor agonist (RA) within 30 days before screening.
10. Uncontrolled and potentially unstable diabetic retinopathy or maculopathy. 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.
11. 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 is allowed.
12. Personal or first degree relative(s) history of MEN2 or MTC.
13. End stage renal disease or chronic or intermittent haemodialysis or peritoneal dialysis.
14. History of major surgical procedures involving the stomach or small intestine potentially affecting absorption of drugs and/or nutrients, as judged by the investigator.

Algeria, Argentina, Austria, Belgium, Brazil, Denmark, Thailand and United Kingdom: For country specific requirements, please see Appendix 8.

6.3 Lifestyle restrictions

Not applicable.

6.4 Screen failures

Screen failures are defined as patients who consent to participate in the clinical trial but are not eligible for participation according to in/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 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).

Due to the long recruitment period re-screening is allowed. A new patient number must be assigned in the IWRS.

6.5 Assessment of eligibility

It is the responsibility of the investigator to have sufficient evidence to ensure eligibility. If a patient is not from the investigators practice; reasonable efforts must be made to obtain a copy of the patient's medical records from relevant party e.g. the primary physician and hospitals. It is at the investigator's discretion on a case by case basis to decide if the complete medical records are needed or if the available documentation is enough to determine whether a patient is eligible. The values used to assess eligibility must reflect the patient's current health status.

7 Treatments

7.1 Treatments administered

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

Table 7-1 Trial products provided by Novo Nordisk A/S

Trial product	Strength	Dosage form	Route of administration	Container/ delivery device
Semaglutide 3 mg tablet (IMP, test product)	3 mg	Tablet	Oral	Dose-pack[a]
Semaglutide 7 mg tablet (IMP, test product)	7 mg			
Semaglutide 14 mg tablet (IMP, test product)	14 mg			
Placebo tablet (IMP, reference therapy)	NA			

[a] A dose-pack contains one blister card with 7 tablets

The active trial product and the corresponding placebo are packed blinded and are identical with regard to visual appearance. Furthermore, all oral semaglutide tablets are visually identical to each other, irrespective of dose levels. Strength will be written on the dose-pack e.g. Semaglutide 3 mg or placebo.

All baseline assessments must be done prior to administration of the first dose of trial product. The patients must be trained in dosing instructions (see Section 7.2.1). The investigator must document that patients are trained in the dosing instructions according to Section 2.

Auxiliary supplies are provided by Novo Nordisk:

- blood glucose meters including lancets, test strips, control solutions and instructions for use

At (or after) the randomisation visit patients may be provided with a blood glucose meter. The patients will be instructed in how to use the device and the instructions will be repeated during the trial as needed. The investigator or the individual patient may choose to continue using their own glucose meter or decide that self-measurement of glucose is not needed. If circumstances change, then the glucose meter can be provided.

7.2 Dose modification

Randomised patients will initiate treatment with 3 mg oral semaglutide/placebo OD and follow a fixed 4-week dose escalation regimen until reaching the treatment dose of 14 mg oral semaglutide/ placebo OD as illustrated in Table 7-2.

The 4-week dose escalation interval is applied in order to mitigate the risk of gastrointestinal AEs.

Patients should remain on the 14 mg dose level until the end of treatment visit; however, dose reductions, extensions of dose escalation intervals and treatment pauses are allowed e.g. if treatment with the trial product is associated with unacceptable AEs or due to other circumstances.

Table 7-2 Treatment and trial periods

Trial periods	**Screening**	**Dose escalation**	**Dose escalation**	**Maintenance**	**Follow-up**
Visits in each period	Visit 1 to Visit 2	Visit 2 to Visit 3	Visit 3 to Visit 4	Visit 4 to end of treatment Visit	End of treatment Visit to Follow-up Visit
Duration	Up to 3 weeks	4 weeks	4 weeks	Up to ~58 months	5 weeks
Daily dose	-	3 mg	7 mg	14 mg	-

Any change to trial product dose including date of change or discontinuation should be recorded in the eCRF throughout the trial.

If trial product is discontinued, patients should continue to follow the trial schedule without being withdrawn from the trial. Treatment with trial product should be resumed if deemed safe at the discretion of the investigator.

7.2.1 Dosing instructions

Absorption of oral semaglutide is significantly affected by food and fluid in the stomach, therefore dosing should be in the morning in a fasting state and at least 30 minutes before the first meal of the day. Oral semaglutide can be taken with up to half a glass of water (approximately 120 mL/ 4 fluid oz.). The tablet should be taken immediately after removal from the blister and swallowed whole and must not be broken or chewed. Other oral medication should not be taken together with trial product but can be taken 30 minutes after trial product.

7.2.2 Missed doses

The trial product should be administered once daily; however, if one or more doses of trial product are missed due to circumstances not related to the safe use of the trial product (as judged by the investigator) and treatment with trial product is resumed, the below recommendations for dose adjustment apply:

- If ≤ 21 consecutive doses of 14 mg oral semaglutide/placebo are missed, the once daily regimen can be resumed as prescribed without dose reduction.
- If 22-35 consecutive doses of 14 mg oral semaglutide/placebo are missed, it is recommended to resume treatment at 7 mg oral semaglutide/placebo and subsequently, escalate to the higher dose after 4 weeks of treatment.
- If ≥ 36 consecutive doses of 14 mg oral semaglutide/placebo are missed, it is recommended to resume treatment at 3 mg oral semaglutide/placebo and subsequently, escalate to the higher doses with 4-week dose escalation steps.

Please refer to section 8.1.1 for instructions on how to use the IWRS in relation to patients discontinuing and resuming trial product treatment.

In case of questions related to resuming trial treatment, the investigator can consult Novo Nordisk.

7.3 Method of treatment assignment

All patients will be centrally randomised using an IWRS and assigned to the next available treatment according to randomisation schedule. Trial product will be dispensed at the trial visits summarised in the flowchart, Section 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.

7.4 Blinding

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

The IWRS is used for blind-breaking instructions. The blind may be broken in a medical emergency if knowing the actual treatment would influence the treatment of the patient. Novo Nordisk will be notified immediately after breaking the blind. The date when and reason why the blind was broken must be recorded in the source documentation.

Whenever the blind is broken, the person breaking the blind must print the "code break confirmation" notification generated by the IWRS, record the reason and sign and date the document.

When the blind is broken, the treatment allocation will be accessible to the investigator and the Novo Nordisk Global Safety department. If IWRS is not accessible at the time of blind break, the IWRS helpdesk should be contacted. Contact details are listed in Attachment I.

7.5 Preparation/Handling/Storage/Accountability

Only patients enrolled in the trial may use trial product and only authorised site staff may supply or administer trial product.

Product storage, in-use conditions and in-use time will be available on the 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 first shipment to each site will be triggered by the first patient screened.

The investigator must confirm that appropriate temperature conditions have been maintained during transit for all trial products received and 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 authorised site staff.

The investigator must inform Novo Nordisk immediately if any trial product has been stored outside specified conditions. Additional details regarding handling of temperature deviations can be found in the TMM.

Trial product that has been stored improperly must not be dispensed to any patient before it has been evaluated and approved for further use by Novo Nordisk.

Patients must return all used, partly used and unused trial products including empty packaging material as instructed by the investigator.

The investigator is responsible for drug accountability and record maintenance (i.e. receipt, accountability and final disposition records).

Drug accountability is performed by using the IWRS and must be done on tablet level.

Destruction of trial products can be performed on an ongoing basis and will be done according to local procedures after accountability is finalised by the site and reconciled by the monitor.

Destruction of trial products must be documented in the IWRS.

All returned, expired or damaged trial products (for technical complaint samples see Appendix 6) 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 trial site.

7.5.1 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.

Japan: For country specific requirements, please see Appendix 8.

7.6 Treatment compliance

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

Treatment compliance will be assessed by monitoring of drug accountability and by discussing treatment compliance and dosing conditions with the patient. Treatment compliance is defined as taking between 80%-120% of the dose as prescribed between visits. The investigator must assess the amount of trial products returned compared to what was dispensed at the previous visit and, in case of discrepancies, question the patient.

If a patient is found to be non-compliant, the investigator will remind the patient of the importance of following the instructions given including taking the trial products as prescribed and should document this discussion in the patient's medical record.

If the patient has been off treatment, continuation of trial product should be encouraged if considered safe as per the investigator's discretion. Previous dose and gastrointestinal adverse reactions as well as number of missed doses should be taken into consideration when evaluating whether to repeat dose escalation (see section 7.2.2).

7.7 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
- 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

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

For antidiabetic medication, the total daily dose needs to be included in the eCRF. Stable dose changes (2 weeks or more) should be captured as new concomitant medication with the new dose and relevant start and stop date.

Changes in concomitant medication listed above must be recorded at each visit. If a change is due to an SAE, then this must be reported according to Section 9.2.

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 3.3.1.

Importantly, investigators should ensure that patients are treated according to recommended standard of care for both glycaemic management as well as CV risk management. Recommendations for this will be provided in guidance documents from the steering committee and global expert panel during trial conduct. Surveillance of adherence to standard of care will be performed centrally by Novo Nordisk. For patients where standard of care is not achieved, investigators may be asked for an optimisation plan which will be recorded in the eCRF or approached to discuss treatment options. If allowed according to local regulation, Novo Nordisk may compensate parts of the cost of some concomitant medication used to ensure glycaemic control and CV risk management.

Brazil and Turkey: For country specific requirements, please see Appendix 8.

7.8 Treatment after the end of the 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. Oral semaglutide will not be available for prescription until marketing authorisation is issued.

Argentina and Brazil: For country specific requirements, please see Appendix 8.

8 Discontinuation/Withdrawal criteria

8.1 Discontinuation of trial treatment

The patient must be discontinued from trial product at any time during the trial, if any of the following applies:

1. Pregnancy
2. Intention of becoming pregnant
3. Simultaneous participation in another clinical trial of an approved or non-approved investigational medicinal product
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

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: 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.

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.

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 eCRF, and drug accountability must be performed.

8.1.1 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 7.1). Similarly, patients who discontinue trial product on their own initiative should be encouraged to resume the treatment (Section 7.1). At both instances dose escalation may be necessary (Section 7.2.2). 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.

8.2 Withdrawal from the trial

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

If considering withdrawing from the trial, the patient should, as an alternative, be offered flexible participation in the trial. This could be attending fewer visits (i.e. reduced visit schedule), converting site visits to phone contacts, treatment pause, or only being followed-up for AEs, especially those related to the primary objective. Another alternative could be to cease all trial related activities including trial product, and simply receive a phone call at trial end to collect AEs. It must be explained to the patient that this must include information on their AEs, especially those related to the primary objective that occurred since last contact to the patient. Only if the patient declines all alternatives, should the patient be recorded as withdrawn.

Final drug accountability must be performed even if the patient is not able to come to the trial site.

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.

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

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 eCRF.

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 5.2 for further details.

Mexico: For country specific requirements, please see Appendix 8.

8.2.1 Replacement of patients

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

8.3 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 trial site.

- Before a patient is deemed lost to follow-up, the investigator must make every effort to regain contact with the patient as described in Section 5.2.
- A patient cannot be declared lost to follow-up before all the attempts have been repeated and the trial has come to an end as described in Section 5.2.

The attempts to contact the patient must be documented in medical records at the site.

9 Trial assessments and procedures

- Trial procedures and their timing are summarised in the flowchart, Section 2.
- Informed consent must be obtained before any trial related activity, see Appendix 3.
- All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility 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.
- At screening, patients will be provided with a card stating that they are participating in a trial and giving contact details of relevant trial site staff.
- Adherence to the trial design requirements, including those specified in the flowchart, is essential and required for trial conduct.
- The investigator should inform the patients' primary physician about the patients' participation in the trial if the patient has a primary physician and if the patient agrees to the primary physician being informed.
- Each patient should be asked to provide contact information for persons (preferably at least 3), e.g. relatives, primary care provider or other, whom investigator can contact in case of issues when trying to contact the patient during the trial. The sites are encouraged to maintain these details as current as possible throughout the course of the trial.
- The randomisation visit can be performed on the same day as the screening visit if the patient is assessed as eligible (Section 6) and if sufficient trial product is available.
- It is the responsibility of the investigator to schedule the visits and contacts as per protocol (flowchart, Section 2) and to ensure they take place.

- After V6, all odd numbered site visits (V7, V9, V11 etc.) can be conducted as a phone contact, however the patients must collect dispensed trial product.
- The investigator must ensure they keep regular contact with each patient throughout the entire trial, and at all times have updated contact information. Even if a visit (or phone contact) is missed and it is not possible to re-schedule, the investigator must take every effort to have all patients followed for endpoint related outcomes including MACE.
- 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.
- Review of completed laboratory reports etc. must be documented either on the documents or in the patient's source documents.
- Repeat samples may be taken for technical issues and unscheduled samples or assessments may be taken for safety reasons. Please refer to Appendix 2 for further details on laboratory samples.
- The investigator may provide the patients with a mobile phone to mediate easier contact if allowed according to local regulation and approved by institutional review board (IRB)/independent ethics committee (IEC). The investigator should consider sending text messages to the patients to remind them of site visits, dosing of trial product, and other trial requirements.

9.1 Efficacy assessments

Planned time points for all efficacy assessments are provided in the flowchart Section 2.

9.1.1 HbA_{1c} point of care

HbA_{1c} can be measured while patient is at site for assessing eligibility at Visit 1 and at site visits during the trial as a supportive measurement for investigator's treatment decisions. Sites will either use their own equipment or a device provided by Novo Nordisk. Local laboratory can be used if the HbA_{1c} point of care device for any reason cannot be used. Point of care device measurements performed at scheduled visits should be recorded in the eCRF starting at Visit 3.

9.1.2 Self-measured plasma glucose

If deemed helpful by the investigator, patients may be provided with a BG meter including auxiliaries as well as instructions for use. The patients will be instructed in how to use the device and the instruction will be repeated as needed. The investigator will advise the individual patient of when the self-measured plasma glucose values should be measured and how to note the values and dates. The measurements are supportive for investigator's treatment decisions when optimising glycaemic control, and should be filed at site.

9.1.3 Clinical efficacy laboratory assessments

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

9.1.4 Cognitive testing, patient surveys and visits to emergency room/urgent care unit

The Montreal Cognitive Assessment (MoCA) is the cognitive testing used in this trial. If clarification of the test is needed, care must be taken not to bias the patient.

Patient surveys will be performed in a subset of patients in selected countries:

- A patient expectations and experience survey. This data will not be transferred to the trial database.
- A patient engagement assessment. This data will not be transferred to the trial database.

Visits to emergency room/urgent care unit will be recorded in the eCRF for the US.

9.2 Adverse events

The definitions of AEs and SAEs can be found in Appendix 4.

Japan: For AE reporting requirements please see Appendix 8.

This trial employs a selective approach for collection of safety data. The investigator is responsible for detecting, documenting, recording and following up on:

- SAEs
- AEs requiring event adjudication or additional data collection on specific event forms, irrespective of seriousness, see Table 9-1
- AEs leading to discontinuation of trial product, irrespective of seriousness
- Pregnancies
- Technical complaints

Table 9-1 AEs requiring event adjudication or additional data collection

Event type (serious and non-serious) including description	Adjudication outcome	Additional form(s) required
Death All cause death	• Cardiovascular death • Renal death • Non-cardiovascular, non-renal death	• Adjudication form
Acute coronary syndrome (ACS) All types of acute myocardial infarction Unstable angina pectoris requiring hospitalisation	• Acute myocardial infarction • Hospitalisation for unstable angina pectoris	• Adjudication form and • Specific event form in case of revascularisation
Events leading to coronary artery revascularisation (non-ACS) Non-ACS events (e.g. stable angina pectoris) leading to a 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 the AE diagnosis	• Not applicable	• Specific event form
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 ischemia, with or without infarction	• Stroke	• Adjudication form • Modified Rankin scale form*
Heart failure requiring hospitalisation or urgent heart failure visits New episode or worsening of existing heart failure leading to an urgent, unscheduled hospital admission or clinic/office/emergency department visit	• Heart failure hospitalisation • Urgent heart failure visit	• Adjudication form
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	• Acute limb ischemia hospitalisation • Chronic limb ischemia hospitalisation	• Adjudication form
Acute pancreatitis Events of acute pancreatitis	• Acute pancreatitis	• Adjudication form
Events leading to renal replacement therapy Dialysis treatment (haemodialysis or peritoneal dialysis) Kidney transplantation Note: The underlying condition should be reported as the AE diagnosis	• Chronic renal replacement therapy	• Adjudication form
Malignant neoplasm Malignant neoplasm by histopathology or other substantial clinical evidence	• Not applicable	• Specific event form
Diabetic retinopathy New onset or worsening of diabetic retinopathy	• Not applicable	• Specific event form
Acute gallbladder disease Events of symptomatic acute gallbladder disease (including gallstones and cholecystitis)	• Not applicable	• Specific event form

Event type (serious and non-serious) including description	Adjudication outcome	Additional form(s) required
Medication errors related to trial product Medication error (accidental errors related to trial product): Wrong drug administered instead of trial product. Wrong route of administration or accidental administration of a lower or higher dose than intended where clinical consequences for the patient were likely to happen, although they did not necessarily occur	• Not applicable	• Specific event form
Severe hypoglycaemic episode An episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. Plasma glucose values 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 (American Diabetes Association[11])	• Not applicable	• Specific event form • If the episode fulfils the criteria of an SAE, an AE form and a safety information form must also be completed Japan: For country specific require-ments, see Appendix 8

* Disability after a stroke or TIA event, see section 9.4.5

Description of events is to guide investigators with regards to reporting of AEs. Event definitions are included in the charter for the event adjudication committee (EAC).

9.2.1 Time period and frequency for collecting AE and SAE information

All events meeting the definition of an SAE (see Appendix 4) and AEs leading to discontinuation of trial product, pregnancies and events specified in Table 9-1 must be collected and reported. These events will be collected from the day of randomisation and until the follow-up visit, at the time points specified in the flowchart.

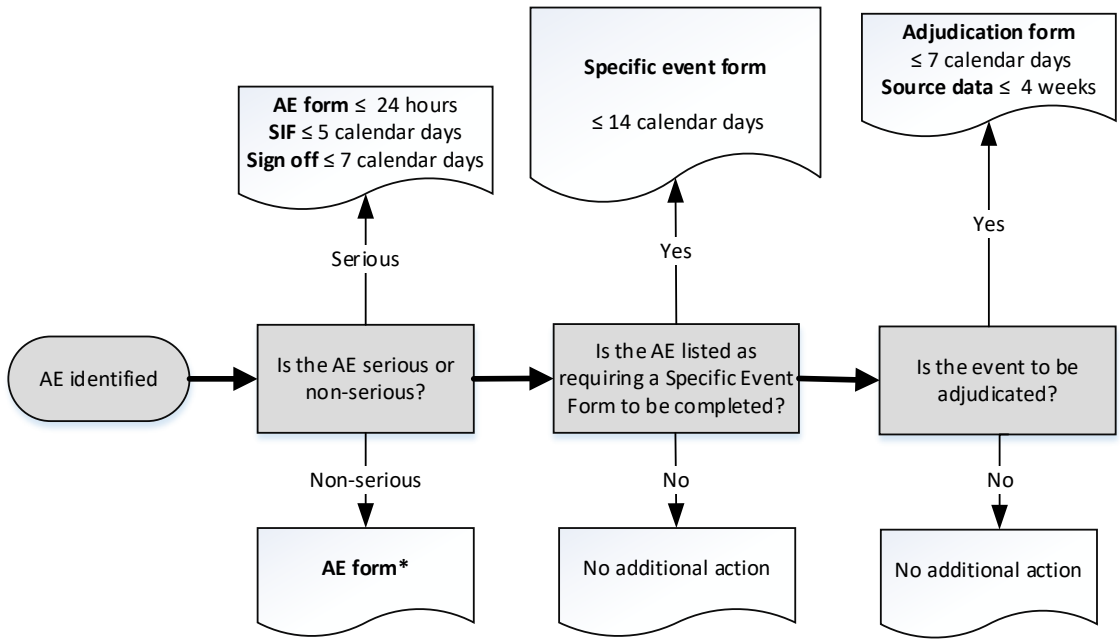
All SAEs will be recorded and reported to Novo Nordisk or designee within 24 hours of investigator's knowledge of the SAE, as indicated in Appendix 4. The investigator must submit any updated SAE data to Novo Nordisk within 24 hours of it being available.

Investigators are not obligated to actively seek for AEs or SAEs 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 investigational trial product or trial participation, the investigator must promptly notify Novo Nordisk.

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 4.

Timelines for reporting of AEs, including events for adjudication, Section 9.2.1.1, are listed in Figure 9-1.

Some AEs require additional data collection via a specific event form. The relevant AEs are listed in Table 9-1 and the reporting timelines in Figure 9-1.



Timelines are from the awareness of an AE.
Queries and follow-up requests to be resolved ≤ 7 calendar days.
* Only for non-serious adverse events required to be reported according to section 9.2
AE: Adverse Events, SAE: Serious Adverse Events, SIF: Safety Information Form

Figure 9-1 Safety reporting timelines

9.2.1.1 Events for adjudication

The list of events for adjudication can be found in Table 9-1 and the reporting timelines in Figure 9-1. Event adjudication will be performed for events in randomised patients. These events are reviewed by an independent external event adjudication committee in a blinded manner, refer to Appendix 3 for further details.

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

1. Investigator-reported events for adjudication: When reporting AEs, the investigator must select the appropriate AE category based on pre-defined criteria (see Table 9-1). If the selected AE category is in scope for adjudication, an adjudication form should be completed. Relevant

source documents (as specified in the Event Adjudication Site Manual) must, if obtainable, be collected and uploaded to the Event Adjudication System (EAS).

2. Deaths (AEs reported with fatal outcome): When an AE is reported with fatal outcome, a death adjudication form will appear in the eCRF. This form must be completed and all source documents associated with the patients' death must, if obtainable, be collected and uploaded to the EAS.
3. AE search (standardised screening): All AEs not directly reported by the investigator as requiring adjudication, will undergo screening to identify potential events for adjudication. If the AE is deemed relevant for adjudication, an adjudication form will be generated in the eCRF. This form must be completed, and all source documents (as specified in the Event Adjudication Site Manual) must, if obtainable, be collected and uploaded to the EAS.
4. EAC-identified events: During review of source documents provided for another event for adjudication, the EAC may identify additional events in scope for adjudication that were not initially reported by the investigator. In these instances, the investigator will be notified of the newly identified event and has the option to report the EAC-identified event. Regardless of whether the investigator decides to report the event, it will undergo adjudication. Occasionally, EAC-identified events may require the investigator to collect additional source documents and upload these, if obtainable, to the EAS.

The adjudication form for the event in question should be completed in the eCRF within 7 calendar days from the AE is reported in the eCRF.

Copies of source documents should be labelled with trial ID, patient number, AE number (if applicable), redacted (anonymised of personal identifiers) and uploaded to the EAS as soon as possible and preferably within 4 weeks. 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.

The assessments made by both the event adjudication committee and the investigator will be evaluated and included in the clinical trial report.

9.2.2 Method of detecting AEs and SAEs

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.

9.2.3 Follow-up on AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow all events until resolution, stabilization, or if the event is otherwise explained (e.g. chronic condition). Further information on follow-up procedures is given in Appendix 4.

9.2.4 Regulatory reporting requirements for SAEs

Prompt notification by the investigator to Novo Nordisk 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, IRB/IEC, and investigators.

To avoid introducing bias and to maintain the integrity of the primary analysis, Novo Nordisk will exempt SAEs that are part of the primary objective evaluation (MACE) from unblinding and regulatory reporting during trial conduct, even though the cases fulfil the definition of suspected unexpected serious adverse reactions (SUSARs). The definition of MACE is: Cardiovascular death, non-fatal myocardial infarction, non-fatal stroke. The independent DMC (Appendix 3) receives unblinded data and makes recommendations to the Novo Nordisk safety committee on an ongoing basis. This ensures adequate monitoring of safety while maintaining SAE reports related to the primary endpoint blinded for Novo Nordisk.

At the end of the trial, when treatment is revealed, all exempted cases which meet the criteria for expedited reporting SUSARs will be submitted to the regulatory authorities. Because multiple cases will be identified simultaneously, Novo Nordisk will not be able to fulfil the 7 days requirement for fatal or life-threatening events but will within 60 days after code break have all SUSARs submitted to the regulatory authorities.

In case a regulatory authority requires the blinded report on an expedited basis, Novo Nordisk will submit individual blinded case reports related to investigational product to the relevant regulatory authorities on an expedited basis.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Novo Nordisk policy and forwarded to investigators as necessary.

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[8] and will notify the IRB/IEC, if appropriate according to local requirements.

9.2.5 Pregnancies and associated adverse events

Details of pregnancies in female patients will be collected after randomisation and until pregnancy outcome.

If a pregnancy is reported in female patients, the investigator should inform Novo Nordisk within 14 calendar days of learning of the pregnancy and should follow the procedures outlined in Appendix 5.

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.

The investigator should report information on the patient and the pregnancy outcome until the new-born infant is one month of age in accordance with European Medicines Agency (EMA).[12] Information about the pregnancy and pregnancy outcome/health of the new-born infant has to be reported on paper pregnancy forms and be forwarded to Novo Nordisk either by fax, encrypted e-mail or courier.

9.2.6 Technical complaints

The investigator must assess whether a technical complaint is related to an AE. The definitions and reporting process for technical complaints can be found in Appendix 6.

9.3 Treatment of overdose

There is no specific antidote for overdose with semaglutide. Limited data are available with regard to overdose in patients treated with oral semaglutide. Based on data from treatment with s.c. semaglutide, the most commonly reported adverse reaction was nausea and all patients recovered without complications. In the event of an overdose, appropriate supportive treatment should be initiated according to the patients' clinical signs and symptoms. A prolonged period of observation and treatment for these symptoms may be necessary, taking into account the half-life of semaglutide of approximately one week.

In the event of an overdose, the investigator should closely monitor the patient for overdose-related AE/SAEs. Decisions regarding dose interruptions or modifications will be made by the investigator based on the clinical evaluation of the patient. Accidental overdose must be reported as a medication error. Refer to Section 9.2.1 for further details. For more information on overdose, also consult the current version of the oral semaglutide IB.[8]

9.4 Safety assessments

Planned time points for all safety assessments are provided in the flowchart Section 2.

A **concomitant illness** is any illness that is present at the start of the trial 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 has experienced in the past, i.e. prior to randomisation.

The following concomitant illness/medical history should be recorded in the eCRF:

- Type 2 diabetes - date of diagnosis
- Diabetes complications
- History of cardiovascular and chronic kidney diseases. This also includes each medical condition(s) that qualified the patient for participation in the trial according to inclusion criterion #5 a-d
- History of eye diseases
- History of gallbladder diseases
- History of pancreatitis
- Other relevant concomitant illness/medical history including malignant neoplasms

In case of an abnormal and clinically significant finding, the investigator must record the finding on relevant disease specific history form or the Medical History/Concomitant Illness form if it is present before randomisation. Any new finding fulfilling the AE definition (see Appendix 4) during the trial and any clinically significant worsening from baseline (visit 2) must be reported as an AE, if applicable, (see Section 9.2).

9.4.1 Physical examinations

Physical examinations should be performed according to local procedures, when indicated in Section 2.

A physical examination will include assessments of the:

- General appearance
- Thyroid gland
- Respiratory system
- Cardiovascular system
- Gastrointestinal system incl. mouth
- Extremities
- Central and peripheral nervous system

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

Relevant findings present at or prior to randomisation should be recorded on the concomitant illness/medical history forms in the eCRF in accordance with Section 9.4. Findings not present at randomisation should be reported as AEs according to Section 9.2.

Body measurements (e.g. height, weight and waist circumference) will be measured and recorded as specified in the flowchart Section 2.

Height should be measured without shoes in centimetres (cm) or inches (in) and recorded in the eCRF.

Body weight should be measured in kilogram (kg) or pound (lb), with an empty bladder, without shoes and only wearing light clothing. The actual value of the weight should be recorded in the eCRF without rounding and the same equipment should be used throughout the trial.

Waist circumference is the abdominal circumference measured midway between the lower rib margin and the iliac crest. It should be measured when the patient is in a standing position with a non-stretchable measuring tape and to the nearest cm or inch.

Waist circumference and liver parameters are measured at baseline for calculation of fatty liver index.

9.4.2 Vital signs

Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the patient in a quiet setting without distractions (e.g. television, cell phones). The measured values should be recorded in the eCRF without rounding. Blood pressure and pulse measurements should be assessed in a sitting position with a completely automated device. Manual techniques should be used only if an automated device is not available.

9.4.3 Clinical laboratory assessments

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

9.4.4 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.

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 the flowchart in Section 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 according to section 9.2.

9.4.5 Disability after a stroke or TIA event

The modified Rankin Scale is used to measure the degree of disability in daily activities after a stroke. A modified Rankin Scale form should be completed for all events sent to adjudication for stroke including evens of TIA to ensure that all events of an EAC confirmed stroke will have a disability outcome recorded. The degree of disability according to the scale should be assessed after a minimum of 90 days post-event (most often this will be at the patient's second site visit after the stroke or TIA). The event should be recorded in the eCRF.

9.5 Pharmacokinetics

Not applicable.

9.6 Pharmacodynamics

Not applicable.

9.7 Genetics

A blood sample for DNA analysis will be collected from patients who have consented to participate in the optional biobank component of the trial. Refer to Section 9.8 and Appendix 7 for further details.

Algeria, Brazil, China, Columbia, Israel, South Korea and Turkey: For country specific requirements, please see Appendix 8.

9.8 Biomarkers

Collection of samples for biomarker research is a component 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 and stored for future use.

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

Genetic analyses will include analysis of candidate genes or genetic markers throughout the genome with the purpose of understanding and predicting response to semaglutide as well as to understand cardiometabolic diseases. Analyses of circulating biomarkers will measure hormones, metabolites or other non-genetic serum entity with the purpose of understanding and predicting response to semaglutide as well as understanding cardiometabolic diseases.

These samples need to be frozen and should be sent at monthly intervals in batches 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 7).

Algeria, Brazil, China, Columbia, Israel, South Korea and Turkey: For country specific requirements, please see Appendix 8.

10 Statistical considerations

10.1 Sample size determination

The trial is designed with 90% power to confirm superiority for the primary endpoint, i.e. reject the null-hypothesis of hazard ratio (HR) ≥ 1.0 against the one-sided alternative of HR < 1.0, where HR is the hazard ratio of oral semaglutide versus placebo. An alpha spending function will be used that approximates O'Brian Fleming stopping boundaries for the overall Type I error probability of 2.5% (one-sided). Based on a randomisation ratio of 1:1 and assuming a true HR of 0.83 a total of 1,225 primary endpoint events are required for 90% power. For calculation the number of randomised patients the following is assumed:

- annual primary endpoint rate in the placebo group of 3.5%
- uniform recruitment occurs in 18 months
- annual lost to follow-up rate in both treatment groups of 1%
- trial duration is five years and five weeks

Under these assumptions, a total of 9,642 patients are needed for randomisation.

Confirmatory secondary endpoints

If superiority is confirmed for the primary endpoint the below confirmatory secondary endpoints will be controlled for multiplicity through a hierarchical testing strategy. The marginal powers below are calculated under the assumptions that the trial continues to the final analysis and a significance level of 2.5% (one-sided).

The marginal power for superiority in favour of oral semaglutide for the CKD endpoint with 9,642 randomised patients is 94%. This is based on an assumed hazard ratio of 0.80 and an annual event rate of 2.8% in the placebo group.

The marginal power for superiority in favour of oral semaglutide for CV death with 9,642 randomised patients is 56%. This is based on an assumed hazard ratio of 0.83 and an annual event rate of 1.4% in the placebo group.

The marginal power for superiority in favour of oral semaglutide for the MALE endpoint with 9,642 randomised patients is 44%. This is based on an assumed hazard ratio of 0.75 and an annual event rate of 0.44% in the placebo group.

The assumptions for annual event rate of primary endpoint and confirmatory secondary endpoints, lost to follow-up rates and the true hazard ratios are based on the LEADER[13] and SUSTAIN 6[1] CV outcomes trials.

10.2 Definition of analysis sets

The full analysis set (FAS) is defined as all randomised patients and grouped in analyses according to the treatment assigned at randomisation.

Patients continue in the trial and are part of FAS regardless of discontinuation of randomised treatment and any other intercurrent event. A patient is considered lost to follow-up (LTFU) if the patient does not complete the trial and does not withdraw consent. Trial completers are defined as patients that either attend the end-of-trial follow-up visit or who die during the in-trial period.

The in-trial observation period for a patient is defined as the period from date of randomisation to the first of (both inclusive):

- date of follow-up visit
- date when patient withdrew consent
- date of last contact with patient (for patient lost to follow-up)
- date of death

10.3 Statistical analyses

A comprehensive statistical analysis plan (SAP) will be available before first patient first visit (FPFV), including further details of interim testing.

Novo Nordisk will perform the statistical analyses except interim testing, see Section 10.3.4. A statistician independent of trial conduct, DMC analyses, interim testing, and external to Novo Nordisk will repeat the statistical analyses of the primary endpoint and secondary confirmatory endpoints.

General considerations

For confirmatory endpoints controlled for multiplicity, estimated treatment effects will be presented together with two-sided 95% confidence intervals (CIs) and one-sided p-values for test of the hypothesis of superiority. For reporting of results, the estimated treatment effect and the 95% confidence interval will be accompanied by the two-sided p-value.

For non-confirmatory endpoints, the estimated treatment effects will be reported together with two-sided 95% CIs and two-sided p-values.

Baseline value is defined as the latest available measurement from the randomisation visit or the screening visit. Thus, if a randomisation assessment is missing then the assessment from screening is used as the baseline assessment, if available.

Missing data are defined as data that are planned and can be observed but are not present in the database. This implies that data that are structurally missing due to death or administrative censoring are not considered missing.

If adjudicated, time-to-event endpoints are defined based on outcomes of the EAC evaluations. If a patient experiences the event of interest during the in-trial observation period, the endpoint is the time from randomisation to the date of event. While vital status is ascertained systematically throughout the trial, non-fatal events (e.g. non-fatal MI or non-fatal stroke) cannot be systematically collected after withdrawal of consent, lost-to-follow-up, or after end-of-trial visit. For this reason, any event occurring after the in-trial observation period is not included in analyses, unless otherwise stated.

Time-to-event endpoints are censored at the end of the in-trial period if the event of interest did not happen during this period and the patient is alive at the end of the period. Censoring due to LTFU and withdrawal of consent assume independent censoring. Additional anticipated intercurrent events and handling of these in context of the estimand for the primary and confirmatory secondary time-to-event endpoints are described in Table 10-1.

10.3.1 Primary endpoint

The HR for comparing oral semaglutide versus placebo will be estimated from a Cox proportional hazards model with treatment group (semaglutide, placebo) as fixed factor together with the 2-sided 95% CI and one-sided fixed design p-value for hypothesis testing. The score test from the Cox model will be used for testing. The following superiority hypothesis will be tested:

H_0: HR $\geq$ 1.0 against H_a: HR < 1.0.

Superiority of oral semaglutide versus placebo will be considered confirmed if the associated H_0 is rejected based on nominal significance level derived from the pre-specified alpha spending based on the actual observed number of events available for the analysis. Final inference on termination is

adjusted for the group sequential design by using the likelihood ratio ordering for the p-value, 95% CI and HR.

Competing risk from non-CV deaths will be handled as censorings in the primary Cox analysis. Please, refer to Table 10-1 for handling of other intercurrent events.

Sensitivity analysis

If superiority is established for the primary endpoint, the following sensitivity analysis is performed. The primary analysis assumes independent censoring for patients who are LTFU or who withdrawn consent. To investigate the impact of this assumption on the superiority results of the primary analysis, a tipping point analysis will be made. In this analysis, patients in the oral semaglutide treatment group will have their event times imputed with an increasing penalty in the sense that their risk of MACE is increased (the penalty) following censoring compared to while under observation. The placebo patients will be imputed with no penalty, i.e. assuming same event before and after censoring. Multiple imputed data sets will be analysed for each penalty using the above Cox model and results will be combined using Rubin's rule. The tipping point is then defined as the penalty needed to turn around the superiority conclusion.

10.3.2 Secondary endpoints

Secondary endpoints are categorised as being confirmatory when they are analysed under multiplicity control.

10.3.2.1 Confirmatory secondary endpoints

If superiority is established for the primary endpoint, the superiority hypothesis stated in section 10.3.1 is tested for the confirmatory secondary endpoints under multiplicity control via a hierarchical testing scheme using the following order:

- composite CKD endpoint
- CV death
- MALE endpoint

The testing procedure is stopped the first time an analysis fails to confirm superiority of the endpoint in question using a one-sided significance level of 2.5%. No adjustments of the nominal significance level of the confirmatory secondary endpoint analyses due to the group sequential design are planned.

The confirmatory secondary endpoints will be analysed and tested separately with a Cox proportional hazards model as described for the primary endpoint including tipping point analyses.

For the composite CKD endpoint, the analysis will exclude patients who already have met relevant renal components at baseline. Furthermore for this endpoint, missing data for eGFR, due to missing blood samples while patients are still being followed, will be imputed using multiple imputation.

The following Table 10-1 describes how anticipated intercurrent events during the trial are handled for confirmatory endpoints.

Table 10-1 Statistical handling of intercurrent events for the confirmatory endpoints

Endpoint	Intercurrent event	Handling
Time to first occurrence of MACE	• Treatment discontinuations • Medication modifying cardio-renal risk • Initiation of chronic renal replacement therapy	Patients will be followed and events collected after intercurrent events and used in the analysis
	• Trial discontinuation (withdrawal of consent or lost-to follow-up)	Censoring at time of trial discontinuation
	• Non-CV death (competing risk)	Censoring at time of non-CV death in the Cox model
Time to first occurrence of composite CKD	• Treatment discontinuations • Medication modifying cardio-renal risk	Events and follow-up time will be collected after intercurrent events and used in the analysis
	• Trial discontinuation (withdrawal of consent or lost-to follow-up)	Censoring at time of trial discontinuation
	• Non-renal and Non-CV death (competing risk)	Censoring at time of non-renal or non-CV death in the Cox model
Time to occurrence of CV death	• Treatment discontinuations • Medication modifying cardio-renal risk • Initiation of chronic renal replacement therapy	Events and follow-up time will be collected after intercurrent events and used in the analysis
	• Trial discontinuation (withdrawal of consent or lost-to follow-up)	Censoring at time of trial discontinuation
	• Non-CV death (competing risk)	Censoring at time of non-CV death in the Cox model
Time to first occurrence of MALE	• Treatment discontinuations • Medication modifying cardio-renal risk • Initiation of chronic renal replacement therapy	Patients will be followed and events collected after intercurrent events and used in the analysis
	• Trial discontinuation (withdrawal of consent or lost-to follow-up)	Censoring at time of trial discontinuation
	• All cause death (competing risk)	Censoring at time of death in the Cox model

10.3.2.2 Supportive secondary endpoints

Each of the supportive secondary time-to-event endpoints will be analysed with the same Cox proportional hazards model as the primary endpoint.

The continuous supportive secondary endpoints (change from baseline to 2 years) are analysed using multiple imputation for missing values. An imputation model (linear regression) is estimated separately for each treatment group. It will include baseline value as a covariate estimated based on patients having an observed data point, irrespective of adherence to randomised treatment, at 2 years. The fitted model is used to impute values for all patients that do not have an observed data point at 2 years to create 500 complete data sets. The completed data sets are analysed by an

ANCOVA adjusted for treatment as fixed factor and baseline value as covariate. Rubin's rule is used to combine the results.

Number of severe hypoglycaemic episodes will be analysed using a marginal recurrent event regression model taking into account the competing risk of all-cause death.

10.3.3 Exploratory endpoints

The continuous exploratory endpoints (change from baseline to 2 years) will be analysed using multiple imputation for missing values as described for the supportive secondary endpoints.

Current smoking at year two (yes/no) will be analysed using a binary regression model adjusted for baseline smoking status (yes/no).

10.3.4 Interim testing for efficacy

Interim testing evaluating the primary endpoint for superiority will be performed based on locked snapshot of the study database at the time-point of an interim testing. Patients without a primary endpoint event prior to the analysis cut-off date will be censored with the censoring date defined as the first of in-trial end-date and analysis cut-off date.

Interim testing will be performed by a statistician independent of trial conduct and external to Novo Nordisk. The DMC evaluates the unblinded interim testing using the group sequential stopping boundaries as guidance. Stopping the trial for superiority is allowed if a stopping boundary is crossed and the DMC makes the decision to recommend early trial termination.

If the trial is terminated early for superiority following an interim testing, definitive evaluation of superiority for the primary endpoint will be performed based on updated nominal significance levels. All events from the in-trial observation period including events collected after interim cut-off date will be included in this confirmatory evaluation.

10.3.5 Sequential safety analysis and safety monitoring

Blinded and unblinded data analyses during trial conduct will be performed by the DMC, as described in the DMC charter. Trial integrity will be ensured by using a statistician independent of trial conduct and external to Novo Nordisk to prepare data for the DMC. The sequential analyses performed by the DMC will be based on accumulated efficacy (see Section 10.3.4) and safety data and will be performed to make recommendations regarding the ongoing conduct of the trial to ensure acceptable benefit/risk ratio for patients in the trial.

10.4 Pharmacokinetic and/or pharmacodynamic modelling

Not applicable.

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12 Appendices

Appendix 1 Abbreviations and Trademarks

ABI	ankle-brachial index
ACS	acute coronary syndrome
ADA	American Diabetes Association
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BG	blood glucose
CI	confidence interval
CKD	chronic kidney disease
CKD-EPI	chronic kidney disease – epidemiology collaboration
CRF	case report form
CT	computerized tomography
CTR	clinical trial report
CV	cardiovascular
CVD	cardiovascular disease
CVOT	cardiovascular outcome trial
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DUN	dispensing unit number
EAC	event adjudication committee
EAS	event adjudication system
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EOT	end of treatment
eGFR	estimated glomerular filtration rate
FAS	full analysis set
FDA	U.S. Food and Drug Administration

FDAAA	FDA Amendments Act
FPFV	first patient first visit
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GLP-1 RA	glucagon-like peptide-1 receptor agonist
HbA_{1c}	glycosylated haemoglobin
HDL	high-density lipoprotein
hCG	human chorionic gonadotropin
HR	hazard ratio
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICH	International Council for Harmonisation
IEC	independent ethics committee
IMP	investigational medicinal product
IRB	institutional review board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IWRS	interactive web response system
LAR	legally acceptable representative
LDL	low-density lipoprotein
LPLV	last patient last visit
LTFU	lost to follow-up
MACE	major adverse cardiovascular events
MALE	major adverse limb events
MEN2	multiple endocrine neoplasia type 2
MI	myocardial infarction
MoCA	Montreal Cognitive Assessment
MR	magnetic resonance
MTC	medullary thyroid cancer
NYHA	New York Heart Association
OD	once daily

PAD	peripheral artery disease
PCD	primary completion date
PCI	percutaneous coronary intervention
PG	plasma glucose
PP	per protocol
RA	receptor agonist
SAE	serious adverse event
SAP	statistical analysis plan
s.c.	subcutaneous(-ly)
SMPG	self-measured plasma glucose
SUSAR	suspected unexpected serious adverse reaction
TIA	transient ischemic attack
TMM	trial materials manual
T2D	type 2 diabetes
ULN	upper limit of normal
WOCBP	woman of child bearing potential

Appendix 2 Clinical laboratory tests

- The laboratory analyses will be performed by a central laboratory, unless otherwise specified. A list of laboratory supplies and procedures for obtaining, handling, transportation and storage of samples, will be described in laboratory flow charts/manual and provided to all sites.
- Blood samples need to be obtained. The tests detailed in Table 12-1 will be performed by the central laboratory.
- Additional tests may be performed at any time during the trial as determined necessary by the investigator or required by local regulations. Only laboratory samples specified in the protocol should be sent to the central laboratory for analysis; if additional laboratory sampling is needed, e.g. to follow up on AEs, this must be done at a local laboratory
- The laboratory equipment may provide analyses not requested in the protocol but produced automatically in connection with the requested analyses according to specifications in the laboratory standard operating procedures. Such data will not be transferred to the trial database. Brazil: For country specific requirements, please see Appendix 8.
- The investigator must review all laboratory results for concomitant illnesses and AEs.
- Ambient laboratory samples will be destroyed shortly after the analyses have taken place.
- Human biosamples for retention will be stored as described in Appendix 7.

Table 12-1 Protocol-required central laboratory assessments

Laboratory assessments	Parameters
Glucose metabolism	• HbA_{1c}

Renal function	• Creatinine
	• eGFR, calculated per CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration)
	• A confirmatory test is needed when
	  • onset of ≥ 50% reduction in eGFR (CKD-EPI)
	  • onset of eGFR (CKD-EPI) < 15 mL/min/1.73 m^2
	• When a confirmatory test is needed, it should be done at the next scheduled contact, but no earlier than 4 weeks after eGFR has reached the threshold, by obtaining blood samples for the central laboratory for measurement of creatinine
	• Confirmation of a ≥ 50% reduction in eGFR (CKD-EPI) compared with baseline is needed unless a persistent 50% reduction in eGFR compared with baseline, has previously been confirmed for this patient
	• Confirmation of a eGFR (CKD-EPI) < 15 mL/min/1.73 m^2 is needed unless persistent eGFR below < 15 mL/min/1.73 m^2 has previously been confirmed for this patient
	• For the central laboratory calculation of the eGFR information on race (black/white/other) and year of birth will be collected on the laboratory requisition form. 01-Jan of the year of birth will be used for the calculation

Liver parameters	• Alanine aminotransferase (ALT) • Aspartate aminotransferase (AST) • Gamma glutamyltransferase (GGT) • Total bilirubin
Lipids (non-fasting)	• Total cholesterol • High density lipoprotein (HDL) cholesterol • Low density lipoprotein (LDL) cholesterol • Triglycerides
Biobank	• These samples need to be frozen and should be sent at monthly intervals in batches to the central laboratory
Inflammation	• High sensitivity C-Reactive Protein (hsCRP)
Pregnancy testing	• Urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[1]
Notes: [1] Local urine testing will be standard unless serum testing is required by local regulation or IRB/IEC.	

Appendix 3 Trial governance considerations

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[14] and applicable ICH Good Clinical Practice (GCP) Guideline[15]
  - Applicable laws and regulations
- The protocol, informed consent form, investigator's brochure (as applicable) and other relevant documents (e.g. advertisements), must be submitted to an IRB/IEC and reviewed and approved by the IRB/IEC before the trial is initiated.
- Regulatory authorities will receive the clinical trial application, protocol amendments, reports on SAEs, and the clinical trial report 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 trial 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 clinical trial report (CTR) synopsis to the IRB/IEC.

Japan, Mexico and Russia: For country specific requirements please see Appendix 8.

2) Financial disclosure

Investigators and subinvestigators 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 trial sites: verification under disclosures per Code of Federal Regulations (CFR) of Financial Conflict of Interest.

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. This includes the use of an impartial witness where required according to local requirements.
- 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 will be required to sign and date a statement of informed consent that meets the requirements of local regulations, ICH guidelines[15], Declaration of Helsinki[14] and the IRB/IEC or trial site.
- The medical record must include a statement that written informed consent was obtained before any trial related activity and the date when the written consent was obtained. The authorised person obtaining the informed consent must also sign and date the informed consent form before any trial related activity.
- The responsibility of seeking informed consent must remain with the investigator, but the investigator may delegate the task of informing to a medically qualified person, in accordance with local requirements.
- Patients and/or their legal authorised representative (LAR) 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 or the patient's LAR

Brazil: For country specific requirements, please see Appendix 8.

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.

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; patient names or any information which would make the patient identifiable will not be transferred.

- 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 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.

6) Committee structure

Novo Nordisk safety committee

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

Data monitoring committee

The data monitoring committee (DMC) is an independent, external committee composed of members whose expertise covers relevant specialties including statistics. The DMC is established to review and evaluate accumulated data from the trial at predefined time points as well as ad hoc. This is done in order to protect the safety of the patients and to evaluate the benefit-risk balance. The DMC will have access to unblinded data, and will provide recommendations on trial continuation, modification or termination.

Information regarding responsibilities, procedures and workflow to be used by the DMC are specified in the DMC charter.

Event adjudication committee

An independent external event adjudication committee is established to perform ongoing blinded adjudication of selected AEs and deaths (see Table 9-1). The EAC will evaluate events sent for adjudication using pre-defined definitions and guidelines in accordance with the EAC Charter. The evaluation is based on review of pre-defined clinical data collected by the investigational 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 purpose of the adjudication is to confirm events in a consistent manner according to standardized criteria using independent external medical experts.

Steering committee

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

Supportive panels

Global expert panel

A global expert panel (GEP) will consist of selected principal investigators, identified as national leaders and scientific experts, and of designated Novo Nordisk employees. The panel will discuss and advise on global and local operational issues related to trial conduct. The panel will operate under a charter agreed with Novo Nordisk. National investigators that are not part of the global panel may be appointed in some of the large countries.

Patient recruitment and retention panel

A patient recruitment and retention panel (PRRP) will consist of study coordinators, highly experienced in the conduct of diabetes and CV outcomes trials, and designated Novo Nordisk employees. The panel will discuss and advise on global recruitment, retention and adherence issues related to trial conduct. The panel will operate under a charter agreed with Novo Nordisk.

National study coordinators

For each country participating in the trial, where it is appropriate, a national study coordinator (NSC) will be selected. The national study coordinators will provide operational input to patient recruitment, retention and adherence related topics. The national study coordinators will operate under a charter agreed with Novo Nordisk.

7) 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 clinical trial report for this trial.

A chair of the steering committee will be appointed by Novo Nordisk to review and sign the clinical trial report (signatory investigator) on behalf of all participating investigators.

Communication of results

Novo Nordisk commits to communicate and disclose results of trials regardless of outcome. Disclosure includes publication of a manuscript in a peer-reviewed scientific journal, abstract submission with a poster or oral presentation at a scientific meeting or disclosure by other means.

The results of this trial will be subject to public disclosure on external web sites according to international and national regulations. Novo Nordisk reserves the right to defer the release of data until specified milestones are reached, for example when the clinical trial report is available. This includes the right not to release the results of interim testing, 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.

Authorship

The steering committee will be responsible for communication of primary trial results. This will include appointing the publication group and authorship, overseeing the preparations and final approval of manuscripts and congress communications of trial results.

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.[16]

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 trial site will be named in an acknowledgement or in the supplementary material, as specified by the journal.

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.

Investigator access to data and review of results

As owner of the trial database, Novo Nordisk has the discretion to determine who will have access to the database. Individual investigators will have their own research patients' data, and will be provided with the randomisation code after results are available.

8) 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)[17], the Food and Drug Administration Amendments Act (FDAAA)[18, 19, 20], European Commission Requirements[19, 20] 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 trial is event-driven. The Primary Completion Date (PCD) is the last assessment of the primary endpoint, and is for this trial the last patient last visit (LPLV). The trial will therefore be registered with an estimated PCD corresponding to the estimated LPLV, which is first patient randomised plus 61 months. The PCD determines the deadline for results disclosure at Clinicaltrials.gov according to FDA Amendments Act.

China: For country specific requirements, please see Appendix 8.

9) Data quality assurance

Case Report Forms (CRFs)

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 data, cognitive testing and patient surveys). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF and for ensuring that all relevant questions are

answered, and that no empty data field exists. If a test or an assessment has not been done and will not be available, or if the question is irrelevant (e.g. is not applicable), indicate this by choosing the appropriate option. Free-text comments are discouraged.

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

- AE forms
- Safety information forms
- Technical complaint forms (also to be used to report complaints that are not patient related, e.g. discovered at trial site before allocation)

The following will be provided as paper CRFs, if needed:

- Pregnancy forms
- Other CRFs

In case of the use of paper forms, they need to be forwarded to Novo Nordisk either by fax, encrypted e-mail or courier.

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.

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 trial 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 trial sites.
- Monitors will review the patient's medical records and other source data to ensure consistency and/or identify omissions compared to the CRF.

Protocol compliance

Deviations from the protocol should be avoided. If deviations do occur, the investigator must inform the monitor without any 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) Source documents

- All data entered in the CRF must be verifiable in source documentation other than the CRF.
- Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the trial site.
- Data reported on the paper CRF or entered in the electronic CRF 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 trial site. There will only be one source document defined at any time for any data element.

11) 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 and other patient data will be provided in an electronic readable format to the investigator before access is revoked to the systems 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 trial site. If the provided electronic data (e.g. the CD-ROM) is not readable during the entire storage period, the investigator can request a new copy. A copy of all data will be stored by Novo Nordisk.
- Patient's medical records must be kept for the maximum period permitted by the hospital, institution or private practice.

12) Trial and site closure

Novo Nordisk reserves the right to close the trial 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.

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

The investigator may initiate trial 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 trial 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.

Pre-planned interim testing may allow for premature termination of the trial.

13) Responsibilities

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

14) 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.

Austria, Belgium, France and Mexico: For country specific indemnity statements, please see Appendix 8.

Appendix 4 Adverse events: definitions and procedures for recording, evaluation, follow-up, and reporting

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

Events meeting the AE definition
• Any abnormal laboratory test results or safety assessments, including those that worsen from randomisation, considered clinically significant in the medical and scientific judgment of the investigator. • Abuse: Persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects (e.g. overdose with the intention to cause harm) • Misuse: Situations where the medicinal product is intentionally or inappropriately used not in accordance with the protocol • Exacerbation of a chronic or intermittent pre-existing 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 trial product regardless of intent.
Events NOT meeting the AE definition
• Pre-existing conditions, anticipated day-to-day fluctuations of pre-existing conditions, including those identified during screening or other trial procedures performed before exposure to trial product. Note: pre-existing conditions should be recorded as medical history/concomitant illness. • Pre-planned procedures, unless the condition for which the procedure was planned has worsened from randomisation.

Definition of an SAE
An SAE is an AE that fulfils at least one of the following criteria:
• Results in death
• 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.
• 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 serious 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 of a pre-existing condition that did not worsen from randomisation is not considered an AE. Note: ▪ Hospitalisations for administrative, trial related and social purposes do not constitute AEs and should therefore not be reported as AEs or SAEs. ▪ Hospital admissions for surgical procedures, planned before trial inclusion, are not considered AEs or SAEs.
• 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.

- Is a congenital anomaly/birth defect

- 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 trial product.
  - 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).

Description of AEs requiring additional data collection (via specific event form) and events for adjudication can be found in Table 9-1

Medication error:

A medication error is an unintended failure in the trial drug 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 DUN is not considered a medication error unless it results in administration of wrong drug.
- Wrong route of administration
- 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 to be reported as a medication error.

AE and SAE recording

- All SAEs, AEs leading to discontinuation of trial product, AEs described in Table 9-1 must be recorded by the investigator on an AE form. 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 "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 intensity 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: Severe is a category used for rating the intensity of an event; and both an AE and SAE can be assessed as severe. An event is defined as 'serious' when it meets at least one of the outcomes described in the definition of an SAE and not when it is rated as severe

Assessment of causality

The investigator is obligated to assess the relationship between trial product and the occurrence of each AE/SAE.

Relationship between an AE/SAE and the relevant trial product(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 trial product.

Alternative aetiology, such as underlying disease(s), concomitant medication, and other risk factors, as well as the temporal relationship of the event to trial product 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 at the first trial-related activity after the patient signed the informed consent.
- **Recovering/resolving:** The condition is improving and the patient is expected to recover from the event. This term is only applicable if the patient has completed the trial or has died from another AE.
- **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 sequelae 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.
- **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.
New or updated information will be recorded in the CRF.

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 box 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, see section 9.2.1.
- After the trial is completed at a given site, 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.

SAE reporting via paper CRF

- Relevant CRF forms (AE and safety information form) must be forwarded to Novo Nordisk either by fax, encrypted e-mail or courier.
- 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 time frames (as illustrated in Figure 9-1):
  - AE form within 24 hours.
  - Safety information form within 5 calendar days.
  - Both forms must be signed within 7 calendar days from the investigators knowledge of the event.
- Contact details for SAE reporting can be found in the investigator trial master file.

Appendix 5 Contraceptive guidance and collection of pregnancy information

It must be recorded in the CRF whether female patients are of childbearing potential.

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile.

Women in the following categories are not considered WOCBP

1. Premenopausal female with one of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   Note: Documentation can come from the site personnel's review of patient's medical records, medical examination or medical history interview.
2. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high Follicle Stimulating Hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or Hormonal Replacement Therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the trial. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before trial enrolment.

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 12-2.

Table 12-2 Highly effective contraceptive methods

Highly effective contraceptive methods

Highly effective contraceptive methods that are user dependent [a and b] Failure rate of <1% per year when used consistently and correctly.
Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation • oral • intravaginal • transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation • oral • injectable
Highly effective methods that are user independent [a and b]
• Implantable progestogen only hormonal contraception associated with inhibition of ovulation • Intrauterine Device (IUD) • Intrauterine hormone-releasing System (IUS) • Bilateral tubal occlusion
Vasectomised partner A vasectomised partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
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 product. 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] Failure rates may differ when used consistently and correctly. [b] Contraception should be utilised during the treatment period and for at least 5 weeks after the last dose of trial product.

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 known intolerance to the highly effective methods mentioned above or where the use of any listed highly effective contraceptive measures are contraindicated in the individual patient, and/ or
- if the risk of initiating treatment with a specific highly effective method outweigh the predicted benefits of trial participation for the female patient.

Justification for accepting double barrier method should be at the discretion of the investigator. The justification must be stated in the medical records.

Algeria, Argentina, Belgium, Brazil, Denmark, Thailand and United Kingdom: For country specific requirements, please see Appendix 8.

Pregnancy testing

- Highly sensitive serum testing (sensitivity of 5-25 mIU/mL) is only mandatory if required by local regulations or ethics committees, or to resolve an indeterminate test or to confirm a positive urine test.
- WOCBP should only be included after a negative highly sensitive urine pregnancy test.
- Pregnancy testing should be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.
- Additional urine pregnancy testing should be performed during the treatment period, if required locally (Appendix 8).
- Home urine pregnancy testing may be performed between visits during the trial, if additional urine pregnancy testing is required locally.
- WOCBP needs the last pregnancy test at least 5 weeks after the last dose. As the FU visit is a phone contact, the patients can take a urine test at home and inform the investigator of the result.

Austria: For country specific requirements, please see Appendix 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.
- 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. 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 pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-trial pregnancy which is considered possibly/probably related to the trial product by the investigator will be reported to Novo Nordisk as described in Appendix 4. 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.
- For abnormal pregnancy outcomes collection of information on the paternal form for male partners of female patients require signing of specific informed consent.

Any female patient who becomes pregnant while participating in the trial will discontinue trial product.

Appendix 6 Technical complaints: Definition and procedures for recording, evaluation, follow-up and reporting

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).
- Problems with packaging material including labelling.

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

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

Timelines for reporting of technical complaints to Novo Nordisk
The investigator must complete the technical complaint form in the CRF within 24 hours if related to an SAE. All other technical complaints within 5 days. If the CRF is unavailable or when reporting a technical complaint that is not patient related, the information must be provided on a paper form by fax, e-mail or courier to Customer Complaint Center, Novo Nordisk, within the same timelines as stated above. When the 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 trial 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.

Appendix 7 Retention of human biosamples for biomarkers and genetic analyses

In countries where allowed, the trial will involve collection of human biosamples to be stored in a central archive for future use as noted in section 9.7 and 9.8.

The following samples will be stored:

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

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.

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

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 9.8.

Algeria, Brazil, China, Columbia, Israel, South Korea and Turkey: For country specific requirements, please see Appendix 8.

Appendix 8 Country-specific requirements

Algeria:

- Section 6.2, exclusion criterion #3 and Appendix 5: For women who expressly declare free of the risk of pregnancy, either by not engaging in sexual activity or by having sexual activity with no birth potential risk, use of contraceptive method will not be mandatory.

- Section 9.7, 9.8 and Appendix 7: No subjects from Algeria will participate in the optional biobank part of the trial, and no genetic testing will be performed as noted in section 9.7 and 9.8.

Argentina:

- Section 6.2, exclusion criterion #3 and Appendix 5 as described in Table 12-2: The contraceptive methods and pregnancy tests will be reimbursed by the sponsor. Monthly testing with highly sensitive urine pregnancy tests are required for WOCBP. Use of double contraceptive method is required for WOCBP.
- Section 7.8: In reference to Protocol section Treatment after discontinuation of trial products: The sponsor commits to comply with what is stated in point 6.8 of the current local regulation, disposition 6677/10. According to it, commits to comply with the following: "For Argentina, after the conclusion of subjects participation in the study, trial doctor will discuss with subjects the best alternatives for future treatment. If trial doctor, based on his/her adequately justified medical analysis, decides that the Sponsor's study drug is the best available treatment option for the subject, trial doctor will prescribe the study drug, which must be approved by the Ethics Committee. The Sponsor (Novo Nordisk Pharma Argentina S.A.) will provide access to the Sponsor's study drug to the subject for the time the Ethics Committee decides or until access is ensured by any other means and in accordance with the applicable provisions in Argentina. Subjects must visit trial doctor to receive the Sponsor's study drug and will have to provide information about health status and any possible side effects that may have been experienced since last visit

Austria:

- Appendix 3: Indemnity statement: Arzneimittelgesetz (BGBI. Nr. 185/1983) last amended with BGBl. I Nr. 59/2018
- Section 6.2, exclusion criterion #3 and Appendix 5: A monthly pregnancy test (urine) is required for all women of childbearing potential.

Belgium:

- Appendix 3: Indemnity statement: 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 subject and/or his rightful claimants sustain and which shows either a direct or an indirect connection with the trial.

- Section 6.2, exclusion criterion #3 and Appendix 5: Only highly effective methods of birth control are accepted (i.e. one that results in less than 1% per year failure rate when used consistently and correctly such as implants, injectables, combined oral contraceptives, some intrauterine device), or true sexual abstinence (i.e. refraining from heterosexual intercourse during the entire period of risk associated with the study treatments) or vasectomised partner.

Brazil:

- Section 6.2, exclusion criterion #3 and Appendix 5: For women who expressly declare free of the risk of pregnancy, either by not engaging in sexual activity or by having sexual activity with no birth potential risk, use of contraceptive method will not be mandatory.
- Section 6.2, exclusion criterion #4: Participation in other trials within one year prior to the screening visit (Visit 1) unless there is a direct benefit to the research subject at the investigator's discretion.
- Section 7.7: Novo Nordisk will reimburse costs of standard-of-care treatment for T2D.
- Section 7.8: At the end of the trial, all participant subjects should be assured the access to the best proved prophylactic, diagnostic and therapeutic methods identified during the study (according to resolution CNS 466/12).
- Section 9.7, 9.8 and Appendix 7: No subjects from Brazil will take part of the optional biobank part of the trial, and no genetic testing will be performed as noted in section 9.7 and 9.8.
- Appendix 2: All laboratory results will be communicated to the investigators.
- Appendix 3, section 3: Two original informed consent forms will be signed and dated and one original will be given to the subject (according to resolution CNS 466/12).

China:

- Section 9.7, 9.8 and Appendix 7: No subjects from China will participate in the optional biobank part of the trial, and no genetic testing will be performed as noted in section 9.7 and 9.8.
- Appendix 2: Laboratory samples for Chinese subjects will be destroyed according to local regulatory requirements, both for samples tested inside and outside China. No sample will be stored after the latest date of local regulatory approval.
- Appendix 3: Information of the trial will be disclosed at clinicaltrials.gov, china, drugtrials.org.cn and novonordisk-trials.com as China HA has requested to disclose trial information (phase 1-3) at chinadrugtrials.org.cn since 2013.

Columbia:

- Section 9.7, 9.8 and Appendix 7: No subjects from Columbia will participate in the optional biobank part of the trial, and no genetic testing will be performed as noted in section 9.7 and 9.8.

Denmark:

- Section 6.2, exclusion criterion #3 and Appendix 5: Contraceptive measures considered adequate includes intrauterine devices or hormonal contraception (oral contraceptive pills, implants, transdermal patches, vaginal rings or long-acting injections).

France:

- Appendix 3, section 14: Indemnity statement: The sponsor is responsible for identification of the harmful consequences of the biomedical research for the person lending himself thereto and for indemnification of his beneficiaries, except in case of proof, incumbent on it, that the prejudice is not attributable to his fault of or the fault of any intervening party, without the sponsor's being entitled to call on acts by a third party or the voluntary withdrawal of the person who had initially consented to cooperating in the research (according to The French Public Health Code article L.1121-10 (law n° 2004-806 of 9 August 2004 art. 88 I, IX Journal Officiel of 11 August 2004).

Germany:

- Subject's full Date of Birth is not allowed to be collected and must be shortened to year of birth.

Israel:

- Section 9.7, 9.8 and Appendix 7: No subjects from Israel will participate in the optional biobank part of the trial, and no genetic testing will be performed as noted in section 9.7 and 9.8.

Japan:

- Section 7.5: The head of the study site or the trial product storage manager assigned by the head of the study site (a pharmacist in principle) is responsible for control and accountability of the trial products.
- Section 9.2: Table 9-1: 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 3, section 1: A name and seal is accepted as a signature.

Mexico:

- Section 8.2: Should the subject his/her family members parents or legal representative decide to withdraw the consent for participation in the trial, the subject will be entitled to receive appropriate, free of charge medical care and/or trial drug during the follow up period of the protocol when it will be established with certainty that no untoward medical consequences of the subject´s participation in the research occurred.

- Appendix 3, section 1: The following responsibilities will be included for the head of the Institution/Health Care Establishment, Ethics, Research and, when applicable, Biosafety Committees and sponsor within their scope of responsibility:
    - Investigation follow-up
    - Damages to health arising from the investigation development; as well as those arising from interruption or advanced suspension of treatment due to non-attributable reasons to the Subject;
    - Timely compliance of the terms in which the authorization of a research for health in human beings had been issued;
    - To present in a timely manner the information required by the Health Authority.

Appendix 3, section 14:

- Novo Nordisk carries product liability for its products assumed under the special laws, acts/and/or guidelines for conducting trials in any country, including those applicable provisions on the Mexican United States. If the subject feels that something goes wrong during the course of this trial, the subject should contact the trial staff in the first instance.
- If during their participation in the trial the subject experiences a disease or injury that, according to the trial doctor and the sponsor, is directly caused by the trial medication and/or a trial procedure that otherwise would not have been part of his/her regular care, the subject will receive from the Institution or Medical Care Establishment and free of charge, the appropriate medical treatment as required. In this case, the costs resulting from such treatment as well as the costs of any indemnification established by law will be covered by the trial sponsor in accordance with the terms provided by all applicable regulations; even if the subject discontinues his/her participation in the trial by his own will or by a decision from the investigator.
- By signing the informed consent, the subject will not renounce to any compensation or indemnification he/she may be entitled to by law, nor will he/she will incur any additional expense as a result of his/her participation in the trial; any additional expense resulting from the subject's participation in the trial will be covered by the trial sponsor.

Russia:

- Appendix 3, section 1: The trial should be conducted in compliance with the protocol, Ministry of Healthcare of Russian Federation' order #200н from April, 01, 2016 "Approval of rules of good clinical practice" and legal requirements of the Russian Federation regulating circulation of medicines.

South Korea:

- Section 9.7, 9.8 and Appendix 7: No subjects from South Korea will participate in the optional biobank part of the trial, and no genetic testing will be performed as noted in section 9.7 and 9.8.

Thailand:

- Section 6.2, exclusion criterion #3 and Appendix 5: Adequate contraceptive measures are: diaphragm, condom (by the partner), intrauterine device in place for last three months before trial starts, sponge, cap with spermicide, contraceptive patch, approved hormonal implant (i.e. Norplant), oral contraceptives taken without difficulty for the last three months before trial starts, post-menopausal state or sterilisation.

Turkey:

- Section 7.7: In case a subject needs to change their regular dose of a concomitant medication due to a protocol requirement, this medication will be reimbursed by Novo Nordisk.
- Section 9.7, 9.8 and Appendix 7: No subjects from Turkey will participate in the optional biobank part of the trial, and no genetic testing will be performed as noted in section 9.7 and 9.8.

United Kingdom:

- Section 6.2, exclusion criterion #3 and Appendix 5: Contraceptive measures considered adequate include highly effective contraceptive methods in accordance with the CTFG (Clinical Trial Facilitation Group) guideline: Recommendations related to contraception and pregnancy testing in clinical trials, as listed in Table 12-2: This means use of double barrier methods is not applicable.

2. Final protocol

Protocol

Updated protocol including:

Protocol version 1.0, dated 17-Jan-2019

Protocol version 2.0, including protocol amendment no. 1, Argentina, Canada, Colombia, Mexico, Spain, United Kingdom and United States, dated 12-Jun-2019

Protocol version 3.0, including protocol amendment no. 2, dated 17-Nov-2020

Protocol version 4.0, including protocol amendment no. 3, China, dated 26-Jan-2021

Protocol title: Semaglutide cardiovascular outcomes trial in patients with type 2 diabetes (SOUL)

Substance: Oral semaglutide

Universal Trial Number: U1111-1218-5368

EUdraCT Number: 2018-003141-42

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	Date	Version
Updated protocol including amendment 3 (China)	26 January 2021	4.0
Updated protocol including amendment 2	17 November 2020	3.0
Updated protocol including amendment 1 (Argentina, Canada, Colombia, Mexico, Spain, United Kingdom and United States)	12 June 2019	2.0
Original protocol	17 January 2019	1.0

Protocol amendment no. 3 (protocol version 4.0 dated 26 January 2021)

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

For China, co-participation in COVID-19 trials is not allowed due to local requirements, and not allowing co-participation in COVID-19 trials does not affect patient safety.

Section # and name	Description of change	Rationale
Appendix 8 Country-specific requirements for China, amendment 3	Section 6.2, exclusion criteria #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 postinfectious conditions is allowed if the last dose of the investigational medicinal product has been received more than 30 days before screening is not applicable for China.	Co-participation in COVID-19 trials is not allowed in China due to local requirements
Appendix 8 Country-specific requirements for China, amendment 3	Section 8.1, discontinuation/withdrawal criteria: *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 postinfectious conditions is allowed at the investigator discretion without discontinuing trial product is not applicable for China.	Co-participation in COVID-19 trials is not allowed in China due to local requirements

Table of Contents

1 Synopsis

Rationale

To evaluate the hypothesis that oral semaglutide lowers the risk of cardiovascular events in patients with type 2 diabetes at high risk for cardiovascular disease.

Objectives and endpoints

The primary objective

To demonstrate that oral semaglutide lowers the risk of major adverse cardiovascular events compared to placebo, both added to standard of care in patients with type 2 diabetes and at high risk of cardiovascular events.

The key secondary objectives

To compare the effects of oral semaglutide versus placebo, both added to standard of care in patients with type 2 diabetes and at high risk of cardiovascular events with regards to:

- Chronic kidney disease
- Cardiovascular events
- Peripheral artery disease
- Glycaemic control and body weight
- Safety

The primary endpoint

The primary endpoint is time from randomisation to first occurrence of a major adverse cardiovascular event, a composite endpoint consisting of: cardiovascular death, non-fatal myocardial infarction or non-fatal stroke.

Key confirmatory secondary endpoints

Time from randomisation to first occurrence of:

- A composite chronic kidney disease endpoint consisting of: cardiovascular death, renal death, onset of persistent ≥ 50% reduction in estimated glomerular filtration rate (CKD-EPI) compared with baseline, onset of persistent eGFR (CKD-EPI) < 15 mL/min/1.73 m^2 or initiation of chronic renal replacement therapy (dialysis or kidney transplantation)
- cardiovascular death
- Major adverse limb events, a composite endpoint consisting of: acute limb ischemia hospitalisation or chronic limb ischemia hospitalisation

Estimand

The estimand for all objectives is the intention-to-treat estimand evaluating the effect of the randomised treatment intervention irrespective of adherence to treatment and changes to background medication.

Overall design

This is a randomised, double-blind, parallel-group, placebo-controlled trial comparing oral semaglutide versus placebo both administered once daily and added to standard of care in patients with type 2 diabetes at high risk of cardiovascular events. Patients will be randomised 1:1 to receive either oral semaglutide or placebo.

All inclusion criteria are based on the patients' medical records, except for inclusion criterion for HbA_{1c} (local laboratory or point-of-care device). The key inclusion criteria are:

- Male or female, age ≥50 years at the time of signing informed consent
- Diagnosed with type 2 diabetes mellitus
- HbA_{1c} 6.5% - 10.0% (47 - 86 mmol/mol) (both inclusive)[a]
- At least one of the below conditions (a-d):
  a) Coronary heart disease defined as at least one of the following:
     i. Prior myocardial infarction
     ii. Prior coronary revascularisation procedure
     iii. ≥50% stenosis in coronary artery documented by cardiac catheterisation, computerized tomography coronary angiography
     iv. Coronary heart disease with ischaemia documented by stress test with any imaging modality
  b) Cerebrovascular disease defined as at least one of the following:
     i. Prior stroke
     ii. Prior carotid artery revascularisation procedure
     iii. ≥50% stenosis in carotid artery documented by X-ray angiography, magnetic resonance angiography, computerized tomography angiography or Doppler ultrasound
  c) Symptomatic peripheral artery disease (PAD) defined as at least one of the following:
     i. Intermittent claudication with an Ankle-brachial index (ABI) < 0.85 at rest
     ii. Intermittent claudication with a ≥50% stenosis in peripheral artery (excluding carotid) documented by X-ray angiography, magnetic resonance angiography, computerized tomography angiography or Doppler ultrasound
     iii. Prior peripheral artery (excluding carotid) revascularization procedure
     iv. Lower extremity amputation at or above ankle due to atherosclerotic disease (excluding e.g. trauma or osteomyelitis)
  d) Chronic kidney disease defined as:
     i. eGFR < 60 mL/min/1.73 m^2 [b]

[a] Latest available and no more than 30 days old local laboratory assessment based on medical records or point of care measurement.

[b] Based on medical records using latest available and no more than 6 months old assessment.

The key exclusion criteria are:

- Any of the following: myocardial infarction, stroke, hospitalisation for unstable angina pectoris or transient ischaemic attack within the past 60 days prior to the day of screening
- Planned coronary, carotid or peripheral artery revascularisation known on the day of screening
- Heart failure presently classified as being in New York Heart Association Class IV
- Treatment with any glucagon-like peptide-1 receptor agonist within 30 days before screening

Number of patients

In this trial, 9,642 patients are planned to be randomly assigned to trial product.

Treatment groups and duration

The trial is event driven; therefore, end of trial will be scheduled according to projected trial closure. Trial duration is expected to be 61 months or more following randomisation of the first patient. Trial duration for each subject is expected to be approximately 3.5 to 5 years.

Trial products

Oral semaglutide 3 mg, 7 mg and 14 mg tablets
Placebo tablets

2 Flowchart

Trial Periods	Protocol Section	Screening	Randomisation	First year						Remaining period		End of treatment	Follow-up
Site visit (V)/Phone contact (P)		V1	V2	V3	V4	V5	V6	V7[a]	V8	V9/V10/V11/ V13/V14/V15 V17/V18/V19 V21/V22/V23	V12 V16 V20 V24	V-EOT[b]	P-FU
Timing of visit (weeks)		Up to -3 weeks	0	4	8	13	26	39	52	Every 13 weeks	Yearly	EOT	V-EOT +5 weeks
Visit window (days)				±3	±3	±3	±7	±7	±7	±7	±7	±7	+7
PATIENT-RELATED INFO/ASSESSMENTS													
Informed consent	Appendix 3	X											
Hand out ID card		X											
Inclusion/exclusion criteria	6.1; 6.2	X											
Tobacco use[c]			X								X		
Demography[d]		X											
Medical history/concomitant illness	9.4		X										
Concomitant medication	7.7		X	X	X	X	X	X	X	X	X	X	X
Ensure updated contact persons list	9	X	X	X	X	X	X	X	X	X	X	X	
Trial product dose	7.2			X	X	X	X	X	X	X	X	X	
Training in trial product and dosing instructions	7.1		X	(X)[e]	(X)[e]	(X)[e]	(X)[e]	(X)[e]	(X)[e]	(X)[e]	(X)[e]		
Hand out and instruct in BG meter[i]	7.1		(X)[i]	(X)[i]	(X)[i]	(X)[i]	(X)[i]	(X)[i]	(X)[i]	(X)[i]	(X)[i]	(X)[i]	
CLINICAL ASSESSMENTS													
Height	9.4.1		X										
Body weight			X			X			X		X	X[f]	
Waist circumference			X										
Physical examination			X									X	
Eye examination	9.4.4	X[g]							X[h]		X[h]	X[f]	
Vital signs	9.4.2		X			X			X		X	X[f]	

Trial Periods	Protocol Section	Screening	Randomisation	First year						Remaining period		End of treatment	Follow-up
Site visit (V)/Phone contact (P)		V1	V2	V3	V4	V5	V6	V7[a]	V8	V9/V10/V11/ V13/V14/V15 V17/V18/V19 V21/V22/V23	V12 V16 V20 V24	V-EOT[b]	P-FU
Timing of visit (weeks)		Up to -3 weeks	0	4	8	13	26	39	52	Every 13 weeks	Yearly	EOT	V-EOT +5 weeks
Visit window (days)				±3	±3	±3	±7	±7	±7	±7	±7	±7	+7
HbA_{1c} point of care	6.1;9.1.1	X		X	X	X	X	X	X	X	X	X	
Montreal cognitive assessment	9.1.4		X								X		
PROTECT cognitive tests[o]	9.1.4		X[o]						X[o]		X[o]		
Patient surveys[j]	9.1.4		X[j]				X[j]		X[j]	X[j]	X[j]	X[j]	X[j]
Adverse events	9.2		X	X	X	X	X	X	X	X	X	X	X
Severe hypoglycaemic episodes	9.2		X	X	X	X	X	X	X	X	X	X	X
Technical complaints	9.2.6		X	X	X	X	X	X	X	X	X	X	
Urine pregnancy test[k]	9.2.5	X										X	X[l]
CENTRAL LABORATORY ASSESSMENTS													
HbA_{1c}	Appendix 2		X			X			X		X	X[f]	
Creatinine			X			X			X		X	X[f]	
High sensitivity C-Reactive Protein			X			X					X[n]		
Liver parameters			X										
Lipids			X			X			X		X	X[f]	
Biosamples for future analysis (biobank, genetics)[m]			X										
Biosamples for future analysis (biobank, biomarkers)[m]			X			X					X[n]		
TRIAL MATERIAL													
IWRS session		X	X	X	X	X	X	X	X	X	X	X	
Dispensing visit			X	X	X	X	X	X	X	X	X		
Drug accountability	7.5		X	X	X	X	X	X	X	X	X	X	
End of trial	5.3												X

[a] After V6, all odd numbered visits (V7, V9, V11 etc.) can be conducted as a phone contact, however the investigator needs to ensure that the subject has enough trial product within the expiry date.
[b] Will be scheduled according to trial completion.
[c] Tobacco use/smoking is defined as smoking at least one cigarette or equivalent daily.
[d] Demography: date of birth, sex, ethnicity and race (according to local regulation).
[e] As needed.
[f] If done within the past 5 weeks, assessment can be skipped.
[g] Must be performed within 90 days before screening or in the period between screening and randomisation, and results available at randomisation.
[h] Must be performed between 8 weeks before the visit and the day of visit (both included).
[i] Lancets, test strips and control solutions will be provided with the BG meter (if supplied) and during the trial as needed. Training will also be provided as needed.
[j] Patient engagement assessment will be performed every half year, i.e. V2, V6, V8, V10, V12, V14, V16, V18, V20, V22, V24 and V-EOT at all US sites. Patient expectations and experience survey will be performed at Visit 2, Visit 12 and at end-of-treatment at only a sub-set of US sites.
Visits to emergency room/urgent care unit will be recorded at every visit from V3 at all US sites.
[k] Only applicable for women of childbearing potential; urine HCG.
[l] Can be done at home.
[m] Only applicable for patients that have provided informed consent for biosamples for biomarkers and genetic analyses.
[n] Only applicable for the year two visit (V12).
[o] Only for English and/or Spanish speaking patients in Argentina, Canada, Colombia, Mexico, Spain, United Kingdom and United States. Online cognitive testing will be performed every year, i.e. V2, V8, V12, V16, V20 and V24.

3 Introduction

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

3.1 Trial rationale

The cardiovascular (CV) effect of oral semaglutide 14 mg once daily (OD) and s.c. semaglutide 0.5 and 1 mg once weekly were assessed in 2 CV outcomes trials (NN9924-4221, PIONEER 6 and NN9535-3744, SUSTAIN 6), each designed to rule out an 80% increased CV risk in patients with type 2 diabetes (T2D) at high risk for CV disease (CVD) in accordance with FDA guidance. PIONEER 6 demonstrated CV safety with a favourable point estimate. SUSTAIN 6 however demonstrated a statistically significant 26% risk reduction with s.c. semaglutide compared with placebo for the primary endpoint (time from randomisation to first occurrence of a major adverse cardiovascular event (MACE) consisting of: CV death, non-fatal myocardial infarction (MI) or non-fatal stroke).[2] Clinical pharmacology and clinical efficacy data indicate that the action of semaglutide is the same whether administrated via a subcutaneous injection or orally in a tablet. Hence, once semaglutide has entered systemic circulation, the properties and actions of the molecule are similar and independent of the route of administration. Accordingly it is hypothesised that oral semaglutide in the dose of 14 mg OD can reduce CV risk.

The current trial serves the purpose of confirming that oral semaglutide reduces the risk of MACE in patients with T2D and established CVD and/or chronic kidney disease (CKD).

3.2 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, including hyperglycaemia.[3] However, many patients with T2D do not achieve glycaemic control, so an unmet need for simple and convenient as well as safe and efficacious treatment options exists.[4, 5] In addition, CV disease is the predominant cause of death in patients with T2D, and diabetes increased the risk for coronary heart disease, stroke and CV death[6] with an about a two-fold excess, underscoring the need for therapies lowering the risk of CV events in patients with T2D.

Semaglutide is a next-generation glucagon-like peptide-1 (GLP-1) analogue with a high degree of homology to human GLP-1.[7] For oral administration, semaglutide has been co-formulated with an absorption enhancer (SNAC, 300 mg) in a tablet formulation. Non-clinical and clinical studies have established that oral semaglutide is safe and well tolerated and that it provides dose-dependent reductions in HbA_{1c} and body weight when used in compliance with the specified simple dosing conditions.[8] Detailed information for oral semaglutide is available in the current edition and any updates of the Investigator's Brochure (IB).

The trial will include patients with T2D and high CV risk defined as having established CVD and/or CKD. A population at high risk for CV events is an appropriate target population for a risk reduction intervention and will ensure that the primary objective of the trial can be met within a reasonable timeframe and sample size.

3.3 Benefit-risk assessment

3.3.1 Risks

The sections below describe identified and potential risks associated with oral semaglutide treatment. For classification and further details of the risks, please refer to the current edition and any updates of the IB. The identified/potential risks are based on findings in non-clinical studies and clinical trials with semaglutide (s.c. as well as oral) as well as other glucagon-like peptide-1 receptor agonists (GLP-1 RAs). For each of these risks, mitigating actions have been implemented to minimise the risks for patients enrolled in this trial.

Gastrointestinal adverse events

Consistent with the other GLP-1 RAs, the most frequent adverse events (AEs) with oral semaglutide are gastrointestinal AEs (nausea, vomiting, diarrhoea, dyspepsia and constipation). A low starting dose and gradual dose escalation with 4 weeks dose escalation increments have been implemented in the recent clinical trials with the intent to lower the risk of gastrointestinal AEs.

Impaired kidney function

In patients treated with GLP-1 RAs including oral semaglutide, gastrointestinal AEs such as nausea, vomiting and diarrhoea may lead to significant dehydration. This should be considered when treating patients with impaired renal function with GLP-1 RAs as it may cause a deterioration of renal function. Impaired renal function may increase the risk of metformin associated lactic acidosis.

Patients and providers should be advised to monitor hydration levels in order to avoid dehydration in connection with gastrointestinal AEs.

Hypoglycaemia

The risk of hypoglycaemic episodes associated with the use of GLP-1 RAs, including oral semaglutide, is low when used as monotherapy. Patients treated with semaglutide in combination with a sulfonylurea or insulin may have an increased risk of hypoglycaemia compared to patients treated with semaglutide as monotherapy or in combination with other anti-hyperglycaemic medications. The risk of hypoglycaemia can be lowered by reducing the dose of sulfonylurea or insulin when initiating treatment with oral semaglutide. It is also recommended that the investigator ensures that patients taking or initiating sulphonylurea or insulin perform adequately frequent blood glucose monitoring to ensure patient safety.

Allergic reactions

As expected for a protein-based drug, patients treated with oral semaglutide may develop localised or generalised immune and allergic reactions including urticaria, rash or pruritus. Severe allergic reactions such as anaphylactic reactions could potentially also pose a risk to patients treated with oral semaglutide. Data from the both the s.c. and the oral semaglutide development programmes indicate that the potential risk of allergic reactions is low.

Acute pancreatitis

Acute pancreatitis has been observed with the use of GLP-1 RA drug class. As a precaution, trial product should be discontinued in case of suspicion of acute pancreatitis in accordance with Section 8.1.

Acute gallstone disease (cholelithiasis)

Patients with T2D are often overweight or obese and have an inherent risk of developing gallstones (cholelithiasis). Events of cholelithiasis have been associated with the use of GLP-1 RAs including semaglutide. In the clinical development programme, events were mainly mild and non-serious and did not lead to an increased risk of complications such as cholecystitis or pancreatitis.

Diabetic retinopathy complications

The cardiovascular outcome trial in the s.c. semaglutide development programme (SUSTAIN 6) showed an increased risk of events related to diabetic retinopathy complications in patients treated with semaglutide compared to placebo, albeit the proportion of patients with an event of diabetic retinopathy complications was low. The imbalance was driven by patients with a history of diabetic retinopathy at baseline and patients who were treated with insulin. As a precaution, patients with a history of uncontrolled and potentially unstable diabetic retinopathy or maculopathy will be excluded from the trial, and eye examination will be performed according to flowchart (see Section 2).

Pancreatic cancer

There is currently no support from non-clinical studies, clinical trials or post-marketing data that GLP-1 RA-based therapies increase the risk of pancreatic cancer. However, pancreatic cancer has been classified as a potential class risk for all marketed GLP-1 RAs by regulatory agencies based on the unknown long-term effects on β-cell stimulation and α-cell suppression.

Medullary thyroid cancer (MTC) (based on non-clinical data)

Thyroid C-cell tumours were seen in the mice and rat carcinogenicity studies, after daily exposure to semaglutide for 2 years. No C-cell tumours were observed in monkeys after 52 weeks exposure of up to 40-fold higher doses than the clinical plasma exposure at 14 mg/day. The GLP-1 receptor is not expressed in the normal human thyroid[9]; and therefore, these findings are not likely to be

clinically relevant. 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.

Pregnancy and fertility

Studies in animals have shown reproductive toxicity. There are limited data from the use of semaglutide in pregnant women. Therefore, oral semaglutide should not be used during pregnancy. If a patient wishes to become pregnant, or pregnancy occurs, treatment with oral semaglutide should be discontinued immediately. Exclusion and discontinuation criteria related to pregnancy have been implemented in the trial.

3.3.2 Benefits

In clinical trials oral 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 statistical significant reduction in CV events has been demonstrated for semaglutide s.c. (SUSTAIN 6[2]) and this finding was supported by the results from the PIONEER 6 trial with oral semaglutide.

During this 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 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.

3.3.3 Risk and benefit 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 high 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 oral 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 oral semaglutide may be found in the Investigator's Brochure and any updates thereof.

4 Objectives and endpoints

4.1 Primary, secondary and exploratory objective(s)

The primary objective
To demonstrate that oral semaglutide lowers the risk of major adverse cardiovascular events (MACE) compared to placebo, both added to standard of care in patients with T2D and at high risk of CV events.

The secondary objectives
To compare the effects of oral semaglutide versus placebo, both added to standard of care in patients with T2D and at high risk of CV events with regards to:

- CKD
- CV events
- Peripheral artery disease (PAD)
- Glycaemic control and body weight
- Safety

The exploratory objectives

To compare the effects of oral semaglutide versus placebo, both added to standard of care in patients with T2D and at high risk of CV events with regards to:

- Cognitive function
- Smoking

Estimand

The estimand for all objectives is the intention-to-treat estimand evaluating the effect of the randomised treatment intervention irrespective of adherence to treatment and changes to background medication.

4.2 Primary, secondary and exploratory endpoint(s)

4.2.1 Primary endpoint

Endpoint title	Time Frame	Unit
Time to first occurrence of MACE, a composite endpoint consisting of: • CV death • non-fatal myocardial infarction • non-fatal stroke	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Month(s)

[a] Trial is event driven.

4.2.2 Secondary endpoints

4.2.2.1 Confirmatory secondary endpoints

Endpoint title	Time Frame	Unit
Time to first occurrence of a composite endpoint consisting of: • CV death • renal death • onset of persistent ≥ 50% reduction in eGFR (CKD-EPI)[b] • onset of persistent eGFR (CKD-EPI) < 15 mL/min/1.73 m^2 • initiation of chronic renal replacement therapy (dialysis or kidney transplantation)	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Month(s)
Time to occurrence of CV death	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Month(s)
Time to first occurrence of major adverse limb events (MALE), a composite endpoint consisting of: • acute limb ischemia hospitalisation • chronic limb ischemia hospitalisation	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Month(s)

[a] Trial is event driven.

[b] Compared with baseline.

Abbreviations: eGFR, estimated glomerular filtration rate; CKD-EPI, chronic kidney disease – epidemiology collaboration

Definitions

Estimated glomerular filtration rate (eGFR) will be calculated using the – CKD-EPI formula.[10] A persistent change in eGFR is defined as having 2 consecutive samples meeting the criteria. The 2 samples must be at least 4 weeks apart.

4.2.2.2 Supportive secondary endpoints

Endpoint title	Time Frame	Unit
Time to first occurrence of an expanded MACE composite endpoint consisting of: • CV death • non-fatal myocardial infarction • non-fatal stroke • coronary revascularisation • unstable angina requiring hospitalisation	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Month(s)
Time to first occurrence of a composite heart failure endpoint consisting of: • CV death • heart failure requiring hospitalisation • urgent heart failure visit	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Month(s)
Time to first occurrence of a composite CKD endpoint consisting of: • renal death • onset of persistent ≥ 50% reduction in estimated glomerular filtration rate (eGFR) (CKD-EPI)[b] • onset of persistent eGFR (CKD-EPI) < 15 mL/min/1.73 m^2 • initiation of chronic renal replacement therapy (dialysis or kidney transplantation)	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Month(s)
Time to occurrence of all-cause death	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Month(s)
Time to first occurrence of non-fatal myocardial infarction (MI)	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Month(s)
Time to first occurrence of non-fatal stroke	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Month(s)
Time from randomisation to heart failure requiring hospitalisation or urgent heart failure visit	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Month(s)
Time to first occurrence of coronary revascularisation	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Month(s)
Time to first occurrence of unstable angina requiring hospitalisation	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Month(s)
Time to occurrence of renal death	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Month(s)
Time to first occurrence of onset of persistent ≥ 50% reduction in eGFR (CKD-EPI)[b]	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Month(s)
Time to first occurrence of onset of persistent eGFR (CKD-EPI) < 15 mL/min/1.73 m^2	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Month(s)

Endpoint title	Time Frame	Unit
Time to first occurrence of initiation of chronic renal replacement therapy (dialysis or kidney transplantation)	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Month(s)
Time to first occurrence of a composite endpoint consisting of: • all-cause death • non-fatal myocardial infarction • non-fatal stroke	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Month(s)
Time to first occurrence of acute limb ischemia hospitalisation	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Month(s)
Time to first occurrence of chronic limb ischemia hospitalisation	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Month(s)
Annual rate of change in eGFR (CKD-EPI) (total eGFR slope)	From randomisation (week 0) to end of treatment (up to 60 months or more[a])	ml/min/1.73 m^2 per year
Change in glycosylated haemoglobin (HbA_{1c})	From randomisation (week 0) to 2 years (visit 12)	%-points
Change in body weight	From randomisation (week 0) to 2 years (visit 12)	Kilogram
Number of severe hypoglycaemic episodes[11]	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Number of events
Time to first occurrence of a severe hypoglycaemic episode [11]	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Month(s)

[a] Trial is event driven.

[b] Compared with baseline.

4.2.2.3 Exploratory endpoints

Endpoint title	Time Frame	Unit
Change in Montreal Cognitive Assessment (MoCA) score	From randomisation (week 0) to 2 years (visit 12)	Score (0-30)
Change in Montreal Cognitive Assessment (MoCA) score	From randomisation (week 0) to 3 years (visit 16)	Score (0-30)
Current smoking	At year 2	Yes/no

English and/or Spanish speaking patients in Argentina, Canada, Colombia, Mexico, Spain, United Kingdom and United States:

Endpoint title	Time Frame	Unit
Change in Working Memory Index	From randomisation (week 0) to 2 years (visit 12)	Score
Change in Verbal Reasoning	From randomisation (week 0) to 2 years (visit 12)	Score

Change in Attentional Intensity Index	From randomisation (week 0) to 2 years (visit 12)	msec
Change in Cognitive Reaction Time	From randomisation (week 0) to 2 years (visit 12)	msec
Change in Sustained Attention Index	From randomisation (week 0) to 2 years (visit 12)	%-points

5 Trial design

5.1 Overall design

This is a randomised, double-blind, parallel-group, placebo-controlled trial comparing oral semaglutide versus placebo OD added to standard of care in patients with T2D at high risk of CV events. Patients will be randomised 1:1 to receive either oral semaglutide or placebo.

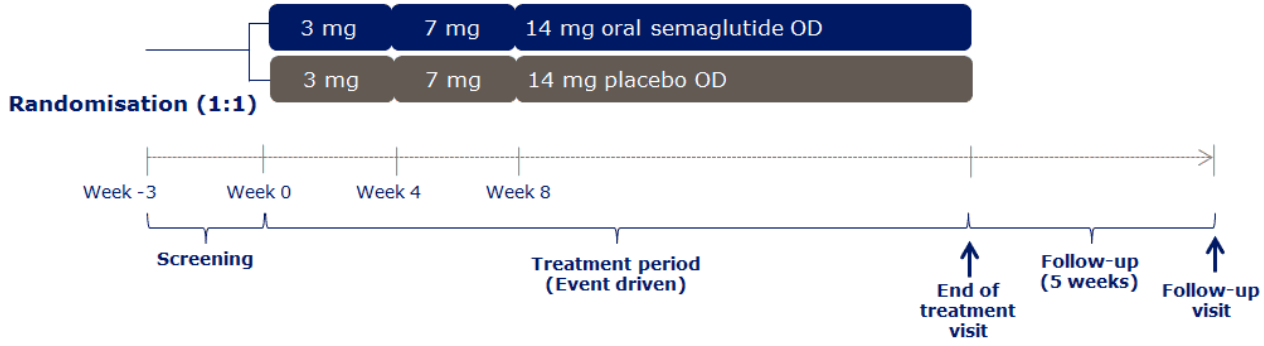
The trial is event driven with trial closure being performed when the targeted number of primary endpoint events (1225) has been reached. The trial will employ a group sequential design and interim testing for efficacy will be performed by an independent external Data Monitoring Committee (DMC). With the assumed event rate and a recruitment period of approximately 18 months, expected trial duration for an individual patient is approximately 3.5 to 5 years including the follow-up period. The follow-up period is 5 weeks after end of treatment.

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. A schematic overview of the trial design is shown in Figure 5-1 below.

The trial is designed to evaluate CV outcomes and will apply a targeted approach to collection of safety data focusing on serious AEs (SAEs), AEs leading to discontinuation of trial product and other selected AEs. An adequate characterisation of the less serious and more common AEs are evaluated in the phase 3a trials conducted with oral semaglutide comprising more than 5,500 patients with T2D.

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 5-1 Trial design



5.2 Patient and trial completion

In this trial 9,642 patients are planned to be randomly assigned to trial product. The recruitment period is expected to be approximately 18 months.

Trial period completion for a patient is defined as when the randomised patient has:

- attended the final scheduled visit (follow-up visit (P-FU) according to the flowchart)

or

- died during trial.

The trial is event driven; therefore, end of treatment visit (V-EOT) and follow-up contact (P-FU) will be scheduled according to projected trial closure. When trial closure is initiated the investigators will be notified and instructed by Novo Nordisk regarding the visit schedules for their patients.

When the trial comes to an end, the investigator must make every effort to ascertain efficacy endpoint data and AEs with a focus on those related to the primary objective for all patients. This should be done by direct contact with the patient whenever possible. If a patient proves difficult to reach for the FU visit, all attempts to re-establish direct contact must be made as noted below. If establishing direct contact is not possible, AE status should be obtained from any available source including electronic medical records, the patients' primary physician or other health care professionals and, as a last resort, vital status (dead or alive) should be obtained. Publicly available data sources should also be searched. A search agency may be used to facilitate identifying updated contact details for a missing patient or provide vital status (dead or last alive date). The above suggestions should be followed unless prohibited by local regulation and may be modified according to practical aspects.

In a case where several attempts are required to establish direct contact to a patient, it may be necessary to exceed the visit window of a follow-up visit. In order for the data set to be as complete as possible, end of trial follow-up information can be collected until the randomisation codes are broken.

As a minimum the following contact attempts will be made and documented in the source documents:

- To patients: three phone calls and one written contact
- To primary physician and/or other health care professionals: calls until contact is established
- To relatives or other(s) on the contact persons list: three phone calls and one written contact
- Search/contact to public registries of deceased persons, if available and allowed by local regulation

5.3 End of trial definition

The end of the trial is defined as the date of the last visit (P-FU) of the last patient in the trial.

5.4 Scientific rationale for trial design

To minimise bias the trial is randomised, double-blinded and placebo-controlled. Blinded treatment with oral semaglutide or placebo offers a robust method for assessment of the effects of oral semaglutide. 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 oral semaglutide 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 every 13th week throughout the trial. A multinational design has been chosen to ensure a sufficient screening pool of patients and to reflect the anticipated patient population. The 5-week follow up is chosen due to the half-life of oral semaglutide and is considered appropriate for end of systemic exposure.

The trial will include a population of patients with T2D and established CV disease and/or CKD which is an appropriate high risk target population for a CV risk reduction intervention and will ensure that the primary objective of the trial can be evaluated within a reasonable timeframe and sample size.

6 Trial population

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

6.1 Inclusion criteria

All inclusion criteria are based on the patients' medical records, except for inclusion criterion for HbA_{1c} (local laboratory or point-of-care device). 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 ≥50 years at the time of signing informed consent.
3. Diagnosed with type 2 diabetes mellitus.
4. HbA_{1c} 6.5% - 10.0% (47 - 86 mmol/mol) (both inclusive).[a]
5. At least one of the below conditions (a-d):
   a) Coronary heart disease defined as at least one of the following:
      i. Prior myocardial infarction
      ii. Prior coronary revascularisation procedure
      iii. ≥50% stenosis in coronary artery documented by cardiac catheterisation or CT coronary angiography
      iv. Coronary heart disease with ischaemia documented by stress test with any imaging modality
   b) Cerebrovascular disease defined as at least one of the following:
      i. Prior stroke
      ii. Prior carotid artery revascularisation procedure
      iii. ≥50% stenosis in carotid artery documented by X-ray angiography, MR angiography, CT angiography or Doppler ultrasound
   c) Symptomatic peripheral artery disease (PAD) defined as at least one of the following:
      i. Intermittent claudication with an Ankle-brachial index (ABI) < 0.85 at rest
      ii. Intermittent claudication with a ≥50% stenosis in peripheral artery (excluding carotid) documented by X-ray angiography, MR angiography, CT angiography or Doppler ultrasound
      iii. Prior peripheral artery (excluding carotid) revascularization procedure
      iv. Lower extremity amputation at or above ankle due to atherosclerotic disease (excluding e.g. trauma or osteomyelitis)
   d) Chronic kidney disease defined as:
      i. eGFR < 60 mL/min/1.73 m^2 [b]

[a] Latest available and no more than 30 days old local laboratory assessment based on medical records or point of care measurement.

[b] Based on medical records using latest available and no more than 6 months old assessment.

6.2 Exclusion criteria

All exclusion criteria are based on the patients' medical records, except for exclusion criterion 3, urine pregnancy test. Patients are excluded from the trial if any of the following criteria apply:

1. Known or suspected hypersensitivity to trial product 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.
4. Participation in any clinical trial of an approved or non-approved investigational medicinal product within 30 days before screening.*
5. Any disorder, which in the investigator's opinion might jeopardise patient's safety or compliance with the protocol.
6. Any of the following: myocardial infarction, stroke, hospitalisation for unstable angina pectoris or transient ischaemic attack (TIA) within the past 60 days prior to the day of screening
7. Planned coronary, carotid or peripheral artery revascularisation.
8. Heart failure presently classified as being in New York Heart Association (NYHA) Class IV.
9. Treatment with any GLP-1 receptor agonist (RA) within 30 days before screening.
10. Uncontrolled and potentially unstable diabetic retinopathy or maculopathy. 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.
11. 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 is allowed.
12. Personal or first degree relative(s) history of MEN2 or MTC.
13. End stage renal disease or chronic or intermittent haemodialysis or peritoneal dialysis.
14. History of major surgical procedures involving the stomach or small intestine potentially affecting absorption of drugs and/or nutrients, as judged by 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 postinfectious conditions is allowed if the last dose of the investigational medicinal product has been received more than 30 days before screening.

Argentina, Austria, Belgium, Brazil, China, Denmark, Thailand and United Kingdom: For country specific requirements, please see Appendix 8.

6.3 Justification for dose

Three doses of oral semaglutide have been investigated in the phase 3a development programme: 3 mg, 7 mg and 14 mg. The selected doses are based on the data derived from the NN9924-3790 dose-finding trial. For further details regarding the results obtained in the phase 2 dose-finding trial (NN9924-3790), please refer to the current edition of the IB for oral administration of semaglutide (NN9924), or any updates thereto.

Similar to other cardiovascular outcomes trials, the maximum treatment dose (14 mg oral semaglutide) will be investigated and compared to placebo in the present trial.

6.4 Lifestyle restrictions

Not applicable.

6.5 Screen failures

Screen failures are defined as patients who consent to participate in the clinical trial but are not eligible for participation according to in/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 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).

Due to the long recruitment period re-screening is allowed. A new patient number must be assigned in the IWRS.

6.6 Assessment of eligibility

It is the responsibility of the investigator to have sufficient evidence to ensure eligibility. If a patient is not from the investigators practice; reasonable efforts must be made to obtain a copy of the patient's medical records from relevant party e.g. the primary physician and hospitals. It is at the investigator's discretion on a case by case basis to decide if the complete medical records are needed or if the available documentation is enough to determine whether a patient is eligible. The values used to assess eligibility must reflect the patient's current health status.

7 Treatments

7.1 Treatments administered

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

Table 7-1 Trial products provided by Novo Nordisk A/S

Trial product	Strength	Dosage form	Route of administration	Container/ delivery device
Semaglutide 3 mg tablet (IMP, test product)	3 mg	Tablet	Oral	Dose-pack[a]
Semaglutide 7 mg tablet (IMP, test product)	7 mg			
Semaglutide 14 mg tablet (IMP, test product)	14 mg			
Placebo tablet (IMP, reference therapy)	NA			

[a] A dose-pack contains one blister card with 7 tablets

The active trial product and the corresponding placebo are packed blinded and are identical with regard to visual appearance. Furthermore, all tablets are visually identical to each other, irrespective of dose levels. Strength will be written on the dose-pack e.g. Semaglutide 3 mg or placebo.

All baseline assessments must be done prior to administration of the first dose of trial product. The patients must be trained in dosing instructions (see Section 7.2.1). The investigator must document that patients are trained in the dosing instructions according to Section 2.

Auxiliary supplies are provided by Novo Nordisk:

- blood glucose meters including lancets, test strips, control solutions and instructions for use

At (or after) the randomisation visit patients may be provided with a blood glucose meter. The patients will be instructed in how to use the device and the instructions will be repeated during the trial as needed. The investigator or the individual patient may choose to continue using their own glucose meter or decide that self-measurement of glucose is not needed. If circumstances change, then the glucose meter can be provided.

7.2 Dose modification

Randomised patients will initiate treatment with 3 mg oral semaglutide/placebo OD and follow a fixed 4-week dose escalation regimen until reaching the treatment dose of 14 mg oral semaglutide/ placebo OD as illustrated in Table 7-2.

The 4-week dose escalation interval is applied in order to mitigate the risk of gastrointestinal AEs.

Patients should remain on the 14 mg dose level until the end of treatment visit; however, dose reductions, extensions of dose escalation intervals and treatment pauses are allowed e.g. if treatment with the trial product is associated with unacceptable AEs or due to other circumstances.

Table 7-2 Treatment and trial periods

Trial periods	Screening	Dose escalation	Dose escalation	Maintenance	Follow-up
Visits in each period	Visit 1 to Visit 2	Visit 2 to Visit 3	Visit 3 to Visit 4	Visit 4 to end of treatment Visit	End of treatment Visit to Follow-up Visit
Duration	Up to 3 weeks	4 weeks	4 weeks	Up to ~58 months	5 weeks
Daily dose	-	3 mg	7 mg	14 mg	-

Any change to trial product dose including date of change or discontinuation should be recorded in the eCRF throughout the trial.

If trial product is discontinued, patients should continue to follow the trial schedule without being withdrawn from the trial. Treatment with trial product should be resumed if deemed safe at the discretion of the investigator.

7.2.1 Dosing instructions

Absorption of oral semaglutide is significantly affected by food and fluid in the stomach, therefore dosing should be in the morning in a fasting state and at least 30 minutes before the first meal of the day. Oral semaglutide can be taken with up to half a glass of water (approximately 120 mL/ 4 fluid oz.). The tablet should be taken immediately after removal from the blister and swallowed whole and must not be broken or chewed. Other oral medication should not be taken together with trial product but can be taken 30 minutes after trial product.

7.2.2 Missed doses

The trial product should be administered once daily; however, if one or more doses of trial product are missed due to circumstances not related to the safe use of the trial product (as judged by the investigator) and treatment with trial product is resumed, the below recommendations for dose adjustment apply:

- If ≤ 21 consecutive doses of 14 mg oral semaglutide/placebo are missed, the once daily regimen can be resumed as prescribed without dose reduction.
- If 22-35 consecutive doses of 14 mg oral semaglutide/placebo are missed, it is recommended to resume treatment at 7 mg oral semaglutide/placebo and subsequently, escalate to the higher dose after 4 weeks of treatment.
- If ≥ 36 consecutive doses of 14 mg oral semaglutide/placebo are missed, it is recommended to resume treatment at 3 mg oral semaglutide/placebo and subsequently, escalate to the higher doses with 4-week dose escalation steps.

Please refer to section 8.1.1 for instructions on how to use the IWRS in relation to patients discontinuing and resuming trial product treatment.

In case of questions related to resuming trial treatment, the investigator can consult Novo Nordisk.

7.3 Method of treatment assignment

All patients will be centrally randomised using an IWRS and assigned to the next available treatment according to randomisation schedule. Trial product will be dispensed at the trial visits summarised in the flowchart, Section 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.

7.4 Blinding

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

The IWRS is used for blind-breaking instructions. The blind may be broken in a medical emergency if knowing the actual treatment would influence the treatment of the patient. Novo Nordisk will be notified immediately after breaking the blind. The date when and reason why the blind was broken must be recorded in the source documentation.

Whenever the blind is broken, the person breaking the blind must print the "code break confirmation" notification generated by the IWRS, record the reason and sign and date the document.

When the blind is broken, the treatment allocation will be accessible to the investigator and the Novo Nordisk Global Safety department. If IWRS is not accessible at the time of blind break, the IWRS helpdesk should be contacted. Contact details are listed in Attachment I.

7.5 Preparation/Handling/Storage/Accountability

Only patients enrolled in the trial may use trial product and only authorised site staff may supply or administer trial product.

Product storage, in-use conditions and in-use time will be available on the 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 first shipment to each site will be triggered by the first patient screened.

The investigator must confirm that appropriate temperature conditions have been maintained during transit for all trial products received and 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 authorised site staff.

The investigator must inform Novo Nordisk immediately if any trial product has been stored outside specified conditions. Additional details regarding handling of temperature deviations can be found in the TMM.

Trial product that has been stored improperly must not be dispensed to any patient before it has been evaluated and approved for further use by Novo Nordisk.

Patients must ensure that all used, partly used and unused trial products including empty packaging material is returned as instructed by the investigator.

The investigator is responsible for drug accountability and record maintenance (i.e. receipt, accountability and final disposition records).

Drug accountability is performed by using the IWRS and must be done on tablet level.

Destruction of trial products can be performed on an ongoing basis and will be done according to local procedures after accountability is finalised by the site.

Destruction of trial products must be documented in the IWRS.

All returned, expired or damaged trial products (for technical complaint samples see Appendix 6) 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 trial site.

7.5.1 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.

Japan: For country specific requirements, please see Appendix 8.

7.6 Treatment compliance

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

Treatment compliance will be assessed by monitoring of drug accountability and by discussing treatment compliance and dosing conditions with the patient. Treatment compliance is defined as taking between 80%-120% of the dose as prescribed between visits. The investigator must assess the amount of trial products returned compared to what was dispensed at the previous visit and, in case of discrepancies, question the patient.

If a patient is found to be non-compliant, the investigator will remind the patient of the importance of following the instructions given including taking the trial products as prescribed and should document this discussion in the patient's medical record.

If the patient has been off treatment, continuation of trial product should be encouraged if considered safe as per the investigator's discretion. Previous dose and gastrointestinal adverse reactions as well as number of missed doses should be taken into consideration when evaluating whether to repeat dose escalation (see section 7.2.2).

7.7 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
- 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
- in relation to a clinical trial for COVID-19 prevention or treatment
- In relation to an approved COVID-19 vaccine

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

For antidiabetic medication, the total daily dose needs to be included in the eCRF. Stable dose changes (2 weeks or more) should be captured as new concomitant medication with the new dose and relevant start and stop date.

Changes in concomitant medication listed above must be recorded at each visit. If a change is due to an SAE, then this must be reported according to Section 9.2.

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 3.3.1.

Importantly, investigators should ensure that patients are treated according to recommended standard of care for both glycaemic management as well as CV risk management. Recommendations for this will be provided in guidance documents from the steering committee and global expert panel during trial conduct. Surveillance of adherence to standard of care will be performed centrally by Novo Nordisk. For patients where standard of care is not achieved, investigators may be asked for an optimisation plan which will be recorded in the eCRF or approached to discuss treatment options. If allowed according to local regulation, Novo Nordisk may compensate parts of the cost of some concomitant medication used to ensure glycaemic control and CV risk management.

Brazil and Turkey: For country specific requirements, please see Appendix 8.

7.8 Treatment after the end of the 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. Oral semaglutide will not be available for prescription until marketing authorisation is issued.

Argentina and Brazil: For country specific requirements, please see Appendix 8.

8 Discontinuation/Withdrawal criteria

8.1 Discontinuation of trial treatment

The patient must be discontinued from trial product at any time during the trial, if any of the following applies:

1. Pregnancy
2. Intention of becoming pregnant
3. Simultaneous participation in another clinical trial of an approved or non-approved investigational medicinal product*
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 postinfectious conditions is allowed at the investigator discretion without discontinuing trial product.

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: 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.

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.

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 eCRF, and drug accountability must be performed.

8.1.1 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 7.1). Similarly, patients who discontinue trial product on their own initiative should be encouraged to resume the treatment (Section 7.1). At both instances dose escalation may be necessary (Section 7.2.2). 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.

8.2 Withdrawal from the trial

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

If considering withdrawing from the trial, the patient should, as an alternative, be offered flexible participation in the trial. This could be attending fewer visits (i.e. reduced visit schedule), converting site visits to phone contacts, treatment pause, or only being followed-up for AEs, especially those related to the primary objective. Another alternative could be to cease all trial related activities including trial product, and simply receive a phone call at trial end to collect AEs. It must be explained to the patient that this must include information on their AEs, especially those related to the primary objective that occurred since last contact to the patient. Only if the patient declines all alternatives, should the patient be recorded as withdrawn.

Final drug accountability must be performed even if the patient is not able to come to the trial site.

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.

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

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 eCRF.

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 5.2 for further details.

Mexico: For country specific requirements, please see Appendix 8.

8.2.1 Replacement of patients

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

8.3 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 trial site.

- Before a patient is deemed lost to follow-up, the investigator must make every effort to regain contact with the patient as described in Section 5.2.
- A patient cannot be declared lost to follow-up before all the attempts have been repeated and the trial has come to an end as described in Section 5.2.

The attempts to contact the patient must be documented in medical records at the site.

9 Trial assessments and procedures

- Trial procedures and their timing are summarised in the flowchart, Section 2.
- Informed consent must be obtained before any trial related activity, see Appendix 3.
- All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility 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.
- At screening, patients will be provided with a card stating that they are participating in a trial and giving contact details of relevant trial site staff.
- Adherence to the trial design requirements, including those specified in the flowchart, is essential and required for trial conduct.
- The investigator should inform the patients' primary physician about the patients' participation in the trial if the patient has a primary physician and if the patient agrees to the primary physician being informed.
- Each patient should be asked to provide contact information for persons (preferably at least 3), e.g. relatives, primary care provider or other, whom investigator can contact in case of issues when trying to contact the patient during the trial. The sites are encouraged to maintain these details as current as possible throughout the course of the trial.
- The randomisation visit can be performed on the same day as the screening visit if the patient is assessed as eligible (Section 6) and if sufficient trial product is available.
- It is the responsibility of the investigator to schedule the visits and contacts as per protocol (flowchart, Section 2) and to ensure they take place.
- After V6, all odd numbered site visits (V7, V9, V11 etc.) can be conducted as a phone contact, however the investigator needs to ensure that the subject has enough trial product within the expiry date.

- The investigator must ensure they keep regular contact with each patient throughout the entire trial, and at all times have updated contact information. Even if a visit (or phone contact) is missed and it is not possible to re-schedule, the investigator must take every effort to have all patients followed for endpoint related outcomes including MACE.
- 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.
- Review of completed laboratory reports etc. must be documented either on the documents or in the patient's source documents.
- Repeat samples may be taken for technical issues and unscheduled samples or assessments may be taken for safety reasons. Please refer to Appendix 2 for further details on laboratory samples.
- The investigator may provide the patients with a mobile phone to mediate easier contact if allowed according to local regulation and approved by institutional review board (IRB)/independent ethics committee (IEC). The investigator should consider sending text messages to the patients to remind them of site visits, dosing of trial product, and other trial requirements.
- If warranted by special circumstances, the investigator may engage with a health care professional from a third party home health care service provider to perform protocol procedures at the subject's home or other alternate location. Prior to the arrangement, the investigator must obtain the subject's consent by means of separate and locally approved consent form. The third party health care professional must have a licence to practice and have received adequate protocol training.

9.1 Efficacy assessments

Planned time points for all efficacy assessments are provided in the flowchart Section 2.

9.1.1 HbA_{1c} point of care

HbA_{1c} can be measured while patient is at site for assessing eligibility at Visit 1 and at site visits during the trial as a supportive measurement for investigator's treatment decisions. Sites will either use their own equipment or a device provided by Novo Nordisk. Local laboratory can be used if the HbA_{1c} point of care device for any reason cannot be used. Point of care device measurements performed at scheduled visits should be recorded in the eCRF starting at Visit 3.

9.1.2 Self-measured plasma glucose

If deemed helpful by the investigator, patients may be provided with a BG meter including auxiliaries as well as instructions for use. The patients will be instructed in how to use the device and the instruction will be repeated as needed. The investigator will advise the individual patient of when the self-measured plasma glucose values should be measured and how to note the values and

dates. The measurements are supportive for investigator's treatment decisions when optimising glycaemic control, and should be filed at site.

9.1.3 Clinical efficacy laboratory assessments

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

9.1.4 Cognitive testing, patient surveys and visits to emergency room/urgent care unit

The Montreal Cognitive Assessment (MoCA) is the cognitive testing used in this trial. If clarification of the test is needed, care must be taken not to bias the patient.

Argentina, Canada, Colombia, Mexico, Spain, United Kingdom and United States:
Online cognitive testing will be performed using the PROTECT Cognitive Test Battery in English and/or Spanish speaking patients. The test battery includes the following tests:

- Verbal Reasoning
- Paired Associate Learning
- Self-Ordered Search
- Digit Vigilance
- Simple Reaction Time
- Choice Reaction Time

Performing the tests comprise doing a pre-test for practice as well as an actual test. The tests should be performed at visits specified in the flowchart (see Section 2).

Patient surveys will be performed in a subset of patients in selected countries:

- A patient expectations and experience survey. This data will not be transferred to the trial database.
- A patient engagement assessment. This data will not be transferred to the trial database.

Visits to emergency room/urgent care unit will be recorded in the eCRF for the US.

9.2 Adverse events

The definitions of AEs and SAEs can be found in Appendix 4.

Japan: For AE reporting requirements please see Appendix 8.

This trial employs a selective approach for collection of safety data. The investigator is responsible for detecting, documenting, recording and following up on:

- SAEs
- AEs requiring event adjudication or additional data collection on specific event forms, irrespective of seriousness, see Table 9-1
- AEs leading to discontinuation of trial product, irrespective of seriousness

- 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
- Technical complaints

Table 9-1 AEs requiring event adjudication or additional data collection

Event type (serious and non-serious) including description	Adjudication outcome	Additional form(s) required
Death All cause death	• Cardiovascular death • Renal death • Non-cardiovascular, non-renal death	• Adjudication form
Acute coronary syndrome (ACS) All types of acute myocardial infarction Unstable angina pectoris requiring hospitalisation	• Acute myocardial infarction • Hospitalisation for unstable angina pectoris	• Adjudication form and • Specific event form in case of revascularisation
Events leading to coronary artery revascularisation (non-ACS) Non-ACS events (e.g. stable angina pectoris) leading to a 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 the AE diagnosis	• Not applicable	• Specific event form
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 ischemia, with or without infarction	• Stroke	• Adjudication form • Modified Rankin scale form*
Heart failure requiring hospitalisation or urgent heart failure visits New episode or worsening of existing heart failure leading to an urgent, unscheduled hospital admission or clinic/office/emergency department visit	• Heart failure hospitalisation • Urgent heart failure visit	• Adjudication form
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	• Acute limb ischemia hospitalisation • Chronic limb ischemia hospitalisation	• Adjudication form
Acute pancreatitis Events of acute pancreatitis	• Acute pancreatitis	• Adjudication form

Event type (serious and non-serious) including description	Adjudication outcome	Additional form(s) required
Events leading to renal replacement therapy Dialysis treatment (haemodialysis or peritoneal dialysis) Kidney transplantation Note: The underlying condition should be reported as the AE diagnosis	• Chronic renal replacement therapy	• Adjudication form
Malignant neoplasm Malignant neoplasm by histopathology or other substantial clinical evidence	• Not applicable	• Specific event form
Diabetic retinopathy New onset or worsening of diabetic retinopathy	• Not applicable	• Specific event form
Acute gallbladder disease Events of symptomatic acute gallbladder disease (including gallstones and cholecystitis)	• Not applicable	• Specific event form
Medication errors related to trial product Medication error (accidental errors related to trial product): Wrong drug administered instead of trial product. Wrong route of administration or accidental administration of a lower or higher dose than intended where clinical consequences for the patient were likely to happen, although they did not necessarily occur	• Not applicable	• Specific event form
Severe hypoglycaemic episode An episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. Plasma glucose values 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 (American Diabetes Association[11])	• Not applicable	• Specific event form • If the episode fulfils the criteria of an SAE, an AE form and a safety information form must also be completed Japan: For country specific require-ments, see Appendix 8.

* Disability after a stroke or TIA event, see section 9.4.5

Description of events is to guide investigators with regards to reporting of AEs. Event definitions are included in the charter for the event adjudication committee (EAC).

9.2.1 Time period and frequency for collecting AE and SAE information

All events meeting the definition of an SAE (see Appendix 4) and AEs leading to discontinuation of trial product, pregnancies and events specified in Table 9-1 must be collected and reported. These

events will be collected from the day of randomisation and until the follow-up visit, at the time points specified in the flowchart.

All SAEs will be recorded and reported to Novo Nordisk or designee within 24 hours of investigator's knowledge of the SAE, as indicated in Appendix 4. The investigator must submit any updated SAE data to Novo Nordisk within 24 hours of it being available.

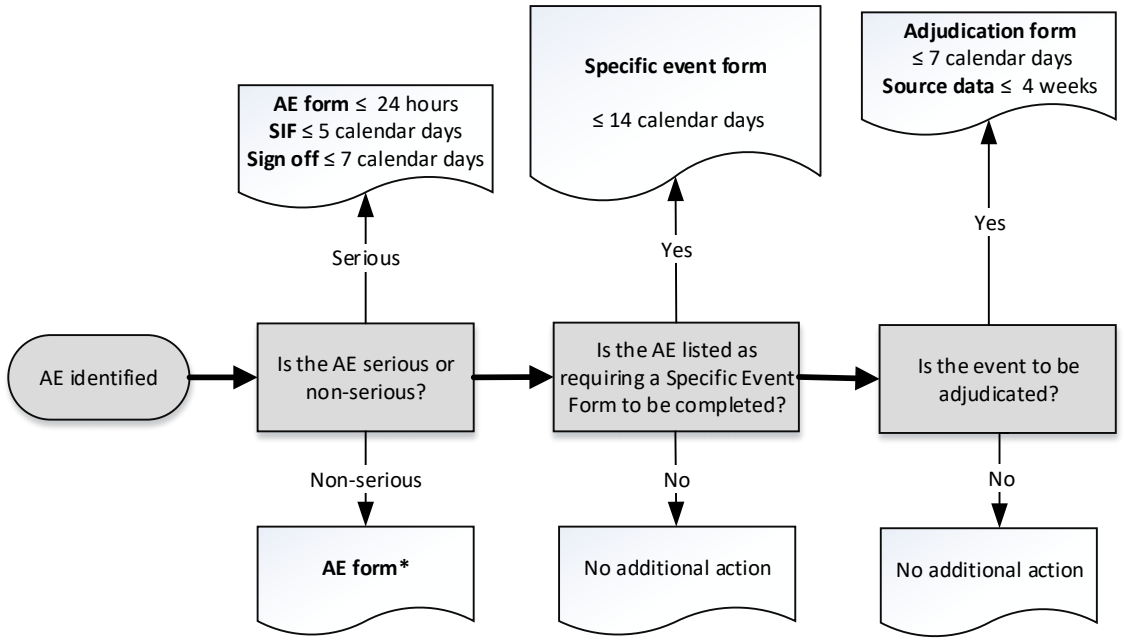
Investigators are not obligated to actively seek for AEs or SAEs in former trial patients. However, if the investigator learns of any SAE, including a death, at any time after a patient has been discontinued from/completed the trial, and the investigator considers the event to be possibly/probably related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

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 4.

Timelines for reporting of AEs, including events for adjudication, Section 9.2.1.1, are listed in Figure 9-1.

Some AEs require additional data collection via a specific event form. The relevant AEs are listed in Table 9-1 and the reporting timelines in Figure 9-1.

Figure 9-1 Safety reporting timelines



Timelines are from the awareness of an AE.
Queries and follow-up requests to be resolved ≤ 7 calendar days.
* Only for non-serious adverse events required to be reported according to section 9.2
AE: Adverse Events, SAE: Serious Adverse Events, SIF: Safety Information Form

9.2.1.1 Events for adjudication

The list of events for adjudication can be found in Table 9-1 and the reporting timelines in Figure 9-1. Event adjudication will be performed for events in randomised patients. These events are reviewed by an independent external event adjudication committee in a blinded manner, refer to Appendix 3 for further details.

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

1. Investigator-reported events for adjudication: When reporting AEs, the investigator must select the appropriate AE category based on pre-defined criteria (see Table 9-1). If the selected AE category is in scope for adjudication, an adjudication form should be completed. Relevant source documents (as specified in the Event Adjudication Site Manual) must, if obtainable, be collected and uploaded to the Event Adjudication System (EAS).
2. Deaths (AEs reported with fatal outcome): When an AE is reported with fatal outcome, a death adjudication form will appear in the eCRF. This form must be completed and all source documents associated with the patients' death must, if obtainable, be collected and uploaded to the EAS.
3. AE search (standardised screening): All AEs not directly reported by the investigator as requiring adjudication, will undergo screening to identify potential events for adjudication. If

the AE is deemed relevant for adjudication, an adjudication form will be generated in the eCRF. This form must be completed, and all source documents (as specified in the Event Adjudication Site Manual) must, if obtainable, be collected and uploaded to the EAS.

4. EAC-identified events: During review of source documents provided for another event for adjudication, the EAC may identify additional events in scope for adjudication that were not initially reported by the investigator. In these instances, the investigator will be notified of the newly identified event and has the option to report the EAC-identified event. Regardless of whether the investigator decides to report the event, it will undergo adjudication. Occasionally, EAC-identified events may require the investigator to collect additional source documents and upload these, if obtainable, to the EAS.

The adjudication form for the event in question should be completed in the eCRF within 7 calendar days from the AE is reported in the eCRF.

Copies of source documents should be labelled with trial ID, patient number, AE number (if applicable), redacted (anonymised of personal identifiers) and uploaded to the EAS as soon as possible and preferably within 4 weeks. 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.

The assessments made by both the event adjudication committee and the investigator will be evaluated and included in the clinical trial report.

9.2.2 Method of detecting AEs and SAEs

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.

9.2.3 Follow-up on AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow all events until resolution, stabilization, or if the event is otherwise explained (e.g. chronic condition). Further information on follow-up procedures is given in Appendix 4.

9.2.4 Regulatory reporting requirements for SAEs

Prompt notification by the investigator to Novo Nordisk 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, IRB/IEC, and investigators.

To avoid introducing bias and to maintain the integrity of the primary analysis, Novo Nordisk will exempt SAEs that are part of the primary objective evaluation (MACE) from unblinding and regulatory reporting during trial conduct, even though the cases fulfil the definition of suspected unexpected serious adverse reactions (SUSARs). The definition of MACE is: Cardiovascular death, non-fatal myocardial infarction, non-fatal stroke. The independent DMC (Appendix 3) receives unblinded data and makes recommendations to the Novo Nordisk safety committee on an ongoing basis. This ensures adequate monitoring of safety while maintaining SAE reports related to the primary endpoint blinded for Novo Nordisk.

At the end of the trial, when treatment is revealed, all exempted cases which meet the criteria for expedited reporting SUSARs will be submitted to the regulatory authorities. Because multiple cases will be identified simultaneously, Novo Nordisk will not be able to fulfil the 7 days requirement for fatal or life-threatening events but will within 60 days after code break have all SUSARs submitted to the regulatory authorities.

In case a regulatory authority requires the blinded report on an expedited basis, Novo Nordisk will submit individual blinded case reports related to investigational product to the relevant regulatory authorities on an expedited basis.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Novo Nordisk policy and forwarded to investigators as necessary.

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.

9.2.5 Pregnancies and associated adverse events

Details of pregnancies in female patients will be collected after randomisation and until pregnancy outcome.

If a pregnancy is reported in female patients, the investigator should inform Novo Nordisk within 14 calendar days of learning of the pregnancy and should follow the procedures outlined in Appendix 5.

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.

The investigator should report information on the patient and the pregnancy outcome until the new-born infant is one month of age in accordance with European Medicines Agency (EMA).[12] Information about the pregnancy and pregnancy outcome/health of the new-born infant has to be reported on paper pregnancy forms and be forwarded to Novo Nordisk either by fax, encrypted e-mail or courier.

9.2.6 Technical complaints

The investigator must assess whether a technical complaint is related to an AE. The definitions and reporting process for technical complaints can be found in Appendix 6.

9.3 Treatment of overdose

There is no specific antidote for overdose with semaglutide. Limited data are available with regard to overdose in patients treated with oral semaglutide. Based on data from treatment with s.c. semaglutide, the most commonly reported adverse reaction was nausea and all patients recovered without complications. In the event of an overdose, appropriate supportive treatment should be initiated according to the patients' clinical signs and symptoms. A prolonged period of observation and treatment for these symptoms may be necessary, taking into account the half-life of semaglutide of approximately one week.

In the event of an overdose, the investigator should closely monitor the patient for overdose-related AE/SAEs. Decisions regarding dose interruptions or modifications will be made by the investigator based on the clinical evaluation of the patient. Accidental overdose must be reported as a medication error. Refer to Section 9.2.1 for further details. For more information on overdose, also consult the current version of the oral semaglutide IB.

9.4 Safety assessments

Planned time points for all safety assessments are provided in the flowchart Section 2.

A **concomitant illness** is any illness that is present at the start of the trial 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 has experienced in the past, i.e. prior to randomisation.

The following concomitant illness/medical history should be recorded in the eCRF:

- Type 2 diabetes - date of diagnosis
- Diabetes complications
- History of cardiovascular and chronic kidney diseases. This also includes each medical condition(s) that qualified the patient for participation in the trial according to inclusion criterion #5 a-d
- History of eye diseases
- History of gallbladder diseases
- History of pancreatitis
- Other relevant concomitant illness/medical history including malignant neoplasms and COVID-19

In case of an abnormal and clinically significant finding, the investigator must record the finding on relevant disease specific history form or the Medical History/Concomitant Illness form if it is present before randomisation. Any new finding fulfilling the AE definition (see Appendix 4) during the trial and any clinically significant worsening from baseline (visit 2) must be reported as an AE, if applicable, (see Section 9.2).

9.4.1 Physical examinations

Physical examinations should be performed according to local procedures, when indicated in Section 2.

A physical examination will include assessments of the:

- General appearance
- Thyroid gland
- Respiratory system
- Cardiovascular system
- Gastrointestinal system incl. mouth
- Extremities
- Central and peripheral nervous system

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

Relevant findings present at or prior to randomisation should be recorded on the concomitant illness/medical history forms in the eCRF in accordance with Section 9.4. Findings not present at randomisation should be reported as AEs according to Section 9.2.

Body measurements (e.g. height, weight and waist circumference) will be measured and recorded as specified in the flowchart Section 2.

Height should be measured without shoes in centimetres (cm) or inches (in) and recorded in the eCRF.

Body weight should be measured in kilogram (kg) or pound (lb), with an empty bladder, without shoes and only wearing light clothing. The actual value of the weight should be recorded in the eCRF without rounding and the same equipment should be used throughout the trial.

Waist circumference is the abdominal circumference measured midway between the lower rib margin and the iliac crest. It should be measured when the patient is in a standing position with a non-stretchable measuring tape and to the nearest cm or inch.

Waist circumference and liver parameters are measured at baseline for calculation of fatty liver index.

9.4.2 Vital signs

Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the patient in a quiet setting without distractions (e.g. television, cell phones). The measured values should be recorded in the eCRF without rounding. Blood pressure and pulse measurements should be assessed in a sitting position with a completely automated device. Manual techniques should be used only if an automated device is not available.

9.4.3 Clinical laboratory assessments

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

9.4.4 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.

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 the flowchart in Section 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 according to section 9.2.

9.4.5 Disability after a stroke or TIA event

The modified Rankin Scale is used to measure the degree of disability in daily activities after a stroke. A modified Rankin Scale form should be completed for all events sent to adjudication for stroke including evens of TIA to ensure that all events of an EAC confirmed stroke will have a disability outcome recorded. The degree of disability according to the scale should be assessed after a minimum of 90 days post-event (most often this will be at the patient's second site visit after the stroke or TIA). The event should be recorded in the eCRF.

9.5 Pharmacokinetics

Not applicable.

9.6 Pharmacodynamics

Not applicable.

9.7 Genetics

A blood sample for DNA analysis will be collected from patients who have consented to participate in the optional biobank component of the trial. Refer to Section 9.8 and Appendix 7 for further details.

Brazil, China, Columbia, Israel, South Korea and Turkey: For country specific requirements, please see Appendix 8.

9.8 Biomarkers

Collection of samples for biomarker research is a component 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 and stored for future use.

The samples are collected for the purpose of allowing future analyses of biomarkers, both genetic and circulating, at a later point in time when new knowledge or improved measurement techniques

may have become available. The analyses may include biomarkers currently known or discovered in the future.

Genetic analyses will include analysis of candidate genes or genetic markers throughout the genome with the purpose of understanding and predicting response to semaglutide as well as to understand cardiometabolic diseases. Analyses of circulating biomarkers will measure hormones, metabolites or other non-genetic serum entity with the purpose of understanding and predicting response to semaglutide as well as understanding cardiometabolic diseases.

These samples need to be frozen and should be sent at monthly intervals in batches 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 7).

Brazil, China, Columbia, Israel, South Korea and Turkey: For country specific requirements, please see Appendix 8.

10 Statistical considerations

10.1 Sample size determination

The trial is designed with 90% power to confirm superiority for the primary endpoint, i.e. reject the null-hypothesis of hazard ratio (HR) ≥ 1.0 against the one-sided alternative of HR < 1.0, where HR is the hazard ratio of oral semaglutide versus placebo. An alpha spending function will be used that approximates O'Brien Fleming stopping boundaries for the overall Type I error probability of 2.5% (one-sided). Based on a randomisation ratio of 1:1 and assuming a true HR of 0.83 a total of 1,225 primary endpoint events are required for 90% power. For calculation the number of randomised patients the following is assumed:

- annual primary endpoint rate in the placebo group of 3.5%
- uniform recruitment occurs in 18 months
- annual lost to follow-up rate in both treatment groups of 1%
- trial duration is five years and five weeks

Under these assumptions, a total of 9,642 patients are needed for randomisation.

Confirmatory secondary endpoints

If superiority is confirmed for the primary endpoint the below confirmatory secondary endpoints will be controlled for multiplicity through a hierarchical testing strategy. The marginal powers below are calculated under the assumptions that the trial continues to the final analysis and a significance level of 2.5% (one-sided).

The marginal power for superiority in favour of oral semaglutide for the CKD endpoint with 9,642 randomised patients is 94%. This is based on an assumed hazard ratio of 0.80 and an annual event rate of 2.8% in the placebo group.

The marginal power for superiority in favour of oral semaglutide for CV death with 9,642 randomised patients is 56%. This is based on an assumed hazard ratio of 0.83 and an annual event rate of 1.4% in the placebo group.

The marginal power for superiority in favour of oral semaglutide for the MALE endpoint with 9,642 randomised patients is 44%. This is based on an assumed hazard ratio of 0.75 and an annual event rate of 0.44% in the placebo group.

The assumptions for annual event rate of primary endpoint and confirmatory secondary endpoints, lost to follow-up rates and the true hazard ratios are based on the LEADER[13] and SUSTAIN 6[2] CV outcomes trials.

10.2 Definition of analysis sets

The full analysis set (FAS) is defined as all randomised patients and grouped in analyses according to the treatment assigned at randomisation.

Patients continue in the trial and are part of FAS regardless of discontinuation of randomised treatment and any other intercurrent event. A patient is considered lost to follow-up (LTFU) if the patient does not complete the trial and does not withdraw consent. Trial completers are defined as patients that either attend the end-of-trial follow-up visit or who die during the in-trial period.

The in-trial observation period for a patient is defined as the period from date of randomisation to the first of (both inclusive):

- date of follow-up visit
- date when patient withdrew consent
- date of last contact with patient (for patient lost to follow-up)
- date of death

10.3 Statistical analyses

A comprehensive statistical analysis plan (SAP) will be available before first patient first visit (FPFV), including further details of interim testing.

Novo Nordisk will perform the statistical analyses except interim testing, see Section 10.3.4. A statistician independent of trial conduct, DMC analyses, interim testing, and external to Novo Nordisk will repeat the statistical analyses of the primary endpoint and secondary confirmatory endpoints.

General considerations

For confirmatory endpoints controlled for multiplicity, estimated treatment effects will be presented together with two-sided 95% confidence intervals (CIs) and one-sided p-values for test of the hypothesis of superiority. For reporting of results, the estimated treatment effect and the 95% confidence interval will be accompanied by the two-sided p-value.

For non-confirmatory endpoints, the estimated treatment effects will be reported together with two-sided 95% CIs and two-sided p-values.

Baseline value is defined as the latest available measurement from the randomisation visit or the screening visit. Thus, if a randomisation assessment is missing then the assessment from screening is used as the baseline assessment, if available.

Missing data are defined as data that are planned and can be observed but are not present in the database. This implies that data that are structurally missing due to death or administrative censoring are not considered missing.

If adjudicated, time-to-event endpoints are defined based on outcomes of the EAC evaluations. If a patient experiences the event of interest during the in-trial observation period, the endpoint is the time from randomisation to the date of event. While vital status is ascertained systematically throughout the trial, non-fatal events (e.g. non-fatal MI or non-fatal stroke) cannot be systematically collected after withdrawal of consent, lost-to-follow-up, or after end-of-trial visit. For this reason, any event occurring after the in-trial observation period is not included in analyses, unless otherwise stated.

Time-to-event endpoints are censored at the end of the in-trial period if the event of interest did not happen during this period and the patient is alive at the end of the period. Censoring due to LTFU and withdrawal of consent assume independent censoring. Additional anticipated intercurrent events and handling of these in context of the estimand for the primary and confirmatory secondary time-to-event endpoints are described in Table 10-1.

10.3.1 Primary endpoint

The HR for comparing oral semaglutide versus placebo will be estimated from a Cox proportional hazards model with treatment group (semaglutide, placebo) as fixed factor together with the 2-sided 95% CI and one-sided fixed design p-value for hypothesis testing. The score test from the Cox model will be used for testing. The following superiority hypothesis will be tested:

H_0: HR $\geq$ 1.0 against H_a: HR < 1.0.

Superiority of oral semaglutide versus placebo will be considered confirmed if the associated H_0 is rejected based on nominal significance level derived from the pre-specified alpha spending based on the actual observed number of events available for the analysis. Final inference on termination is

adjusted for the group sequential design by using the likelihood ratio ordering for the p-value, 95% CI and HR.

Competing risk from non-CV deaths will be handled as censorings in the primary Cox analysis. Please, refer to Table 10-1 for handling of other intercurrent events.

Sensitivity analysis

If superiority is established for the primary endpoint, the following sensitivity analysis is performed. The primary analysis assumes independent censoring for patients who are LTFU or who withdrawn consent. To investigate the impact of this assumption on the superiority results of the primary analysis, a tipping point analysis will be made. In this analysis, patients in the oral semaglutide treatment group will have their event times imputed with an increasing penalty in the sense that their risk of MACE is increased (the penalty) following censoring compared to while under observation. The placebo patients will be imputed with no penalty, i.e. assuming same event before and after censoring. Multiple imputed data sets will be analysed for each penalty using the above Cox model and results will be combined using Rubin's rule. The tipping point is then defined as the penalty needed to turn around the superiority conclusion.

10.3.2 Secondary endpoints

Secondary endpoints are categorised as being confirmatory when they are analysed under multiplicity control.

10.3.2.1 Confirmatory secondary endpoints

If superiority is established for the primary endpoint, the superiority hypothesis stated in section 10.3.1 is tested for the confirmatory secondary endpoints under multiplicity control via a hierarchical testing scheme using the following order:

- composite CKD endpoint
- CV death
- MALE endpoint

The testing procedure is stopped the first time an analysis fails to confirm superiority of the endpoint in question. The statistical significance levels of the confirmatory secondary endpoint analyses are specified in the SAP.

The confirmatory secondary endpoints will be analysed and tested separately with a Cox proportional hazards model as described for the primary endpoint.

The following Table 10-1 describes how anticipated intercurrent events during the trial are handled for confirmatory endpoints.

Table 10-1 Statistical handling of intercurrent events for the confirmatory endpoints

Endpoint	Intercurrent event	Handling
Time to first occurrence of MACE	• Treatment discontinuations • Medication modifying cardio-renal risk • Initiation of chronic renal replacement therapy	Patients will be followed and events collected after intercurrent events and used in the analysis
	• Trial discontinuation (withdrawal of consent or lost-to follow-up)	Censoring at time of trial discontinuation
	• Non-CV death (competing risk)	Censoring at time of non-CV death in the Cox model
Time to first occurrence of composite CKD	• Treatment discontinuations • Medication modifying cardio-renal risk	Events and follow-up time will be collected after intercurrent events and used in the analysis
	• Trial discontinuation (withdrawal of consent or lost-to follow-up)	Censoring at time of trial discontinuation
	• Non-renal and Non-CV death (competing risk)	Censoring at time of non-renal or non-CV death in the Cox model
Time to occurrence of CV death	• Treatment discontinuations • Medication modifying cardio-renal risk • Initiation of chronic renal replacement therapy	Events and follow-up time will be collected after intercurrent events and used in the analysis
	• Trial discontinuation (withdrawal of consent or lost-to follow-up)	Censoring at time of trial discontinuation
	• Non-CV death (competing risk)	Censoring at time of non-CV death in the Cox model
Time to first occurrence of MALE	• Treatment discontinuations • Medication modifying cardio-renal risk • Initiation of chronic renal replacement therapy	Patients will be followed and events collected after intercurrent events and used in the analysis
	• Trial discontinuation (withdrawal of consent or lost-to follow-up)	Censoring at time of trial discontinuation
	• All cause death (competing risk)	Censoring at time of death in the Cox model

10.3.2.2 Supportive secondary endpoints

Each of the supportive secondary time-to-event endpoints will be analysed with the same Cox proportional hazards model as the primary endpoint.

The continuous supportive secondary endpoints (change from baseline to 2 years) are analysed using multiple imputation for missing values. An imputation model (linear regression) is estimated separately for each treatment group. It will include baseline value as a covariate estimated based on patients having an observed data point, irrespective of adherence to randomised treatment, at 2 years. The fitted model is used to impute values for all patients that do not have an observed data point at 2 years to create 500 complete data sets. The completed data sets are analysed by an ANCOVA adjusted for treatment as fixed factor and baseline value as covariate. Rubin's rule is used to combine the results.

Number of severe hypoglycaemic episodes will be analysed using a marginal recurrent event regression model taking into account the competing risk of all-cause death.

10.3.3 Exploratory endpoints

The statistical analyses of the exploratory endpoints based on the PROTECT cognitive tests and the MoCA score will be detailed in the SAP.

Current smoking at year two (yes/no) will be analysed using a binary regression model adjusted for baseline smoking status (yes/no).

10.3.4 Interim testing for efficacy

Interim testing evaluating the primary endpoint for superiority will be performed based on locked snapshot of the study database at the time-point of an interim testing. Patients without a primary endpoint event prior to the analysis cut-off date will be censored with the censoring date defined as the first of in-trial end-date and analysis cut-off date.

Interim testing will be performed by a statistician independent of trial conduct and external to Novo Nordisk. The DMC evaluates the unblinded interim testing using the group sequential stopping boundaries as guidance. Stopping the trial for superiority is allowed if a stopping boundary is crossed and the DMC makes the decision to recommend early trial termination.

If the trial is terminated early for superiority following an interim testing, definitive evaluation of superiority for the primary endpoint will be performed based on updated nominal significance levels. All events from the in-trial observation period including events collected after interim cut-off date will be included in this confirmatory evaluation.

10.3.5 Sequential safety analysis and safety monitoring

Blinded and unblinded data analyses during trial conduct will be performed by the DMC, as described in the DMC charter. Trial integrity will be ensured by using a statistician independent of trial conduct and external to Novo Nordisk to prepare data for the DMC. The sequential analyses performed by the DMC will be based on accumulated efficacy (see Section 10.3.4) and safety data and will be performed to make recommendations regarding the ongoing conduct of the trial to ensure acceptable benefit/risk ratio for patients in the trial.

10.4 Pharmacokinetic and/or pharmacodynamic modelling

Not applicable.

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12 Appendices

Appendix 1 Abbreviations and Trademarks

ABI	ankle-brachial index
ACS	acute coronary syndrome
ADA	American Diabetes Association
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BG	blood glucose
CI	confidence interval
CKD	chronic kidney disease
CKD-EPI	chronic kidney disease – epidemiology collaboration
COVID-19	Coronavirus disease 2019
CRF	case report form
CT	computerized tomography
CTR	clinical trial report
CV	cardiovascular
CVD	cardiovascular disease
CVOT	cardiovascular outcome trial
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DUN	dispensing unit number
EAC	event adjudication committee
EAS	event adjudication system
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EOT	end of treatment
eGFR	estimated glomerular filtration rate
FAS	full analysis set

FDA	U.S. Food and Drug Administration
FDAAA	FDA Amendments Act
FPFV	first patient first visit
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GLP-1 RA	glucagon-like peptide-1 receptor agonist
HbA_{1c}	glycosylated haemoglobin
HDL	high-density lipoprotein
hCG	human chorionic gonadotropin
HR	hazard ratio
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICH	International Council for Harmonisation
IEC	independent ethics committee
IMP	investigational medicinal product
IRB	institutional review board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IWRS	interactive web response system
LAR	legally acceptable representative
LDL	low-density lipoprotein
LPLV	last patient last visit
LTFU	lost to follow-up
MACE	major adverse cardiovascular events
MALE	major adverse limb events
MEN2	multiple endocrine neoplasia type 2
MI	myocardial infarction
MCI	Mild cognitive impairment
MoCA	Montreal Cognitive Assessment
MR	magnetic resonance
MTC	medullary thyroid cancer

NYHA	New York Heart Association
OD	once daily
PAD	peripheral artery disease
PCD	primary completion date
PCI	percutaneous coronary intervention
PG	plasma glucose
PP	per protocol
RA	receptor agonist
SAE	serious adverse event
SAP	statistical analysis plan
s.c.	subcutaneous(-ly)
SMPG	self-measured plasma glucose
SUSAR	suspected unexpected serious adverse reaction
TIA	transient ischemic attack
TMM	trial materials manual
T2D	type 2 diabetes
ULN	upper limit of normal
WOCBP	woman of child bearing potential

Appendix 2 Clinical laboratory tests

- The laboratory analyses will be performed by a central laboratory, unless otherwise specified. A list of laboratory supplies and procedures for obtaining, handling, transportation and storage of samples, will be described in laboratory flow charts/manual and provided to all sites.
- Blood samples need to be obtained. The tests detailed in Table 12-1 will be performed by the central laboratory.
- Additional tests may be performed at any time during the trial as determined necessary by the investigator or required by local regulations. Only laboratory samples specified in the protocol should be sent to the central laboratory for analysis; if additional laboratory sampling is needed, e.g. to follow up on AEs, this must be done at a local laboratory
- The laboratory equipment may provide analyses not requested in the protocol but produced automatically in connection with the requested analyses according to specifications in the laboratory standard operating procedures. Such data will not be transferred to the trial database. Brazil: For country specific requirements, please see Appendix 8.
- The investigator must review all laboratory results for concomitant illnesses and AEs.
- Ambient laboratory samples will be destroyed shortly after the analyses have taken place.
- Human biosamples for retention will be stored as described in Appendix 7.

Table 12-1 Protocol-required central laboratory assessments

Laboratory assessments	Parameters
Glucose metabolism	• HbA_{1c}

Renal function	• Creatinine
	• eGFR, calculated per CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration)
	• A confirmatory test is needed when
	  • onset of ≥ 50% reduction in eGFR (CKD-EPI)
	  • onset of eGFR (CKD-EPI) < 15 mL/min/1.73 m^2
	• When a confirmatory test is needed, it should be done at the next scheduled contact, but no earlier than 4 weeks after eGFR has reached the threshold, by obtaining blood samples for the central laboratory for measurement of creatinine
	• Confirmation of a ≥ 50% reduction in eGFR (CKD-EPI) compared with baseline is needed unless a persistent 50% reduction in eGFR compared with baseline, has previously been confirmed for this patient
	• Confirmation of a eGFR (CKD-EPI) < 15 mL/min/1.73 m^2 is needed unless persistent eGFR below < 15 mL/min/1.73 m^2 has previously been confirmed for this patient
	• For the central laboratory calculation of the eGFR information on race (black/white/other) and year of birth will be collected on the laboratory requisition form. 01-Jan of the year of birth will be used for the calculation

Liver parameters	• Alanine aminotransferase (ALT) • Aspartate aminotransferase (AST) • Gamma glutamyltransferase (GGT) • Total bilirubin
Lipids (non-fasting)	• Total cholesterol • High density lipoprotein (HDL) cholesterol • Low density lipoprotein (LDL) cholesterol • Triglycerides
Biobank	• These samples need to be frozen and should be sent at monthly intervals in batches to the central laboratory
Inflammation	• High sensitivity C-Reactive Protein (hsCRP)
Pregnancy testing	• Urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[1]
Notes: [1] Local urine testing will be standard unless serum testing is required by local regulation or IRB/IEC.	

Appendix 3 Trial governance considerations

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[14] and applicable ICH Good Clinical Practice (GCP) Guideline[15]
  - Applicable laws and regulations
- The protocol, informed consent form, investigator's brochure (as applicable) and other relevant documents (e.g. advertisements), must be submitted to an IRB/IEC and reviewed and approved by the IRB/IEC before the trial is initiated.
- Regulatory authorities will receive the clinical trial application, protocol amendments, reports on SAEs, and the clinical trial report 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 trial 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 clinical trial report (CTR) synopsis to the IRB/IEC.

Japan, Mexico and Russia: For country specific requirements please see Appendix 8.

2) Financial disclosure

Investigators and subinvestigators 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 trial sites: verification under disclosures per Code of Federal Regulations (CFR) of Financial Conflict of Interest.

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. This includes the use of an impartial witness where required according to local requirements.
- 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 will be required to sign and date a statement of informed consent that meets the requirements of local regulations, ICH guidelines[15], Declaration of Helsinki[14] and the IRB/IEC or trial site.
- The medical record must include a statement that written informed consent was obtained before any trial related activity and the date when the written consent was obtained. The authorised person obtaining the informed consent must also sign and date the informed consent form before any trial related activity.
- The responsibility of seeking informed consent must remain with the investigator, but the investigator may delegate the task of informing to a medically qualified person, in accordance with local requirements.
- Patients and/or their legal authorised representative (LAR) 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 or the patient's LAR

Brazil: For country specific requirements, please see Appendix 8

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.

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; patient names or any information which would make the patient identifiable will not be transferred.

- 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 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.

6) Committee structure

Novo Nordisk safety committee

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

Data monitoring committee

The data monitoring committee (DMC) is an independent, external committee composed of members whose expertise covers relevant specialties including statistics. The DMC is established to review and evaluate accumulated data from the trial at predefined time points as well as ad hoc. This is done in order to protect the safety of the patients and to evaluate the benefit-risk balance. The DMC will have access to unblinded data, and will provide recommendations on trial continuation, modification or termination.

Information regarding responsibilities, procedures and workflow to be used by the DMC are specified in the DMC charter.

Event adjudication committee

An independent external event adjudication committee is established to perform ongoing blinded adjudication of selected AEs and deaths (see Table 9-1). The EAC will evaluate events sent for adjudication using pre-defined definitions and guidelines in accordance with the EAC Charter. The evaluation is based on review of pre-defined clinical data collected by the investigational 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 purpose of the adjudication is to confirm events in a consistent manner according to standardized criteria using independent external medical experts.

Steering committee

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

Supportive panels

Global expert panel

A global expert panel (GEP) will consist of selected principal investigators, identified as national leaders and scientific experts, and of designated Novo Nordisk employees. The panel will discuss and advise on global and local operational issues related to trial conduct. The panel will operate under a charter agreed with Novo Nordisk. National investigators that are not part of the global panel may be appointed in some of the large countries.

Patient recruitment and retention panel

A patient recruitment and retention panel (PRRP) will consist of study coordinators, highly experienced in the conduct of diabetes and CV outcomes trials, and designated Novo Nordisk employees. The panel will discuss and advise on global recruitment, retention and adherence issues related to trial conduct. The panel will operate under a charter agreed with Novo Nordisk.

National study coordinators

For each country participating in the trial, where it is appropriate, a national study coordinator (NSC) will be selected. The national study coordinators will provide operational input to patient recruitment, retention and adherence related topics. The national study coordinators will operate under a charter agreed with Novo Nordisk.

7) 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 clinical trial report for this trial.

A chair of the steering committee will be appointed by Novo Nordisk to review and sign the clinical trial report (signatory investigator) on behalf of all participating investigators.

Communication of results

Novo Nordisk commits to communicate and disclose results of trials regardless of outcome. Disclosure includes publication of a manuscript in a peer-reviewed scientific journal, abstract submission with a poster or oral presentation at a scientific meeting or disclosure by other means.

The results of this trial will be subject to public disclosure on external web sites according to international and national regulations. Novo Nordisk reserves the right to defer the release of data until specified milestones are reached, for example when the clinical trial report is available. This includes the right not to release the results of interim testing, 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.

Authorship

The steering committee will be responsible for communication of primary trial results. This will include appointing the publication group and authorship, overseeing the preparations and final approval of manuscripts and congress communications of trial results.

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.[16]

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 trial site will be named in an acknowledgement or in the supplementary material, as specified by the journal.

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.

Investigator access to data and review of results

As owner of the trial database, Novo Nordisk has the discretion to determine who will have access to the database. Individual investigators will have their own research patients' data, and will be provided with the randomisation code after results are available.

8) 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)[17], the Food and Drug Administration Amendments Act (FDAAA)[18, 19, 20], European Commission Requirements[19, 20] 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 trial is event-driven. The Primary Completion Date (PCD) is the last assessment of the primary endpoint, and is for this trial the last patient last visit (LPLV). The trial will therefore be registered with an estimated PCD corresponding to the estimated LPLV, which is first patient randomised plus 61 months. The PCD determines the deadline for results disclosure at Clinicaltrials.gov according to FDA Amendments Act.

China: For country specific requirements, please see Appendix 8.

9) Data quality assurance

Case Report Forms (CRFs)

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 data, cognitive testing and patient surveys). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF and for ensuring that all relevant questions are

answered, and that no empty data field exists. If a test or an assessment has not been done and will not be available, or if the question is irrelevant (e.g. is not applicable), indicate this by choosing the appropriate option. Free-text comments are discouraged.

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

- AE forms
- Safety information forms
- Technical complaint forms (also to be used to report complaints that are not patient related, e.g. discovered at trial site before allocation)

The following will be provided as paper CRFs, if needed:

- Pregnancy forms
- Other CRFs

In case of the use of paper forms, they need to be forwarded to Novo Nordisk either by fax, encrypted e-mail or courier.

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.

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 trial 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 trial sites.
- Monitors will review the patient's medical records and other source data to ensure consistency and/or identify omissions compared to the CRF.

Protocol compliance

Deviations from the protocol should be avoided. If deviations do occur, the investigator must inform the monitor without any 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) Source documents

- All data entered in the CRF must be verifiable in source documentation other than the CRF.
- Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the trial site.
- Data reported on the paper CRF or entered in the electronic CRF 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 trial site. There will only be one source document defined at any time for any data element.

11) 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 and other patient data will be provided in an electronic readable format to the investigator before access is revoked to the systems 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 trial site. If the provided electronic data (e.g. the CD-ROM) is not readable during the entire storage period, the investigator can request a new copy. A copy of all data will be stored by Novo Nordisk.
- Patient's medical records must be kept for the maximum period permitted by the hospital, institution or private practice.

12) Trial and site closure

Novo Nordisk reserves the right to close the trial 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.

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

The investigator may initiate trial 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 trial 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.

Pre-planned interim testing may allow for premature termination of the trial.

13) Responsibilities

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

14) 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.

Austria, Belgium, France and Mexico: For country specific indemnity statements, please see Appendix 8.

Appendix 4 Adverse events: definitions and procedures for recording, evaluation, follow-up, and reporting

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

Events meeting the AE definition
• Any abnormal laboratory test results or safety assessments, including those that worsen from randomisation, considered clinically significant in the medical and scientific judgment of the investigator. • Abuse: Persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects (e.g. overdose with the intention to cause harm) • Misuse: Situations where the medicinal product is intentionally or inappropriately used not in accordance with the protocol • Exacerbation of a chronic or intermittent pre-existing 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 trial product regardless of intent.
Events NOT meeting the AE definition
• Pre-existing conditions, anticipated day-to-day fluctuations of pre-existing conditions, including those identified during screening or other trial procedures performed before exposure to trial product. Note: pre-existing conditions should be recorded as medical history/concomitant illness. • Pre-planned procedures, unless the condition for which the procedure was planned has worsened from randomisation.

Definition of an SAE
An SAE is an AE that fulfils at least one of the following criteria:
• Results in death
• 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.
• 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 serious 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 of a pre-existing condition that did not worsen from randomisation is not considered an AE. Note: ▪ Hospitalisations for administrative, trial related and social purposes do not constitute AEs and should therefore not be reported as AEs or SAEs. ▪ Hospital admissions for surgical procedures, planned before trial inclusion, are not considered AEs or SAEs.
• 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.
• Is a congenital anomaly/birth defect
• 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 trial product. ▪ 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).

Description of AEs requiring additional data collection (via specific event form) and events for adjudication can be found in Table 9-1
Medication error: A medication error is an unintended failure in the trial drug 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 DUN is not considered a medication error unless it results in administration of wrong drug. • Wrong route of administration • 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 to be reported as a medication error.

AE and SAE recording
• All SAEs, AEs leading to discontinuation of trial product, AEs described in Table 9-1 must be recorded by the investigator on an AE form. 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 "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 intensity 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: Severe is a category used for rating the intensity of an event; and both an AE and SAE can be assessed as severe. An event is defined as 'serious' when it meets at least one of the outcomes described in the definition of an SAE and not when it is rated as severe

Assessment of causality

The investigator is obligated to assess the relationship between trial product and the occurrence of each AE/SAE.

Relationship between an AE/SAE and the relevant trial product(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 trial product.

Alternative aetiology, such as underlying disease(s), concomitant medication, and other risk factors, as well as the temporal relationship of the event to trial product 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 at the first trial-related activity after the patient signed the informed consent.
- **Recovering/resolving:** The condition is improving and the patient is expected to recover from the event. This term is only applicable if the patient has completed the trial or has died from another AE.
- **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 sequelae 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.
- **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.

New or updated information will be recorded in the CRF.

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 box 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, see section 9.2.1.
- After the trial is completed, 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.

SAE reporting via paper CRF

- Relevant CRF forms (AE and safety information form) must be forwarded to Novo Nordisk either by fax, encrypted e-mail or courier.

- 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 time frames (as illustrated in Figure 9-1):
  - AE form within 24 hours.
  - Safety information form within 5 calendar days.
  - Both forms must be signed within 7 calendar days from the investigators knowledge of the event.
- Contact details for SAE reporting can be found in the investigator trial master file.

Appendix 5 Contraceptive guidance and collection of pregnancy information

It must be recorded in the CRF whether female patients are of childbearing potential.

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile.

Women in the following categories are not considered WOCBP

1. Premenopausal female with one of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   Note: Documentation can come from the site personnel's review of patient's medical records, medical examination or medical history interview.
2. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high Follicle Stimulating Hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or Hormonal Replacement Therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the trial. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before trial enrolment.

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 12-2.

Table 12-2 Highly effective contraceptive methods

Highly effective contraceptive methods

Highly effective contraceptive methods that are user dependent [a and b] Failure rate of <1% per year when used consistently and correctly.
Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation • oral • intravaginal • transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation • oral • injectable
Highly effective methods that are user independent [a and b]
• Implantable progestogen only hormonal contraception associated with inhibition of ovulation • Intrauterine Device (IUD) • Intrauterine hormone-releasing System (IUS) • Bilateral tubal occlusion
Vasectomised partner A vasectomised partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
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 product. 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] Failure rates may differ when used consistently and correctly. [b] Contraception should be utilised during the treatment period and for at least 5 weeks after the last dose of trial product.

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 known intolerance to the highly effective methods mentioned above or where the use of any listed highly effective contraceptive measures are contraindicated in the individual patient, and/ or
- if the risk of initiating treatment with a specific highly effective method outweigh the predicted benefits of trial participation for the female patient.

Justification for accepting double barrier method should be at the discretion of the investigator. The justification must be stated in the medical records.

Argentina, Belgium, Brazil, Denmark, Thailand and United Kingdom: For country specific requirements, please see Appendix 8.

Pregnancy testing

- Highly sensitive serum testing (sensitivity of 5-25 mIU/mL) is only mandatory if required by local regulations or ethics committees, or to resolve an indeterminate test or to confirm a positive urine test.
- WOCBP should only be included after a negative highly sensitive urine pregnancy test.
- Pregnancy testing should be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.
- Additional urine pregnancy testing should be performed during the treatment period, if required locally (Appendix 8.).
- Home urine pregnancy testing may be performed between visits during the trial, if additional urine pregnancy testing is required locally.
- WOCBP needs the last pregnancy test at least 5 weeks after the last dose. As the FU visit is a phone contact, the patients can take a urine test at home and inform the investigator of the result.

Austria: For country specific requirements, please see Appendix 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.
- 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. 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 pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-trial pregnancy which is considered possibly/probably related to the trial product by the investigator will be reported to Novo Nordisk as described in Appendix 4. 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.
- For abnormal pregnancy outcomes collection of information on the paternal form for male partners of female patients require signing of specific informed consent. Any female patient who becomes pregnant while participating in the trial will discontinue trial product.

Appendix 6 Technical complaints: Definition and procedures for recording, evaluation, follow-up and reporting

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).
- Problems with packaging material including labelling.

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

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

Timelines for reporting of technical complaints to Novo Nordisk
The investigator must complete the technical complaint form in the CRF within 24 hours if related to an SAE. All other technical complaints within 5 days. If the CRF is unavailable or when reporting a technical complaint that is not patient related, the information must be provided on a paper form by fax, e-mail or courier to Customer Complaint Center, Novo Nordisk, within the same timelines as stated above. When the 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 trial 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.

Appendix 7 Retention of human biosamples for biomarkers and genetic analyses

In countries where allowed, the trial will involve collection of human biosamples to be stored in a central archive for future use as noted in section 9.7 and 9.8.

The following samples will be stored:

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

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.

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

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 9.8..

Brazil, China, Columbia, Israel, South Korea and Turkey: For country specific requirements, please see Appendix 8.

Appendix 8 Country-specific requirements

Argentina:

- Section 6.2, exclusion criterion #3 and Appendix 5 as described in Table 12-2: The contraceptive methods and pregnancy tests will be reimbursed by the sponsor. Monthly testing with highly sensitive urine pregnancy tests are required for WOCBP. Use of double contraceptive method is required for WOCBP.
- Section 7.8: In reference to Protocol section Treatment after discontinuation of trial products: The sponsor commits to comply with what is stated in point 6.8 of the current local regulation, disposition 6677/10. According to it, commits to comply with the following: "For Argentina, after the conclusion of subjects participation in the study, trial doctor will discuss with subjects the best alternatives for future treatment. If trial doctor, based on his/her adequately justified medical analysis, decides that the Sponsor's study drug is the best available treatment option for the subject, trial doctor will prescribe the study drug, which must be approved by the Ethics Committee. The Sponsor (Novo Nordisk Pharma Argentina S.A.) will provide access to the Sponsor's study drug to the subject for the time the Ethics Committee decides or until access is ensured by any other means and in accordance with the applicable provisions in Argentina. Subjects must visit trial doctor to receive the Sponsor's study drug and will have to provide information about health status and any possible side effects that may have been experienced since last visit

Austria:

- Appendix 3: Indemnity statement: Arzneimittelgesetz (BGBI. Nr. 185/1983) last amended with BGBl. I Nr. 59/2018
- Section 6.2, exclusion criterion #3 and Appendix 5: A monthly pregnancy test (urine) is required for all women of childbearing potential.

Belgium:

- Appendix 3: Indemnity statement: 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 subject and/or his rightful claimants sustain and which shows either a direct or an indirect connection with the trial.
- Section 6.2, exclusion criterion #3 and Appendix 5: Only highly effective methods of birth control are accepted (i.e. one that results in less than 1% per year failure rate when used consistently and correctly such as implants, injectables, combined oral contraceptives, some intrauterine device), or true sexual abstinence (i.e. refraining from heterosexual intercourse during the entire period of risk associated with the study treatments) or vasectomised partner.

Brazil:

- Section 6.2, exclusion criterion #3 and Appendix 5: For women who expressly declare free of the risk of pregnancy, either by not engaging in sexual activity or by having sexual activity with no birth potential risk, use of contraceptive method will not be mandatory.
- Section 6.2, exclusion criterion #4: Participation in other trials within one year prior to the screening visit (Visit 1) unless there is a direct benefit to the research subject at the investigator's discretion.
- Section 7.7: Novo Nordisk will reimburse costs of standard-of-care treatment for T2D.
- Section 7.8: At the end of the trial, all participant subjects should be assured the access to the best proved prophylactic, diagnostic and therapeutic methods identified during the study (according to resolution CNS 466/12).
- Section 9.7, 9.8 and Appendix 7: No subjects from Brazil will take part of the optional biobank part of the trial, and no genetic testing will be performed as noted in section 9.7 and 9.8.
- Appendix 2: All laboratory results will be communicated to the investigators.
- Appendix 3, section 3: Two original informed consent forms will be signed and dated and one original will be given to the subject (according to resolution CNS 466/12).

China:

- Section 6.2, exclusion criteria #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 postinfectious conditions is allowed if the last dose of the investigational medicinal product has been received more than 30 days before screening.' is not applicable for China.
- Section 8.1, discontinuation/withdrawal criteria: '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 postinfectious conditions is allowed at the investigator discretion without discontinuing trial product.' is not applicable for China.
- Section 9.7, 9.8 and Appendix 7: No subjects from China will participate in the optional biobank part of the trial, and no genetic testing will be performed as noted in section 9.7 and 9.8.
- Appendix 2: Laboratory samples for Chinese subjects will be destroyed according to local regulatory requirements, both for samples tested inside and outside China. No sample will be stored after the latest date of local regulatory approval.
- Appendix 3: Information of the trial will be disclosed at clinicaltrials.gov, china, drugtrials.org.cn and novonordisk-trials.com as China HA has requested to disclose trial information (phase 1-3) at chinadrugtrials.org.cn since 2013.

Columbia:

- Section 9.7, 9.8 and Appendix 7: No subjects from Columbia will participate in the optional biobank part of the trial, and no genetic testing will be performed as noted in section 9.7 and 9.8.

Denmark:

- Section 6.2, exclusion criterion #3 and Appendix 5: Contraceptive measures considered adequate includes intrauterine devices or hormonal contraception (oral contraceptive pills, implants, transdermal patches, vaginal rings or long-acting injections).

France:

- Appendix 3, section 14: Indemnity statement: The sponsor is responsible for identification of the harmful consequences of the biomedical research for the person lending himself thereto and for indemnification of his beneficiaries, except in case of proof, incumbent on it, that the prejudice is not attributable to his fault of or the fault of any intervening party, without the sponsor's being entitled to call on acts by a third party or the voluntary withdrawal of the person who had initially consented to cooperating in the research (according to The French Public Health Code article L.1121-10 (law n° 2004-806 of 9 August 2004 art. 88 I, IX Journal Officiel of 11 August 2004).

Germany:

- Subject's full Date of Birth is not allowed to be collected and must be shortened to year of birth.

Israel:

- Section 9.7, 9.8 and Appendix 7: No subjects from Israel will participate in the optional biobank part of the trial, and no genetic testing will be performed as noted in section 9.7 and 9.8.

Japan:

- Section 7.5: The head of the study site or the trial product storage manager assigned by the head of the study site (a pharmacist in principle) is responsible for control and accountability of the trial products.
- Section 9.2: Table 9-1: 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 3, section 1: A name and seal is accepted as a signature.

Mexico:

- Section 8.2: Should the subject his/her family members parents or legal representative decide to withdraw the consent for participation in the trial, the subject will be entitled to receive appropriate, free of charge medical care and/or trial drug during the follow up period of the

protocol when it will be established with certainty that no untoward medical consequences of the subject´s participation in the research occurred.

- Appendix 3, section 1: The following responsibilities will be included for the head of the Institution/Health Care Establishment, Ethics, Research and, when applicable, Biosafety Committees and sponsor within their scope of responsibility:
    - Investigation follow-up
    - Damages to health arising from the investigation development; as well as those arising from interruption or advanced suspension of treatment due to non-attributable reasons to the Subject;
    - Timely compliance of the terms in which the authorization of a research for health in human beings had been issued;
    - To present in a timely manner the information required by the Health Authority.
- Appendix 3, section 14:
    - Novo Nordisk carries product liability for its products assumed under the special laws, acts/and/or guidelines for conducting trials in any country, including those applicable provisions on the Mexican United States. If the subject feels that something goes wrong during the course of this trial, the subject should contact the trial staff in the first instance.
    - If during their participation in the trial the subject experiences a disease or injury that, according to the trial doctor and the sponsor, is directly caused by the trial medication and/or a trial procedure that otherwise would not have been part of his/her regular care, the subject will receive from the Institution or Medical Care Establishment and free of charge, the appropriate medical treatment as required. In this case, the costs resulting from such treatment as well as the costs of any indemnification established by law will be covered by the trial sponsor in accordance with the terms provided by all applicable regulations; even if the subject discontinues his/her participation in the trial by his own will or by a decision from the investigator.
    - By signing the informed consent, the subject will not renounce to any compensation or indemnification he/she may be entitled to by law, nor will he/she will incur any additional expense as a result of his/her participation in the trial; any additional expense resulting from the subject's participation in the trial will be covered by the trial sponsor.

Russia:

- Appendix 3, section 1: The trial should be conducted in compliance with the protocol, Ministry of Healthcare of Russian Federation' order #200н from April, 01, 2016 "Approval of rules of good clinical practice" and legal requirements of the Russian Federation regulating circulation of medicines.

South Korea:

- Section 9.7, 9.8 and Appendix 7: No subjects from South Korea will participate in the optional biobank part of the trial, and no genetic testing will be performed as noted in section 9.7 and 9.8.

Thailand:

- Section 6.2, exclusion criterion #3 and Appendix 5: Adequate contraceptive measures are: diaphragm, condom (by the partner), intrauterine device in place for last three months before trial starts, sponge, cap with spermicide, contraceptive patch, approved hormonal implant (i.e. Norplant), oral contraceptives taken without difficulty for the last three months before trial starts, post-menopausal state or sterilisation.

Turkey:

- Section 7.7: In case a subject needs to change their regular dose of a concomitant medication due to a protocol requirement, this medication will be reimbursed by Novo Nordisk.
- Section 9.7, 9.8 and Appendix 7: No subjects from Turkey will participate in the optional biobank part of the trial, and no genetic testing will be performed as noted in section 9.7 and 9.8.

United Kingdom:

- Section 6.2, exclusion criterion #3 and Appendix 5: Contraceptive measures considered adequate include highly effective contraceptive methods in accordance with the CTFG (Clinical Trial Facilitation Group) guideline: Recommendations related to contraception and pregnancy testing in clinical trials, as listed in Table 12-2: This means use of double barrier methods is not applicable.

3. Summary of changes to the protocol

Appendix 9 Protocol amendment history

Protocol amendment no. 1 (version 1.0 dated 12 June 2019)

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 amendment no. 1:

People with diabetes have a higher risk for decline in cognitive function and a twofold increased risk for developing dementia compared to people without diabetes. Animal studies and limited clinical data indicate that GLP-1 RA may have an effect on the rate of cognitive decline. A battery of online cognitive testing is introduced to further explore cognitive function and semaglutide's effects on mild cognitive impairment (MCI).

Section # and name	Description of change	Rationale
Section 2 Flowchart	Online cognitive testing included	See overall rationale
Section 4.2.2.3 Exploratory endpoints	Online cognitive testing included	See overall rationale
Section 9.1.4 Cognitive testing, patient surveys and visits to emergency room/urgent care unit	Online cognitive testing included	See overall rationale
Appendix 2	Abbreviation included	See overall rationale

Protocol amendment no. 2 (protocol version 3.0 dated 17 November 2020)

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 amendment no. 2:

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 postinfectious conditions. In addition, the AE collection has been expanded to include the reporting of non-serious COVID-19 events.

This amendment also addresses statistical considerations, as well as administrative changes.

Section # and name	Description of change	Rationale
Throughout the protocol	All information related to Algeria has been removed	Algeria was not included in the trial
Throughout the protocol	Reference to specific IB edition removed	To ensure that the most current version of the IB is always referred to
Section 2 Flowchart and Section 9 Trial assessments and procedures	Changes to footnote a) Sentence revised	To specify that the investigator needs to ensure that the subject has enough trial product within the expiry date
Section 2 Flowchart	Changes to footnote j) removed X at V3, V4, V5 and V7	To clarify when the patient expectations & experience survey and the patient engagement assessments will take place.
Section 2 Flowchart	Ensure updated contact persons list: added X at V-EOT	To ensure that the contact persons list is updated
Section 4.2.2.2 Supportive secondary endpoints	The two HF endpoints combined into one endpoint: Time from randomisation to heart failure requiring hospitalisation or urgent heart failure visit.	To reflect that it differs across countries when worsening of HF symptoms can be handled during an urgent HF visit or during hospitalisation.
Section 4.2.2.2 Supportive secondary endpoints	Description of endpoints updated to 'Time to first occurrence of acute limb ischemia hospitalisation' and 'Time to first occurrence of chronic limb ischemia hospitalisation'	To reflect the description of the combined MALE endpoint and match the data that we collect for adjudication.
Section 4.2.2.3 Exploratory endpoints	Exploratory endpoints related to the online PROTECT Cognitive Test Battery for mild cognitive impairment updated.	The PROTECT Cognitive Test Battery consists of 6 tests and produces 12 individual data points, which individually do not provide room for a clinically meaningful interpretation. Thus, the exploratory endpoints have been updated to consist of change from randomisation (week 0) to 2 years (visit 12) in 5 distinct and clinically meaningful aspects of cognitive function which can be calculated as composites based on the 12 individual data points.

Section 6.2 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 postinfectious conditions is allowed if the last dose of the investigational medicinal product has been received more than 30 days before screening	To allow for co-participation in COVID-19 trials
Section 7.5 Preparation/Handling/Storage/Accountability	The sentence "..and reconciled by the monitor" removed	To specify the procedure of trial product destruction
Section 7.5 Preparation/Handling/Storage/Accountability	'Patients must return all used, partly used and unused trial products including empty packaging material as instructed by the investigator' changed to 'Patients must ensure that all used, partly used and unused trial products including empty packaging material is returned as instructed by the investigator.'	To allow flexibility in case the patient can't come to the site.
Section 7.7 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 8.1 Discontinuation/Withdrawal criteria	Text added to discontinuation criterion 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 postinfectious conditions is allowed at the investigator discretion without discontinuing trial product.	To allow for co-participation in a COVID-19 trial

Section 9 Trial assessments and procedures	Implementation of mitigations for the investigator to engage with a health care professional from a third party home health care service provider to perform protocol procedures at the subject's home or other alternate location.	To ensure subject safety and data integrity under special circumstances and in case of restrictions due to epidemics/pandemics (e.g. COVID-19)
Section 9.2 Adverse events and Figure 9-1	Text regarding COVID-19 AEs included	To describe the inclusion of COVID-19 AEs in the selective data collection approach of this trial
Section 9.4 Safety assessments	Addition of COVID-19 in text	To include COVID-19 to the concomitant illness/medical history that should be reported in the eCRF
Section 10.3.2.1 Confirmatory secondary endpoints	Updated text for the statistical testing strategy for the confirmatory secondary endpoints.	To preserve control of the type 1 error for confirmatory endpoints.
Section 10.3.2.1 Confirmatory secondary endpoints	Deleted: 'including tipping point analyses'	To align with the SAP
Section 10.3.2.1 Confirmatory secondary endpoints	Sentence deleted: For the composite CKD endpoint, the analysis will exclude patients who already have met relevant renal components at baseline.	Patients can be followed for other components of the endpoint. To be detailed in SAP.
Section 10.3.2.1 Confirmatory secondary endpoints	Sentence deleted: Furthermore for this endpoint, missing data for eGFR, due to missing blood samples while patients are still being followed, will be imputed using multiple imputation.	To align with the SAP
Section 10.3.3 Exploratory endpoints	Text updated	To reflect the updates of the PROTECT endpoints in the statistical analyses.

4. Original statistical analysis plan

Trial ID: EX9924-4473

SOUL – Semaglutide cardiovascular outcomes trial in patients with type 2 diabetes

Author:
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Biostatistics Semaglutide s.c.

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List of abbreviations

ANCOVA	analysis of covariance
CI	confidence interval
CKD	chronic kidney disease
CV	cardiovascular
DBL	data base lock
DMC	data monitoring committee
EAC	event adjudication committee
eGFR	estimated glomerular filtration rate
FAS	full analysis set
HbA_{1c}	glycosylated haemoglobin
HF	heart failure
HHF	hospitalisation for heart failure
HR	hazard ratio
LTFU	lost to follow-up
MACE	major adverse cardiovascular event
MI	myocardial infarction
PAD	peripheral arterial disease
SAP	statistical analysis plan
TTE	time-to-event

1 Introduction

1.1 Trial information

1.1.1 Rationale

To evaluate the hypothesis that oral semaglutide lowers the risk of cardiovascular events in patients with type 2 diabetes at high risk for cardiovascular disease.

1.1.2 Objectives, endpoints and estimand

Primary objective

To demonstrate that oral semaglutide lowers the risk of major adverse cardiovascular events compared to placebo, both added to standard of care in patients with type 2 diabetes and at high risk of cardiovascular events.

Key secondary objectives

To compare the effects of oral semaglutide versus placebo, both added to standard of care in patients with type 2 diabetes and at high risk of cardiovascular events with regards to:

- Chronic kidney disease
- Cardiovascular events
- Peripheral artery disease

Primary endpoint

The primary endpoint is time from randomisation to first occurrence of a major adverse cardiovascular event, a composite endpoint consisting of: cardiovascular death, non-fatal myocardial infarction or non-fatal stroke.

Confirmatory secondary endpoints

Time from randomisation to:

- first occurrence of a composite chronic kidney disease endpoint consisting of: cardiovascular death, renal death, onset of persistent ≥50% reduction in estimated glomerular filtration rate (CKD-EPI) compared with baseline, onset of persistent eGFR (CKD-EPI) <15 mL/min/1.73 m^2 or initiation of chronic renal replacement therapy (dialysis or kidney transplantation)
- cardiovascular death
- first occurrence of a major adverse limb events, a composite endpoint consisting of: acute limb ischemia hospitalisation or chronic limb ischemia hospitalisation

Primary estimand

The estimand for all objectives is the intention-to-treat estimand evaluating the effect of the randomised treatment intervention irrespective of adherence to treatment and changes to background medication.

1.1.3 Design

This is a randomised, double-blind, parallel-group, placebo-controlled trial comparing oral semaglutide versus placebo both administered once daily and added to standard of care in patients with type 2 diabetes at high risk of cardiovascular events. Patients are randomised 1:1 to receive either oral semaglutide or placebo.

The trial is event driven; therefore, end of trial is scheduled according to accrual of events. The trial will employ a group sequential design with one interim testing for superiority. Under the design assumptions, the trial duration is approximately 61 months following randomisation of the first patient. 9,642 patients are planned to be randomly assigned to trial products. A schematic overview of the trial design is shown in Figure 1-1.

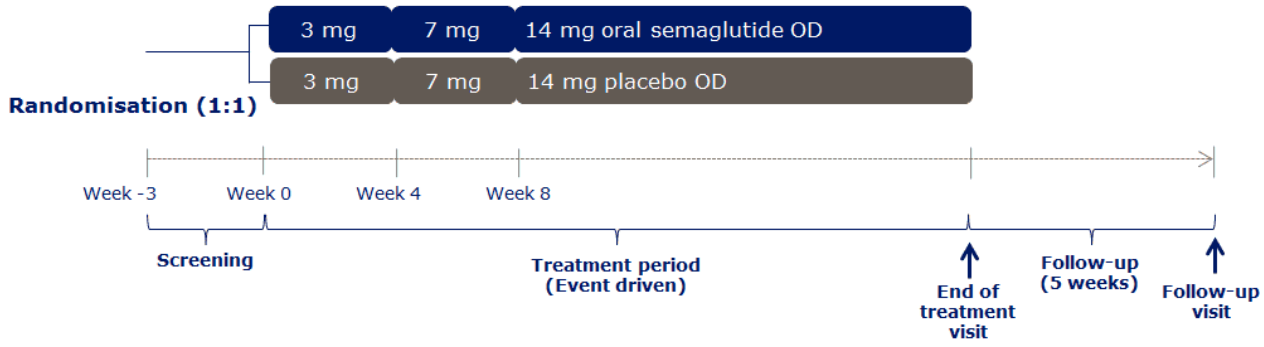

Figure 1-1 Trial design

1.2 Scope of the statistical analysis plan

The SAP includes elaborations on statistical analyses outlined in the protocol for SOUL trial (EX9924-4473) as well as details on the interim testing for superiority. Any changes to the SAP after first patient first visit are documented in a change log.

An external independent statistical service provider will conduct the interim analysis, see also section 3. Novo Nordisk is responsible for all other statistical analyses and reporting of data but will remain blinded to treatment allocations until data base lock (DBL). Additionally, a statistician independent of trial conduct, DMC analyses, interim analysis, and external to Novo Nordisk will independently confirm the statistical analyses of the primary endpoint and secondary confirmatory endpoints.

2 Statistical considerations

2.1 Sample size determination

The trial is designed with 90% power to confirm superiority for the primary endpoint, i.e., reject the null-hypothesis of a hazard ratio (HR) ≥ 1.0 against the one-sided alternative of HR < 1.0, where HR is the hazard ratio of oral semaglutide versus placebo.

The trial is designed with one interim testing for superiority of the primary endpoint when two thirds of the total planned number of primary endpoint events has been accrued. Testing for futility is not included. The Lan-DeMets alpha spending function, approximating the O'Brien-Fleming's stopping boundaries, is used to test superiority at a study-wise one-sided type I error rate of 2.5%. The one-sided alpha spending function is given by

$$f(t) = \min\{2 - 2 \cdot \Phi(z_{\alpha/2}/\sqrt{t}), \alpha\}$$

where *t* is the proportion of information included in the interim analysis (accrued primary endpoint events relative to the total planned primary endpoint events), Φ denotes the standard normal cumulative distribution function, α is the overall one-sided alpha of 2.5% and $z_{\alpha/2}$ is the 98.75% quantile of the standard normal distribution. Based on a randomisation ratio of 1:1 and a design HR of 0.83 a total of 1,225 primary endpoint events are required.

For calculating the number of randomised patients, the following is assumed:

- annual primary endpoint rate in the placebo group of 3.5%
- uniform recruitment in 18 months
- annual lost to follow-up rate in both treatment groups of 1%
- maximum trial duration of five years and five weeks

Under these assumptions, a total of 9,642 patients are needed for randomisation.

A Cox model as described in section 2.3 is used for the interim testing using the fixed sample one-sided lower p-value from the score test. Only a fixed sample p-value below the boundary specified by the error spending function will allow the DMC to recommend early trial termination for superiority. Table 2-1 provides the boundaries based on analyses performed after 817 and 1,225 events, along with the approximate hazard ratio estimates that correspond to those boundaries if the analyse are timed exactly to that schedule. The actual stopping boundaries will be based on the exact number of events available for the interim analysis.

Table 2-1 Stopping boundary scales at interim and scheduled termination

Stopping boundary scale	Interim 817 events	Scheduled termination 1,225 events
Hazard ratio	0.8389	0.8924
Nominal significance level	0.00605	0.02314

Figure 2-1 shows the probability of stopping the trial early at the interim (blue curve) and the overall power for confirming superiority for the primary endpoint (red curve) as a function of alternative values for the true HR. The design HR of 0.83 is marked with a dashed vertical reference line. The stopping probability at the interim and overall power for the design HR of 0.83 can be seen to be 56% and 90%, respectively.

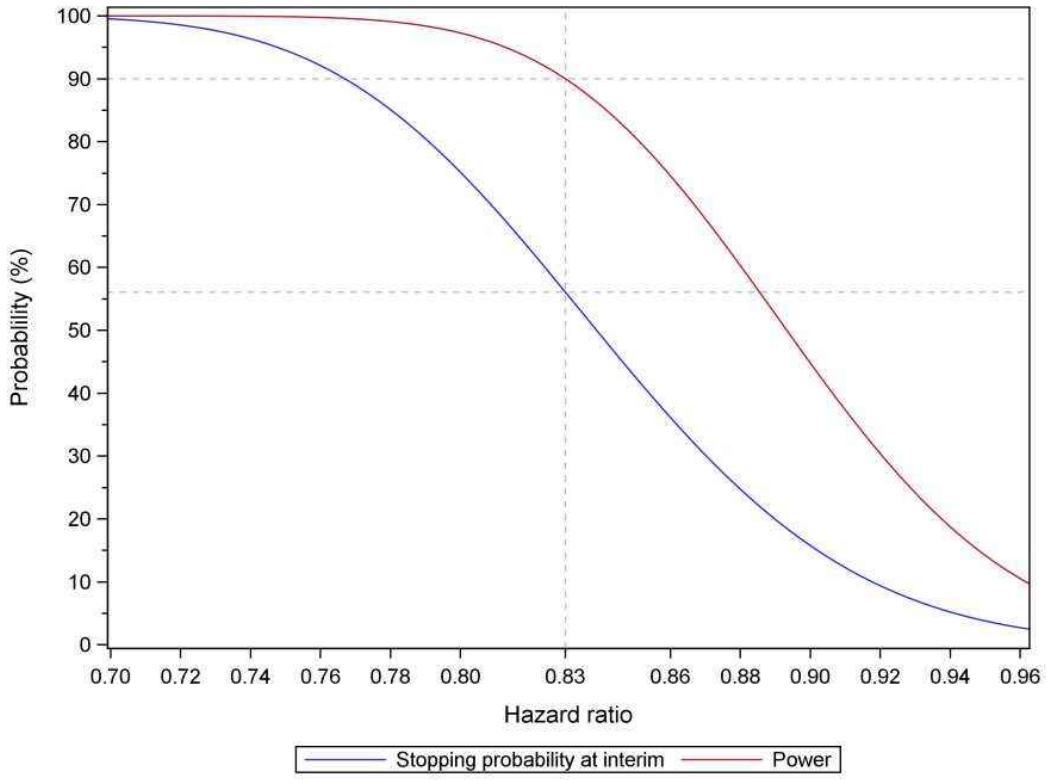

Figure 2-1 Stopping probability at interim and overall power as a function of true hazard ratio

Confirmatory secondary endpoints

If superiority is confirmed for the primary endpoint the confirmatory secondary endpoints are controlled for multiplicity through a hierarchical testing strategy. The marginal powers below are calculated under the assumptions that the trial continues to the scheduled termination, a significance level of 2.5% (one-sided) and 9,642 randomised patients.

The marginal power for superiority in favour of oral semaglutide for the 5-component chronic kidney disease (CKD) endpoint is 94% based on an assumed HR of 0.80 and an annual event rate of 2.8% in the placebo group.

The marginal power for superiority in favour of oral semaglutide for CV death is 56% based on an assumed HR of 0.83 and an annual event rate of 1.4% in the placebo group.

The marginal power for superiority in favour of oral semaglutide for the 2-component (major adverse limb event(s) (MALE)) endpoint is 44% based on an assumed hazard ratio of 0.75 and an annual event rate of 0.44% in the placebo group.

The assumptions for annual event rate of primary endpoint and confirmatory secondary endpoints, lost to follow-up rates and the assumed HRs are based on the LEADER and SUSTAIN 6 CV outcomes trials.

2.2 General considerations

For confirmatory endpoints controlled for multiplicity, estimated treatment effects are presented together with two-sided 95% confidence intervals (CIs) and one-sided p-values for tests of the hypothesis of superiority. For reporting of results, the hazard ratio and the 95% CI are accompanied by the two-sided p-value.

For non-confirmatory endpoints, the estimated treatment effects are reported together with two-sided 95% CIs and two-sided p-values.

Baseline value is defined as the latest available measurement from the randomisation visit or the screening visit. Thus, if a randomisation assessment is missing then the assessment from screening is used as the baseline assessment, if available.

Missing data are defined as data that are planned to be collected and can be observed but are not present in the database. This implies that data that are structurally missing due to death or administrative censoring are not considered missing.

2.2.1 Definition of analysis set

The full analysis set (FAS) is defined as all randomised patients and grouped according to the treatment assigned at randomisation.

2.2.2 Definition of observations period

A trial completer is defined as a patient who either attends the follow-up visit or who dies while active in the trial.

A patient is considered lost to follow-up (LTFU) if the patient does not complete the trial and does not withdraw consent. The date and status for LTFU are determined by investigator at trial

completion, either following interim testing or after accrual of the total planned number of primary endpoint events.

In-trial observation period

The in-trial observation period for a patient is defined as the period from date of randomisation to the first of (both inclusive):

- date of follow-up visit
- date when patient withdrew consent
- date of last contact with patient (patient LTFU)
- date of death

On-treatment observation period

A time-point in the in-trial observation period is considered as on-treatment if any dose of trial product has been administered within the previous 5 weeks (35 days). The on-treatment observation period is defined as all times which are considered on-treatment.

Unless otherwise specified, statistical analyses of all endpoints are based on the FAS using the in-trial observation period.

2.2.3 Estimands

Primary estimand (intention-to-treat)

The estimand for all objectives is an intention-to-treat estimand, evaluating the effect of the randomised treatment intervention irrespective of adherence to treatment and changes to background medication. The estimand is addressed using FAS and the in-trial observation period.

Secondary estimand (on treatment)

This estimand covers confirmatory endpoints and is evaluating the effect of the randomised treatment intervention in all randomised patients had they remained on their randomised treatment for the entire trial. The estimand is addressed using FAS and the on-treatment observation period until first time being off-treatment for 5 consecutive weeks.

2.2.4 Intercurrent events

Intercurrent events, including but not limited to events of or associated with:

- randomised treatment adherence
- change in background medication modifying CV risk
- initiation of chronic renal replacement therapy
- withdrawal
- lost-to follow up
- death (if not part of endpoint)

These are reported using descriptive statistics. Handling of intercurrent events for the statistical analyses of the confirmatory endpoints is described in Table 6-1.

2.2.5 Time-to-event endpoints, censoring and competing risks

Time-to-event endpoints are in general time-to-first-event endpoints but will for simplicity be denoted time-to-event (TTE) endpoints.

If adjudicated, the TTE endpoints are defined based on outcomes of the EAC evaluations. While vital status is ascertained systematically throughout the trial until DBL, other event types cannot be systematically collected after withdrawal, lost-to-follow-up, or after end-of-trial visit. For this reason, any event occurring after the in-trial observation period is not included in analyses, unless otherwise stated.

If a patient experiences the event of interest during the in-trial observation period, the observation of the TTE is the time from randomisation to the date of event. The observation of the TTE is censored if the event of interest does not happen during the in-trial observation period and if the patient is still alive at the end of the observation period. The general assumption for censored observations is that the risk of experiencing an event is not changed by censoring, i.e. an assumption of independent censoring. This is a reasonable assumption for administrative censoring at end-of-trial visit but may not be for patients withdrawing or patients lost to follow-up. Sensitivity analysis addressing the assumption of independent censoring is planned for the primary endpoint, see section 2.3.2.

The observation of the TTE is terminated if the event of interest does not happen before the death of the patient unless death is part of the endpoint. Terminating events (competing risks) is potentially present for all TTE endpoints except for all-cause death; for the primary endpoint, non-CV death is a competing risk terminating the observation for the event of interest (MACE). Figure 2-2 illustrates competing risk as a multi-state model for the primary endpoint. The hazard rate of interest in this trial is denoted by $\lambda(t)$, t being time since randomisation.

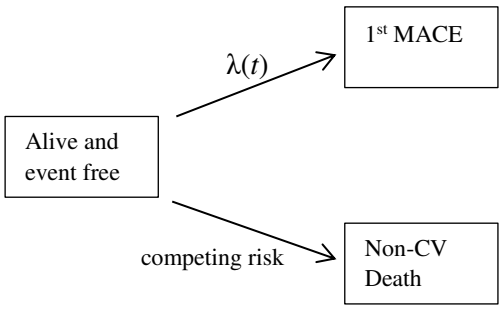

Figure 2-2 Multi-state model illustrating competing risk for primary endpoint

Unless otherwise specified, the statistical analyses of TTE endpoints are done by using a Cox proportional hazards model with treatment group (oral semaglutide, placebo) as fixed factor under the assumption of independent censoring. Terminated observations (due to competing risks) are technically treated as censored observations but are not part of the independent censoring assumption. The population-level summary measure for TTE endpoints is the HR for oral semaglutide versus placebo. The assumption of proportional hazards is investigated by residuals.

Cumulative incidence functions for TTE endpoints are estimated by the Aalen-Johansen estimator which accounts for competing risks.

Table 6-2 provides an overview of the TTE endpoints including any competing risk and whether the TTE endpoint is EAC-confirmed.

2.3 Primary endpoint

Time from randomisation to first occurrence of a composite MACE endpoint consisting of

- CV death
- Non-fatal myocardial infarction (MI)
- Non-fatal stroke.

Fatal MI is defined as an EAC-confirmed MI occurring within (≤) 30 days of an EAC-confirmed CV death classified as cause of death being MI. All other MIs are defined as non-fatal. The same definition is applied for fatal/non-fatal stroke.

Deaths attributed to the category "undetermined cause of death" are presumed cardiovascular death.

2.3.1 Primary analysis

The HR for comparing oral semaglutide versus placebo is estimated from a Cox proportional hazards model with treatment group (oral semaglutide, placebo) as fixed factor together with the 2-sided 95% CI and one-sided fixed design p-value for hypothesis testing. The score test from the Cox model is used for testing. The following superiority hypothesis is tested:

$$H_0: HR \geq 1.0 \text{ against } H_a: HR < 1.0.$$

Superiority of oral semaglutide versus placebo is considered confirmed if the associated H_0 is rejected based on nominal significance level derived from the pre-specified alpha spending using the actual observed number of events available for the analysis. Final inference on termination is adjusted for the group sequential design by using the likelihood ratio ordering.

Competing risk from non-CV death is handled as censorings in the Cox analysis as described in section 2.2.5. Please, refer to Table 6-1 for handling of other intercurrent events.

2.3.2 Sensitivity analysis

If superiority is established for the primary endpoint, the following sensitivity analysis is performed. The primary analysis assumes independent censoring for patients who have withdrawn consent or are lost to follow-up. To investigate the impact of this assumption on the primary analysis, a 2-way tipping point analysis based on the approach described in Zhao et al.[3] is performed. In this analysis, patients in the two treatment groups will have event times imputed from the conditional event distribution with a penalty in the sense that the risk of primary endpoint events is increased following censoring compared to while under observation. Multiple imputed data sets are analysed with separate Cox regressions and results are combined using Rubin's rule. The tipping points are then defined as the combination of penalties (in each of the treatment groups) needed to turn around the superiority conclusion. A range of plausible penalties will be specified based on blinded data and before DBL.

2.3.3 Supplementary analysis

The following supplementary analyses are planned:

- Absolute risk difference: Estimation of the absolute risk difference (and 95% CI) at year 3 between oral semaglutide and placebo based on the cumulative incidence functions for each treatment group. If the trial is stopped early for superiority, year 2 will be used.
- On-treatment: Analysis addressing the secondary estimand using a Cox proportional hazards model, censoring patients at the first time being off-treatment for 5 consecutive weeks.

2.3.4 Subgroup analyses

The consistency in the treatment effect for the primary endpoint is explored by subgroup analyses based on the below baseline information:

- Sex: Female, Male
- Age < 65 years (yes/no)
- Region: EU, North America, Asia, Other
- Race: White, Black or African-American, Asian, Other
- Ethnicity: Hispanic/Latino, Other
- $HbA_{1c} \leq 8.0\%$ (yes/no)
- BMI ≤ 30 kg/m^2 (yes/no)
- Established CV disease only, Chronic kidney disease only, both
- Prior MI or stroke (yes/no)
- Metformin use (yes/no)
- Insulin use (yes/no)
- SGLT-2i use (yes/no)
- Chronic heart failure (yes/no)
- eGFR < 60 ml/min/1.72 m2 per CKD-EPI (yes/no)

The subgroup analyses are based on Cox proportional hazards models with an interaction between treatment group (oral semaglutide, placebo) and the specific subgroup as a factor.

2.4 Secondary endpoints

Confirmatory secondary endpoints are analysed under multiplicity control.

2.4.1 Confirmatory secondary endpoints

If superiority is established for the primary endpoint, superiority hypotheses are tested for the confirmatory secondary endpoints under multiplicity control via a hierarchical testing scheme using the following order:

1. 5-component composite CKD endpoint
2. CV death
3. 2-component MALE endpoint

The testing procedure is stopped the first time an analysis fails to confirm superiority of the endpoint in question using a one-sided significance level of 2.5%. No adjustments of the nominal significance level of the confirmatory secondary endpoint analyses due to the group sequential design are planned.

5-component composite CKD endpoint

The 5-component composite CKD endpoint is analysed using a Cox proportional hazards model as for the primary endpoint. The analysis will exclude patients who already have met relevant renal components at baseline. Missing data for eGFR values due to e.g. missing blood samples while patients are still being followed are not imputed, assuming no eGFR component events observed during in-trial observation period with missing eGFR values.

For the eGFR components, a persistent outcome in eGFR is defined as having two consecutive central laboratory assessments at least 4 weeks apart meeting the criteria. When classifying the events based on consecutive laboratory assessments, the date of the event is the date of the first sample meeting the definition. When classifying chronic renal replacement therapy or kidney transplantation, the date of event is the date of initiation of the therapy or surgery, respectively.

In the case that only one initiating eGFR value fulfils the criteria of ≥50% reduction in eGFR compared with baseline or eGFR <15 ml/min/1.73 m^2 Table 2-2 provides data handling rules for defining endpoint events. Any eGFR assessment made after initiation of chronic renal replacement therapy will not qualify as a confirmatory eGFR value.

Table 2-2 Data handling rules where only one initiating eGFR measurement meets the criteria of ≥50% eGFR reduction or eGFR <15 ml/min/1.73 m^2

Rule number	Event: One initiating eGFR value fulfilling the criteria * with a subsequent **event** without any confirmatory eGFR value measured >4 weeks after the initiating first eGFR measurement being available.	eGFR component	Date of event
1	CV or renal death	No	Date of death
2	Non-CV and non-renal death	Yes	Date of eGFR sample
3	Initiation of chronic renal replacement therapy	No	Date of initiation
4	Lost-to-follow-up or withdrawal of consent	No	Not applicable
5	One initiating eGFR value fulfilling the criteria* at planned end-of-treatment visit	Yes	Date of eGFR sample

* ≥50% reduction in eGFR compared with baseline or eGFR <15 ml/min/1.73 m^2

CV death

The confirmatory secondary endpoint CV death is analysed using a Cox proportional hazards model as described for the primary endpoint.

2-component MALE endpoint

The confirmatory secondary endpoint time to first occurrence of MALE is analysed using a Cox proportional hazards model as described for the primary endpoint.

Supplementary analyses described in section 2.3.3 for the primary endpoint, will similarly be done for the confirmatory secondary endpoints.

Sensitivity analysis for the 5-component composite CKD endpoint

In the analysis for the 5-component composite CKD endpoint, missing data for scheduled central laboratory eGFR values are not imputed. The following sensitivity analysis using multiple imputation is planned. Prior to analysis, missing data are imputed using multiple imputation generating 500 data sets to account for the inherent uncertainty. The imputation is performed separately for each treatment group. In the first step, intermittent missing values are imputed using the Markov Chain Monte Carlo method based on an assumption of multivariate normality. In the second step, imputation of monotone missing values is done within patient groups defined by the treatment group and based on a sequential univariate regression approach. At each scheduled visit starting with the first post-baseline visit the imputation model includes baseline eGFR value and the previous post-baseline scheduled values (observed and imputed) prior to the visit being imputed as covariates. For each eGFR component of the primary endpoint it is evaluated whether an event has occurred (yes/no) within the in-trial observation period. Intermittent imputed data are excluded from this evaluation.

After imputation of missing eGFR data, the primary composite endpoint is derived, and the 500 multiple-imputed data sets are analysed with the primary stratified Cox proportional hazards model described above. Patients that do not experience a primary endpoint event during the in-trial observation period are censored at the in-trial observation period end date. The resulting estimates of the log(HR) are combined using the methods of Rubin and back transformed to HR scale to draw inference.

2.4.2 Supportive secondary endpoints

Time-to-event supportive secondary endpoints

Each of the supportive secondary time-to-event endpoints is analysed with the same Cox proportional hazards model as the primary endpoint. For the time-to-events endpoints involving eGFR, the analyses will exclude patients who already have met relevant renal components at baseline.

Supplementary analyses for all-cause death

In addition, all-cause death is analysed using FAS and an extended in-trial observation period including the follow-up for vital status for patients who withdraw consent or are LFTU. The Cox proportional hazards model as described for the primary endpoint is used.

Supplementary analyses for 5-component MACE and 2-component HF

For the two endpoints 5-component expanded MACE and 2-component HF supplementary analyses will be done by replacing the CV death component with all-cause death.

Continuous supportive secondary endpoints

The continuous supportive secondary endpoints (change from baseline to 2 years) are analysed using multiple imputation for missing values. An imputation model (linear regression) is estimated separately for each treatment group. It will include baseline value as a covariate estimated based on patients having an observed data point, irrespective of adherence to randomised treatment, at 2 years. The fitted model is used to impute values for all patients that have a missing data point at 2 years to create 500 complete data sets. The completed data sets are analysed by an analysis of covariance model adjusted for treatment as fixed factor and baseline value as covariate. Rubin's rule is used to combine the results.

Annual rate of change in eGFR

The annual rate (slope) of decline in eGFR is compared between treatment groups based on a linear random regression model on eGFR values with treatment, time (as a continuous variable) and treatment time interaction as fixed effects and including patient effect as a random intercept and time as a random slope. The random intercept and slope is assumed to be bivariate normal distributed with mean zero and an unstructured covariance matrix. The independent error term is

assumed to be identical univariate normal distributed with mean zero. The model is fitted to observed scheduled eGFR data at baseline and post-baseline. The parameter of interest is the regression coefficient for the treatment and time interaction term, which measures the slope difference between oral semaglutide and placebo.

Supplementary analyses for MI and stroke

In the analyses of MI and stroke supplementary analyses including fatal MI and fatal stroke are performed. Thus, the supplementary analysis will analyse endpoints defined as:

- Time from randomisation to first MI (fatal or non-fatal)
- Time from randomisation to first stroke (fatal or non-fatal).

Analysis of recurrent events

Repeated occurrence of the same type of event over time for the same patient may happen. The following recurrent event endpoints are compared between the treatment arms from randomisation to end of trial:

- Number of MI events (fatal or non-fatal)
- Number of stroke events (fatal or non-fatal)
- Number of MI and stroke events (fatal or non-fatal)
- Number of heart failure events (heart failure requiring hospitalisation or urgent heart failure visit)

Mean number of events is plotted as a function of study time and analysed using a marginal mean regression model for recurrent events accounting for competing risk of dying as described by Ghosh & Lin (2000[1], 2002[2]). Treatment effect is reported as a mean ratio and corresponding 95% robust CI to account for the dependency of within-subject of recurrent events.

Number of severe hypoglycaemic episodes

Number of severe hypoglycaemic episodes is analysed using the same marginal recurrent event regression model described above.

2.5 Exploratory endpoints

Change from baseline to year 2 and 3 in cognitive function: Montreal Cognitive Assessment (MoCA) score is compared between oral semaglutide and placebo using the same analysis as outlined above for continuous endpoints.

The smoking endpoint is analysed using a logistic regression model with treatment (oral semaglutide, placebo) and baseline smoking status (yes/no) as fixed factors. Missing data are handled by multiple imputation.

Table 6-3 gives an overview of planned analyses for all endpoints.

3 Interim testing

The trial design includes *one* pre-planned interim testing for superiority of the primary endpoint. The planned timing is when 817 events (two thirds of the planned total events) of the primary endpoint have been accrued. The interim testing is performed based on a locked snapshot of the study database. The date of the snapshot defines the interim analysis cut-off date for the interim analysis.

Patients without an EAC-confirmed primary endpoint event prior to the date of analysis cut-off are considered censored with the censoring date defined as the first of:

- in-trial observation period end-date
- interim analysis cut-off date

The same Cox model as described in section 2.3 is used for the interim testing addressing the primary estimand.

3.1 Role of DMC

Blinded and un-blinded data analyses during trial conduct are evaluated by the DMC, as described in the DMC charter. Trial integrity is ensured by using an external independent statistical service provider (independent of trial conduct and external to Novo Nordisk) to prepare these data and analyses for the DMC.

The DMC will evaluate the interim result and make recommendation to terminate the trial early for superiority if appropriate. The DMC evaluates the un-blinded interim results using the above group sequential stopping boundary as guidance. Stopping the trial early for superiority is only allowed if the stopping boundary is crossed and the DMC makes the decision to recommend early trial termination based on this and other considerations as specified in the DMC charter.

3.2 Stopping boundary for superiority at interim

The exact number of primary endpoint events used for the interim testing is only known at the time of analysis, and the exact boundary is re-calculated using the Lan-DeMets alpha spending function.

3.3 Analysis on termination

If the trial is terminated early for superiority following the interim testing, definitive evaluation of superiority for the primary endpoint is performed based on all the available data at the end-of-trial, including overrun data. Overrun data include events happening between the cut-off date for the DMC interim analysis and end-of-trial as well as additional confirmed events that were undergoing adjudication at the interim analysis cut-off time point. If the trial is not terminated early for superiority following the interim testing, the analysis at scheduled termination is performed when the planned number of 1,225 events has been accrued. The exact number of primary endpoint events used for the analysis on termination is only known at the time of analysis, and nominal

significance level is updated based on the exact number of total accrued events and the Lan-DeMets alpha spending function.

For reporting of results (p-value, HR and 95% CI), the analysis on termination (either early or at scheduled termination) are adjusted for the group sequential design using the likelihood ratio ordering.

Furthermore, at termination, Novo Nordisk will replicate the interim analysis performed by the independent statistician using the exact same snapshot of data as used at the time of the interim analysis. This analysis is reported in the Clinical Trial Report together with the analysis on termination.

4 Changes to the statistical analyses planned in the protocol

SAP version 1.0 dated 12-MAR-2019

For the confirmatory secondary endpoint 5-component composite CKD the primary analysis is changed not to include multiple imputation for missing values of eGFR. Instead multiple imputation is done in a sensitivity analysis (section 2.4.1).

Sensitivity analysis for the primary endpoint updated to a 2-way tipping point analysis (section 2.3.2).

Additional analyses added in the SAP and not described in the protocol (section 2.3.3 and 2.4.2):

- Supplementary analyses for primary endpoint and confirmatory secondary endpoints:
  - Risk difference at year 3
  - Secondary estimand (on-treatment)
- Supplementary analyses for 5-component MACE and 2-component HF by replacing CV death component with all-cause death
- Analyses of MI and stroke using both fatal and non-fatal events
- Analysis of all-cause death using an extended in-trial observation period
- Recurrent event analyses for selected endpoints

5 References

1. Ghosh D, Lin DY. Nonparametric analysis of recurrent events and death. Biometrics. 2000;56(2):554-62.
2. Ghosh D, Lin D. Marginal regression models for recurrent and terminal events. Statistica Sinica. 2002;12:663-88.
3. Zhao Y, Herring AH, Zhou H, Ali MW, Koch GG. A multiple imputation method for sensitivity analyses of time-to-event data with possibly informative censoring. J Biopharm Stat. 2014;24(2):229-53.

6 Appendix

Table 6-1 Handling of intercurrent events for the confirmatory endpoints

Endpoint	Intercurrent event	Handling
Time to first occurrence of MACE	• Treatment discontinuations • Medication modifying cardio-renal risk • Initiation of chronic renal replacement therapy	Patients are followed, and events collected after intercurrent events and used in the analysis
	• Trial discontinuation (withdrawal of consent or lost-to follow-up)	Censoring at time of trial discontinuation
	• Non-CV death (competing risk)	Censoring at time of non-CV death in the Cox model
Time to first occurrence of composite CKD	• Treatment discontinuations • Medication modifying cardio-renal risk	Events and follow-up time are collected after intercurrent events and used in the analysis
	• Trial discontinuation (withdrawal of consent or lost-to follow-up)	Censoring at time of trial discontinuation
	• Non-renal and Non-CV death (competing risk)	Censoring at time of non-renal or non-CV death in the Cox model
Time to occurrence of CV death	• Treatment discontinuations • Medication modifying cardio-renal risk • Initiation of chronic renal replacement therapy	Events and follow-up time are collected after intercurrent events and used in the analysis
	• Trial discontinuation (withdrawal of consent or lost-to follow-up)	Censoring at time of trial discontinuation
	• Non-CV death (competing risk)	Censoring at time of non-CV death in the Cox model
Time to first occurrence of MALE	• Treatment discontinuations • Medication modifying cardio-renal risk • Initiation of chronic renal replacement therapy	Patients are followed, and events collected after intercurrent events and used in the analysis
	• Trial discontinuation (withdrawal of consent or lost-to follow-up)	Censoring at time of trial discontinuation
	• All cause death (competing risk)	Censoring at time of death in the Cox model

Table 6-2 List of time-to-event endpoints

Endpoint	Composite order/details*	EAC**	Competing risk
Primary			
3-component MACE	- CV death - Non-fatal MI - Non-fatal stroke	Yes Yes Yes	Non-CV death
Confirmatory secondary			
5-component CKD	- Renal death - CV death - Initiation of chronic renal replacement therapy - Onset of persistent eGFR<15 ml/min/1.73 m2 - Onset of persistent ≥50% reduction in eGFR	Yes Yes Yes No No	Non-CV death and non-renal death
CV death	–	Yes	None
MALE	- Acute limb ischemia hospitalisation - Chronic limb ischemia hospitalisation	Yes Yes	All cause death
Supportive secondary			
3-component MACE with all cause death	- All-cause death - Non-fatal MI - Non-fatal stroke	Yes Yes Yes	None
5-component MACE	- CV death - Non-fatal MI - Non-fatal stroke - Coronary revascularisation - Unstable Angina hospitalisation	Yes Yes Yes No Yes	Non-CV death
2-component HF	- CV death - HHF or urgent HF Visit	Yes Yes	Non-CV death
4-component CKD	- Renal death - Initiation of chronic renal replacement therapy - Onset of persistent eGFR<15 ml/min/1.73 m2 - Onset of persistent ≥50% reduction in eGFR	Yes Yes No No	Non-renal death
All cause death	–	Yes	None
Non-fatal MI	–	Yes	All-cause death
Non-fatal stroke	–	Yes	All-cause death
HHF or urgent HF Visit	–	Yes	All-cause death
Coronary revascularisation	–	No	All-cause death
Unstable angina hospitalisation	–	Yes	All-cause death
Renal death	–	Yes	Non-renal death
Onset of persistent ≥50% reduction in eGFR	–	No	All-case death
Onset of persistent eGFR<15	–	No	All-case death and initiation of chronic renal replacement therapy
Initiation of chronic renal replacement therapy	–	Yes	All-case death and initiation of chronic renal replacement therapy
Acute limb ischemia	–	Yes	All-case death
Chronic limb ischemia	–	Yes	All-case death
First severe hypoglycaemic episodes	–	No	All-cause death
No of severe hypoglycaemic episode	–	No	All-cause death

* For composite endpoints this defines the hierarchy of components when reporting events contributing to a composite endpoint in the situation of ties of date of events of the components

** EAC-confirmed event

Table 6-3 Overview of planned analyses for all endpoints

Endpoint	Model/method	Summary measure	Sensitivity analysis	Supplementary analysis
Primary				
3-component MACE	Cox	Hazard ratio	2-way tipping point	Risk difference at year 3 On-treatment Subgroup analyses
Confirmatory secondary				
5-component CKD	Cox	Hazard ratio	Imputation of missing eGFR	Risk difference at year 3 On-treatment
CV deaths	Cox	Hazard ratio	–	Risk difference at year 3 On-treatment
2-component MALE	Cox	Hazard ratio	–	Risk difference at year 3 On-treatment
Supportive secondary				
3-component MACE with all cause death	Cox	Hazard ratio	–	–
5-component MACE	Cox	Hazard ratio	–	Including all-cause death
2-component HF	Cox	Hazard ratio	–	Including all-cause death
4-component CKD	Cox	Hazard ratio	–	
All cause death	Cox	Hazard ratio	–	Extended in-trial period
Non-fatal MI	Cox	Hazard ratio	–	Including fatal MI Recurrent events analysis
Non-fatal stroke	Cox	Hazard ratio	–	Including fatal stroke Recurrent events analysis
HHF or urgent HF Visit	Cox	Hazard ratio	–	Recurrent events analysis
Coronary revascularisation	Cox	Hazard ratio	–	–
Unstable angina hospitalisation	Cox	Hazard ratio	–	–
Renal death	Cox	Hazard ratio	–	–
Onset of persistent ≥50% reduction in eGFR	Cox	Hazard ratio	–	–
Onset of persistent eGFR<15	Cox	Hazard ratio	–	–
Initiation of chronic renal replacement therapy	Cox	Hazard ratio	–	–
Acute limb ischemia	Cox	Hazard ratio	–	–
Chronic limb ischemia	Cox	Hazard ratio	–	–
First severe hypoglycaemic episodes	Cox	Hazard ratio	–	–
No of severe hypoglycaemic episodes	Marginal mean regression	Mean ratio	–	–
Annual rate of change in eGFR	Random regression model	Mean slope difference	–	–
Change in HbA_{1c} to year 2	ANCOVA w MImp	Mean difference	–	–
Change in body weight to year 2	ANCOVA w MImp	Mean difference	–	–
Exploratory				
Change in Montreal Cognitive Assessment score	ANCOVA w MImp	Mean difference	–	–
Smoker at 2 years	Logistic regression and multiple imputation	Odds ratio	–	–

ANCOVA w MImp = Analysis of covariance with multiple imputation

5. Final statistical analysis plan

Statistical Analysis Plan

Trial ID: EX9924-4473

SOUL – Semaglutide cardiovascular outcomes trial in patients with type 2 diabetes

Table of contents

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List of abbreviations

ANCOVA	analysis of covariance
CI	confidence interval
CKD	chronic kidney disease
CKD-EPI	chronic kidney disease - epidemiology collaboration
CV	cardiovascular
DBL	data base lock
DMC	data monitoring committee
EAC	event adjudication committee
eGFR	estimated glomerular filtration rate
FAS	full analysis set
HbA_{1c}	glycosylated haemoglobin
HF	heart failure
HHF	hospitalisation for heart failure
HR	hazard ratio
LTFU	lost to follow-up
MACE	major adverse cardiovascular event
MALE	major adverse limb event
MI	myocardial infarction
PAD	peripheral arterial disease
SAP	statistical analysis plan
TTE	time-to-event

1 Introduction

1.1 Trial information

1.1.1 Rationale

To evaluate the hypothesis that oral semaglutide lowers the risk of cardiovascular events in patients with type 2 diabetes at high risk for cardiovascular disease.

1.1.2 Objectives, endpoints and estimand

Primary objective

To demonstrate that oral semaglutide lowers the risk of major adverse cardiovascular events compared to placebo, both added to standard of care in patients with type 2 diabetes and at high risk of cardiovascular events.

Key secondary objectives

To compare the effects of oral semaglutide versus placebo, both added to standard of care in patients with type 2 diabetes and at high risk of cardiovascular events with regards to:

- Chronic kidney disease
- Cardiovascular events
- Peripheral artery disease

Primary endpoint

The primary endpoint is time from randomisation to first occurrence of a major adverse cardiovascular event, a composite endpoint consisting of: cardiovascular death, non-fatal myocardial infarction or non-fatal stroke.

Confirmatory secondary endpoints

Time from randomisation to:

- first occurrence of a composite chronic kidney disease endpoint consisting of: cardiovascular death, renal death, onset of persistent ≥50% reduction in estimated glomerular filtration rate (CKD-EPI) compared with baseline, onset of persistent eGFR (CKD-EPI) <15 mL/min/1.73 m^2 or initiation of chronic renal replacement therapy (dialysis or kidney transplantation)
- cardiovascular death
- first occurrence of a major adverse limb events, a composite endpoint consisting of: acute limb ischemia hospitalisation or chronic limb ischemia hospitalisation

Primary estimand

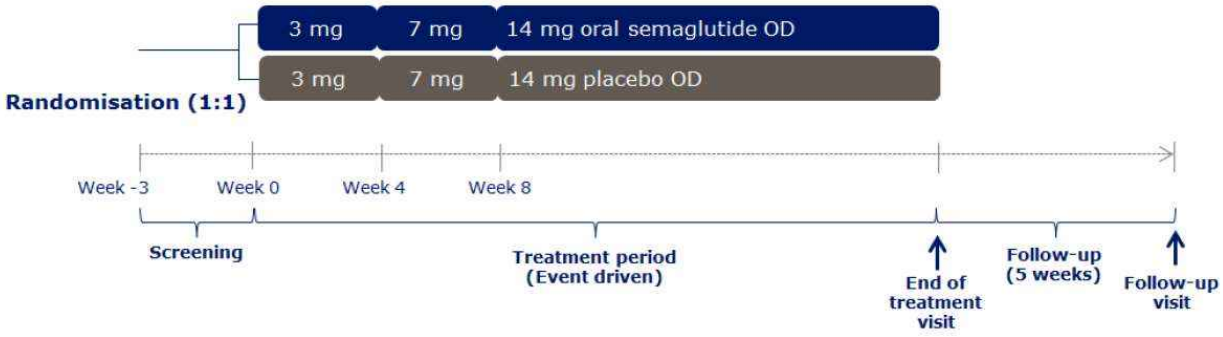
The estimand for all objectives is the intention-to-treat estimand evaluating the effect of the randomised treatment intervention irrespective of adherence to treatment and changes to background medication.

1.1.3 Design

This is a randomised, double-blind, parallel-group, placebo-controlled trial comparing oral semaglutide versus placebo both administered once daily and added to standard of care in patients with type 2 diabetes at high risk of cardiovascular events. Patients are randomised 1:1 to receive either oral semaglutide or placebo.

The trial is event driven; therefore, end of trial is scheduled according to accrual of events. The trial will employ a group sequential design with one interim testing for superiority. Under the design assumptions, the trial duration is approximately 61 months following randomisation of the first patient. 9,642 patients are planned to be randomly assigned to trial products. A schematic overview of the trial design is shown in Figure 1.

Figure 1 Trial design



1.2 Scope of the statistical analysis plan

The SAP includes elaborations on statistical analyses outlined in the protocol for SOUL trial (EX9924-4473) as well as details on the interim testing for superiority. Any changes to the SAP after first patient first visit are documented in a change log.

An external independent statistical service provider will conduct the interim analysis, see also section 3. Novo Nordisk is responsible for all other statistical analyses and reporting of data but will remain blinded to treatment allocations until data base lock (DBL). Additionally, a statistician independent of trial conduct, DMC analyses, interim analysis, and external to Novo Nordisk will independently confirm the statistical primary analyses of the primary endpoint and secondary confirmatory endpoints. This statistician will also be blinded until DBL.

2 Statistical considerations

2.1 Sample size determination

The trial is designed with 90% power to confirm superiority for the primary endpoint, i.e., reject the null-hypothesis of a hazard ratio (HR) ≥ 1.0 against the one-sided alternative of HR < 1.0, where HR is the hazard ratio of oral semaglutide versus placebo.

The trial is designed with one interim testing for superiority of the primary endpoint when two thirds of the total planned number of primary endpoint events has been accrued. Testing for futility

is not included. The Lan-DeMets alpha spending function, approximating the O'Brien-Fleming's stopping boundaries, is used to test superiority at a study-wise one-sided type I error rate of 2.5%. The one-sided alpha spending function is given by

$$f(t) = min\{2 - 2 \cdot \Phi(z_{\frac{\alpha}{2}}/\sqrt{t}), \alpha\}$$

where *t* is the proportion of information included in the interim analysis (accrued primary endpoint events relative to the total planned primary endpoint events), Φ denotes the standard normal cumulative distribution function, α is the overall one-sided alpha of 2.5% and $z_{\alpha/2}$ is the 98.75% quantile of the standard normal distribution. Based on a randomisation ratio of 1:1 and a design HR of 0.83 a total of 1,225 primary endpoint events are required.

For calculating the number of randomised patients, the following is assumed:

- annual primary endpoint rate in the placebo group of 3.5%
- uniform recruitment in 18 months
- annual lost to follow-up rate in both treatment groups of 1%
- maximum trial duration of five years and five weeks

Under these assumptions, a total of 9,642 patients are needed for randomisation.

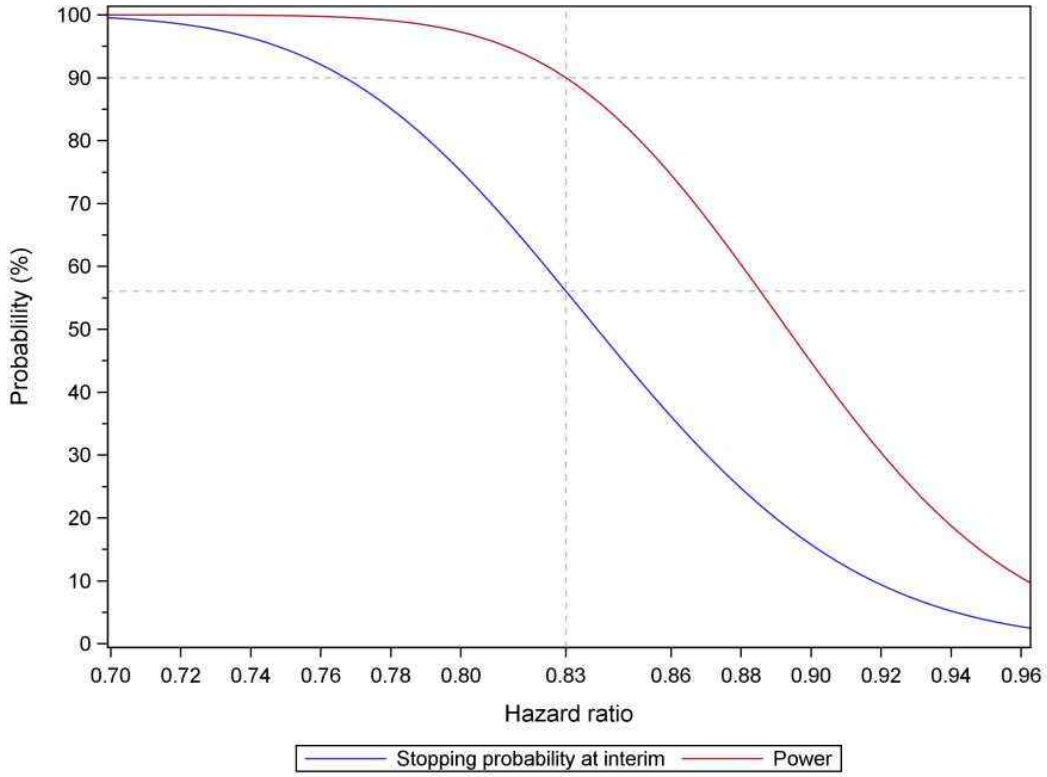
A Cox model as described in section 2.3 is used for the interim testing using the fixed sample one-sided lower p-value from the score test. Only a fixed sample p-value below the boundary specified by the error spending function will allow the DMC to recommend early trial termination for superiority. Table 1 provides the boundaries based on analyses performed after 817 and 1,225 events, along with the approximate hazard ratio estimates that correspond to those boundaries if the analyses are timed exactly to that schedule. The actual stopping boundaries will be based on the exact number of events available for the interim analysis.

Table 1 Stopping boundary scales at interim and scheduled termination

Stopping boundary scale	Interim 817 events	Scheduled termination 1,225 events
Hazard ratio	0.8389	0.8924
Nominal significance level	0.00605	0.02314

Figure 2 shows the probability of stopping the trial early at the interim (blue curve) and the overall power for confirming superiority for the primary endpoint (red curve) as a function of alternative values for the true HR. The design HR of 0.83 is marked with a dashed vertical reference line. The stopping probability at the interim and overall power for the design HR of 0.83 can be seen to be 56% and 90%, respectively.

Figure 2 Stopping probability at interim and overall power as a function of true hazard ratio



Confirmatory secondary endpoints

If superiority is confirmed for the primary endpoint the confirmatory secondary endpoints are controlled for multiplicity through a hierarchical testing strategy. The marginal powers below are calculated under the assumptions that the trial continues to the scheduled termination, a significance level of 2.5% (one-sided) and 9,642 randomised patients.

The marginal power for superiority in favour of oral semaglutide for the 5-component chronic kidney disease (CKD) endpoint is 94% based on an assumed HR of 0.80 and an annual event rate of 2.8% in the placebo group.

The marginal power for superiority in favour of oral semaglutide for CV death is 56% based on an assumed HR of 0.83 and an annual event rate of 1.4% in the placebo group.

The marginal power for superiority in favour of oral semaglutide for the major adverse limb event(s) (MALE) endpoint is 44% based on an assumed hazard ratio of 0.75 and an annual event rate of 0.44% in the placebo group.

The assumptions for annual event rate of primary endpoint and confirmatory secondary endpoints, lost to follow-up rates and the assumed HRs are based on the LEADER and SUSTAIN 6 CV outcomes trials.

2.2 General considerations

For confirmatory endpoints controlled for multiplicity, estimated treatment effects are presented together with two-sided 95% confidence intervals (CIs) and one-sided p-values for tests of the hypothesis of superiority. For reporting of results, the hazard ratio and the 95% CI are accompanied by the two-sided p-value.

For non-confirmatory endpoints, the estimated treatment effects are reported together with two-sided 95% CIs and two-sided p-values.

Baseline value is defined as the eligible measurement associated with the randomisation visit, if this measurement is taken before or at the date of first dose. If a randomisation assessment is missing or if it is taken after the date of first dose, then the assessment from screening is used as the baseline assessment, if available.
If more than one measurement is associated with the same visit, the earliest measurement is considered eligible.

Missing data are defined as data that are planned to be collected and could have been collected but are not present in the database. This implies that data that are structurally missing due to death or administrative censoring are not considered missing. Unless explicitly stated, unobserved data pertaining to subjects who are lost to follow-up or withdrawn and would not have been administratively censored at the time point in question are considered missing, irrespectively of vital status as collected at end of trial.

Assessments of eGFR taken after initiation of chronic renal replacement therapy will not be used for analyses or summary tables.

2.2.1 Definition of analysis set

The full analysis set (FAS) is defined as all unique randomised subjects and grouped according to the treatment assigned at randomisation.

If a subject is randomised more than once, only the subject ID and treatment corresponding to the first randomisation will be included in FAS. The additional randomised subject IDs will be excluded from FAS. The list of subject ID’s to exclude will be part of the DBL minutes.

2.2.2 Definition of observations period

A trial completer is defined as a subject who either attends the follow-up visit or who dies while active in the trial.

A patient is considered lost to follow-up (LTFU) if the patient does not complete the trial and does not withdraw consent. The date and status for LTFU are determined by investigator at trial completion, either following interim testing or after accrual of the total planned number of primary endpoint events.

In-trial observation period

The in-trial observation period for a subject is defined as the period from date of randomisation to the first of (both inclusive):

- date of follow-up visit
- date when subject withdrew consent
- date of last contact with subject for subjects who are LTFU
- date of death

On-treatment observation period

A time-point in the in-trial observation period is considered as on-treatment if any dose of trial product has been administered within the previous 5 weeks (35 days). The on-treatment observation period is defined as all times which are considered on-treatment and may consist of several time intervals with gaps between.

First on-treatment observation period

The first on-treatment observation period is defined as the on-treatment observation period until first time being off treatment for 5 consecutive weeks (35 days). Thus it is the first time interval in the on-treatment period.

2.2.3 Estimands

Primary estimand (intention-to-treat)

The estimand for all objectives is an intention-to-treat estimand, evaluating the effect of the randomised treatment intervention irrespective of adherence to treatment and changes to background medication. The estimand is addressed using FAS and the in-trial observation period.

Secondary estimand (on treatment)

This estimand covers the primary and confirmatory secondary endpoints and is evaluating the effect of the randomised treatment intervention in all randomised subjects had they remained on their randomised treatment for the entire trial. The estimand is addressed using FAS and the first on-treatment observation period.

2.2.4 Intercurrent events

Intercurrent events, including but not limited to events of or associated with:

- randomised treatment adherence
- change in background medication modifying CV risk
- initiation of chronic renal replacement therapy
- withdrawal
- lost-to follow up
- death (if not part of endpoint)

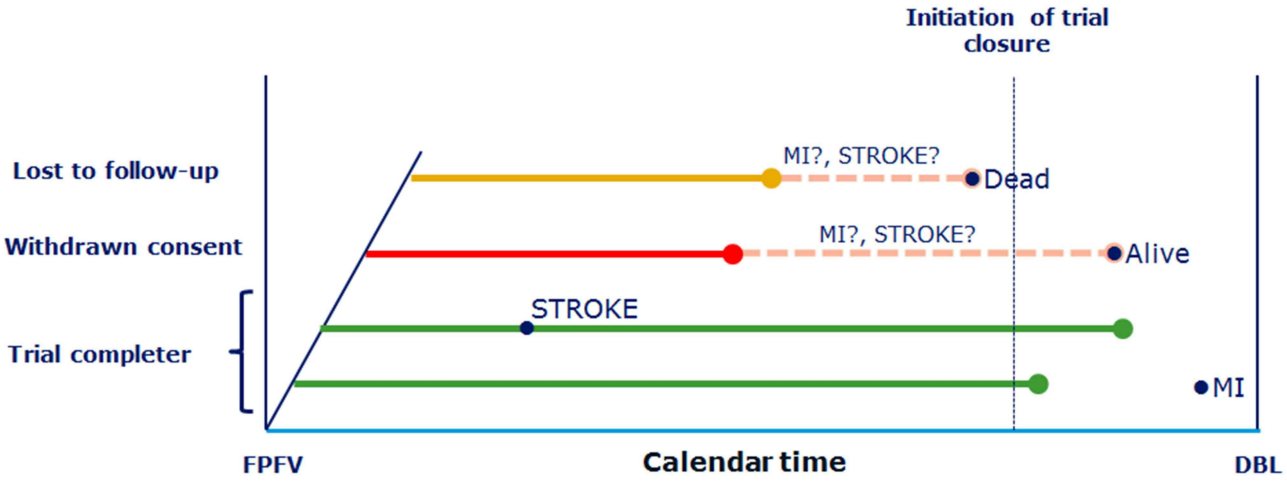
These are reported using descriptive statistics. Handling of intercurrent events for the statistical analyses of the confirmatory endpoints is described in Table 4.

2.2.5 Time-to-event endpoints, censoring and competing risks

Time-to-event endpoints are in general time-to-first-event endpoints but will for simplicity be denoted time-to-event (TTE) endpoints.

If adjudicated, the TTE endpoints are defined based on outcomes of the EAC evaluations. While vital status is ascertained systematically throughout the trial until DBL, other event types cannot be systematically collected after withdrawal, lost-to-follow-up, or after end-of-trial visit as illustrated in Figure 3. For this reason, any event occurring after the in-trial observation period is not included in analyses, unless otherwise stated.

Figure 3 In-trial observation periods used in analysis of time-to-event endpoints reflected by bold limes for four different subjects examples

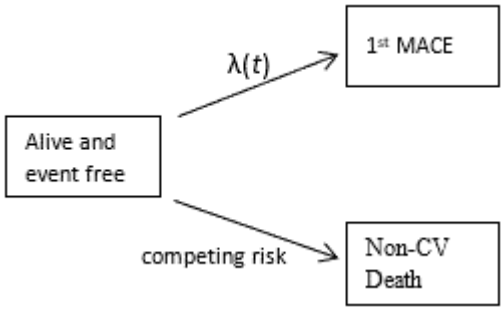


If a subject experiences the event of interest during the in-trial observation period, the observation of the TTE is the time from randomisation to the date of event.

The observation of the TTE is censored if the event of interest does not happen during the in-trial observation period and if the subject is still alive at the end of the observation period. The general assumption for censored observations is that the risk of experiencing an event is not changed by censoring, i.e. an assumption of independent censoring. This is a reasonable assumption for administrative censoring at end-of-trial visit but may not be for subjects withdrawing or subjects lost to follow-up. Sensitivity analysis addressing the assumption of independent censoring is planned for the primary endpoint, see section 2.3.2.

The observation of the TTE is terminated if the event of interest does not happen before the death of the patient unless death is part of the endpoint. Terminating events (competing risks) is potentially present for all TTE endpoints except for all-cause death; for the primary endpoint, non-CV death is a competing risk terminating the observation for the event of interest (MACE). Figure 4 illustrates competing risk as a multi-state model for the primary endpoint. The hazard rate of interest in this trial is denoted by $\lambda(t)$, t being time since randomisation.

Figure 4 Multi-state model illustrating competing risk for primary endpoint



Unless otherwise specified, the statistical analyses of TTE endpoints are done by using a Cox proportional hazards model with treatment group (oral semaglutide, placebo) as fixed factor under the assumption of independent censoring. Terminated observations (due to competing risks) are technically treated as censored observations but are not part of the independent censoring assumption. The population-level summary measure for TTE endpoints is the HR for oral semaglutide versus placebo. The assumption of proportional hazards is investigated by residuals. Tied event times are handled using the exact method and confidence intervals are based on the profile likelihood.

Cumulative incidence functions for TTE endpoints are estimated by the Aalen-Johansen estimator which accounts for competing risks.

Table 5 provides an overview of the TTE endpoints including any competing risk and whether the TTE endpoint is EAC-confirmed.

2.2.6 Continuous and binary endpoints

The population-level summary measure for continuous endpoints is the mean difference for oral semaglutide versus placebo. The population-level summary measure for binary endpoints is the odds ratio for oral semaglutide versus placebo.

2.3 Primary endpoint

Time from randomisation to first occurrence of a composite MACE endpoint consisting of

- CV death
- Non-fatal myocardial infarction (MI)
- Non-fatal stroke.

Fatal MI is defined as an EAC-confirmed MI occurring within (≤) 30 days of an EAC-confirmed CV death classified as cause of death being MI. All other MIs are defined as non-fatal. A similar definition is applied for fatal/non-fatal stroke, where MI is replaced with stroke.

Deaths attributed to the category “undetermined cause of death” are presumed cardiovascular death.

2.3.1 Primary analysis

The primary analysis will address the primary estimand (intention-to-treat). The HR for comparing oral semaglutide versus placebo is estimated from a Cox proportional hazards model with treatment group (oral semaglutide, placebo) as fixed factor together with the 2-sided 95% CI and one-sided

fixed design p-value for hypothesis testing. The score test from the Cox model is used for testing. The following superiority hypothesis is tested:

$$H_0: HR \geq 1.0 \text{ against } H_a: HR < 1.0.$$

Superiority of oral semaglutide versus placebo is considered confirmed if the associated H_0 is rejected. The nominal significance level is calculated using the alpha spending function and the actual observed number of events available for the analysis. Final inference on termination is adjusted for the group sequential design by using the likelihood ratio ordering.

Competing risk from non-CV death is handled as censorings in the Cox analysis as described in section 2.2.5. Please, refer to Table 4 for handling of other intercurrent events.

2.3.2 Sensitivity analyses

If superiority is established for the primary endpoint, the following sensitivity analysis is performed. The primary analysis assumes independent censoring for patients who have withdrawn consent or are lost to follow-up. To investigate the impact of this assumption on the primary analysis, a 2-way tipping point analysis based on the approach described in Zhao et al[1] is performed. In this analysis, subjects in the two treatment groups who have withdrawn or are lost to follow-up will have event times imputed from the conditional event distribution with a penalty in the sense that the risk (hazard) of MACE is changed following censoring compared to while under observation. Multiple imputed data sets are analysed with separate Cox regressions and results are combined using Rubin's rule. The tipping points are then defined as the combination of penalties (in each of the treatment groups) needed to turn around the superiority conclusion.

Two additional sensitivity analyses will be performed by multiple imputation of event times for subjects who are withdrawn or lost to follow-up. If the imputed event time occurs after the subjects planned end-of-trial time the subject will be censored at the planned end-of-trial time

The first will be done by treatment arm using an estimated annual event rate from subjects who discontinue treatment permanently but remain in the trial. The event rate will be based on events and time while these subjects are permanently off-treatment. A time-point in the in-trial observation period is considered as belonging to the permanently off-treatment period if any dose of trial product has been administered more than 5 weeks (35 days) ago and the subject remains off-treatment for the remainder of the trial. This analysis condition on the future in the sense that subjects are only known to be permanently off treatment by the end of the trial.

The second analysis avoids conditioning on the future by using an estimated annual event rate for subjects who discontinue treatment at any point in the trial. The imputations are done by treatment arm. The event rate will be based on events occurring from the first time subjects are off treatment corresponding to when their first on-treatment period ends (section 2.2.2) and until end of the in-trial observation period. This may include time periods where the subjects actually went back on trial treatment.

Technically, the first of the two sensitivity analyses will be performed in the following steps:

1. For the purpose of estimating the off-treatment event rates, a set of retrieved dropouts are selected. The selection criteria are that the subject shall be a trial completer, have their date of last dose during the trial reported as a treatment discontinuation, have ended the on-treatment observation period before the end of the in-trial observation period, and not having had an event before the end of the on-treatment observation period. For each selected subject, the off-treatment event time is calculated from a start date set to the day after the end of the on-treatment observation period. The event time is considered censored at the end of the in-trial observation period.
2. The off-treatment event time data are fitted within treatment arms to an exponential distribution using Bayesian analysis and accounting for censoring. A noninformative prior distribution is used for the rate parameter in each treatment arm. 500 replicates of the two off-treatment event rates are then randomly sampled from the posterior distribution.
3. To prepare the imputation, 500 copies of the original data set are created and linked to the corresponding replicate of the off-treatment event rates. For each subject who is censored due to withdrawal or being lost to follow up, the event time is imputed by adding a random variable to the original censoring date. The random variables are generated from an exponential distribution using the off-treatment event rate for the corresponding replicate and treatment arm, and rounded up to whole days. If the imputed event time lies beyond the planned date of end of trial for the subject, it is considered censored at this date. There will now be 500 complete data sets.
4. Each complete data set is analysed using the same Cox regression as in the primary analysis. The analysis gives the estimated log hazard ratio and associated standard error.
5. The log hazard ratios and standard errors from the 500 data sets are pooled using Rubin's rule to obtain a single point estimate, confidence interval and p-value.

The procedure for the second sensitivity analysis is identical to the first analysis except for step 1. The selection criteria for a retrieved dropout are instead that the subject shall have their date of last dose during the first on-treatment observation period reported as a treatment discontinuation, have ended the first on-treatment observation period before the end of the in-trial observation period and not having had an event during the first on-treatment observation period. The selection may include subjects who are later withdrawn or lost to follow-up. The off-treatment event time is calculated from a start date set to the day after the end of the first on-treatment observation period.

2.3.3 Supplementary analyses

The following supplementary analyses are planned:

- Absolute risk difference: Estimation of the absolute risk difference (and 95% CI) at year 3 between oral semaglutide and placebo based on the Aalen-Johansen estimator for the cumulative incidence functions for each treatment group. If the trial is stopped early for superiority, year 2 will be used.
- On-treatment: Analysis addressing the secondary estimand using a Cox proportional hazards model using the first on-treatment observation period.
- Additionally, an analysis of non-CV death using the same Cox model as for the primary endpoint will be done to evaluate the influence of the competing risk non-CV-death on the primary results.

2.3.4 Subgroup analyses

The consistency in the treatment effect for the primary endpoint is explored by subgroup analyses based on the below baseline information:

- Sex: Female, Male
- Age < 65 years (yes/no)
- Age: <65, 65≤ to <75, ≥75 years
- Race: White, Black or African-American, Asian, Other
- Ethnicity: Hispanic/Latino, Not Hispanic or Latino
- $HbA_{1c} \leq 8.0\%$ (yes/no)
- BMI ≤ 30 kg/m^2 (yes/no)
- Established CV disease only, Chronic kidney disease only, both
- Prior MI or stroke (yes/no)
- Metformin use (yes/no)
- Insulin use (yes/no)
- SGLT-2i use (yes/no)
- Chronic heart failure (yes/no)
- eGFR < 60 ml/min/1.72 m^2 per CKD-EPI (yes/no)
- eGFR: < 30, 30 ≤ to < 45, 45 ≤ to < 60, ≥ 60 mL/min/1.73m^2 (CKD-EPI)
- Peripheral artery disease (yes/no)
- Region: Europe, North America, Asia, Other. The regions are defined as
    - **Europe**: Austria, Belgium, Croatia, Czech Republic, Denmark, Finland, France, Germany, Italy, Netherlands, Romania, Slovakia, Spain, United Kingdom
    - **North America**: Canada, United States
    - **Asia**: China, Hong Kong, India, Israel, Japan, Malaysia, South Korea, Taiwan, Thailand, Turkey
    - **Other**: Argentina, Brazil, Colombia, Mexico, Russia, Serbia, South Africa, Ukraine

The subgroup analyses are based on Cox proportional hazards models with an interaction between treatment group (oral semaglutide, placebo) and the specific subgroup as a factor.

2.3.5 Supplementary analyses evaluating impact of the COVID-19 pandemic

The following supplementary analyses will be made to assess the impact of the COVID-19 pandemic on the primary endpoint. The analyses address two scenarios: one where MACEs are impacted by an increased MACE rate and potentially a different treatment effect for events occurring concurrently with COVID-19 infection; the other with a reduced MACE rate due to concurrent COVID-19 infection leading to fewer CV deaths as the subjects die (prematurely) of COVID-19 infection and not their underlying atherosclerotic disease.

- Time from randomisation to first MACE without concurrent COVID-19 SAE. The definition of MACE is modified so any MACE occurring concurrently with a COVID-19 SAE in a subject is not considered a MACE. The observation period and censoring are not changed. Any subsequent MACE can then qualify to be the first MACE for the subject.
- Time from randomisation to first MACE without concurrent COVID-19 AE. The definition of MACE is modified so any MACE occurring concurrently with a COVID-19 AE in a

subject is not considered a MACE. The observation period and censoring are not changed. Any subsequent MACE can then qualify to be the first MACE for the subject.

- Time from randomisation to first MACE or non-CV death occurring concurrently with a COVID-19 SAE. The definition of MACE is modified to include non-CV deaths potentially related to COVID-19. The observation period and censoring are not changed.

The analyses will be done with the same Cox regression model as for the primary analysis. An event is considered concurring with a COVID-19 AE if the event occurs in the time period from the start day of the COVID-19 AE and until 30 days after the last of the following two dates: the stop date of the COVID-19 AE or the end of hospitalisation date for a hospitalisation reported together with the COVID-19 AE

2.3.6 Supplementary analyses evaluating impact of co-participation in COVID-19 treatment or prevention trials

To assess the potential impact on the primary analysis of subjects being allowed to co-participate in trials with primary objective of evaluating an approved or non-approved investigational medical product for treatment or prevention of COVID-19 disease the following supplementary analysis will be done: An analysis of time to first MACE where all subjects co-participating in a COVID-19 treatment or prevention trial are censored at the day they receive the first trial treatment for preventing or treating COVID-19. This will reduce the observation time.
The analysis will be done with the same Cox regression model as for the primary analysis.
The analysis corresponds to the situation where patients withdraw from the trial when they start co-participation. If less than 10 subjects have co-participated in COVID-19 treatment or prevention trials then this analysis will not be performed.

2.4 Secondary endpoints

Confirmatory secondary endpoints are analysed under multiplicity control.

2.4.1 Confirmatory secondary endpoints

If superiority is established for the primary endpoint, the superiority hypothesis stated in section 2.3.1 is tested for each of the confirmatory secondary endpoints under multiplicity control via a stagewise hierarchical testing scheme using the below order:

- Time from randomisation to first occurrence of 5-component composite CKD endpoint
- Time from randomisation to CV death
- Time from randomisation to first occurrence of MALE endpoint

For the type I error to be strongly controlled at one-sided level of 2.5% (Glimm et al[2]) the same alpha-spending function as for the primary endpoint (section 2.1) is used for the confirmatory secondary endpoints.
No adjustments of results for the confirmatory secondary endpoints due to the group sequential design will be done.

Table 2 provides an example of the nominal significance levels at interim and scheduled termination when the interim testing is conducted at exactly 2/3 of the planned number of primary endpoint events and where the number of events for the secondary endpoint at scheduled termination is 3/2 times the number of secondary endpoint events at the interim.

The actual nominal significance level will be based on the exact number of events available at the interim analysis.

Table 2 Nominal significance level for confirmatory secondary endpoints at interim and scheduled termination – an example

Stopping boundary scale	Interim	Scheduled termination
Nominal significance level	0.00605	0.02314

2.4.1.1 5-component composite CKD endpoint

Time from randomisation to first occurrence of a composite endpoint consisting of:

- Onset of persistent ≥ 50% reduction in eGFR (CKD-EPI) compared with baseline
- Onset of persistent eGFR (CKD-EPI) < 15 mL/min/1.73 m2
- Initiation of chronic renal replacement therapy (dialysis or kidney transplantation)
- Renal death
- CV death

The 5-component composite CKD endpoint is analysed using a Cox proportional hazards model as for the primary endpoint and addressing the primary estimand.

For the eGFR components, a persistent outcome in eGFR is defined as having two consecutive central laboratory assessments at least 4 weeks apart meeting the criteria. When classifying the events based on consecutive laboratory assessments, the date of the event is the date of the first sample meeting the definition.

If eGFR at baseline is persistent below 15 ml/min/1.73m2 the subject will still be included in the analysis as the subject still can experience one of the other four component events.

When classifying chronic renal replacement therapy or kidney transplantation, the date of event is the date of initiation of the therapy or surgery, respectively.

Missing data for eGFR values due to e.g. missing blood samples while patients are still being followed are not imputed, assuming no eGFR component events observed during in-trial observation period with missing eGFR values.

In the case that only a single eGFR value fulfils the criteria of ≥50% reduction in eGFR compared with baseline or eGFR <15 ml/min/1.73 m^2 Table 3 provides data handling rules for defining endpoint events. Any eGFR assessment made after initiation of chronic renal replacement therapy will not qualify as a confirmatory eGFR value.

Table 3 Data handling rules where only one initiating eGFR measurement meets the criteria of ≥50% eGFR reduction or eGFR <15 ml/min/1.73 m2

Rule number	Event: One eGFR value fulfilling the criteria * with a subsequent event without any confirmatory eGFR value measured >=4 weeks after the first eGFR measurement being available.	eGFR component	Date of event
1	CV or renal death	No	Date of death
2	Non-CV and non-renal death	No	Not applicable
3	Initiation of chronic renal replacement therapy	No	Date of initiation
4	Lost-to-follow-up or withdrawal of consent	No	Not applicable
5	One eGFR value fulfilling the criteria* at planned end-of-treatment visit	No	Not applicable

* ≥50% reduction in eGFR compared with baseline or eGFR <15 ml/min/1.73 m^2

A persistent outcome in eGFR in the in-trial period is considered on-treatment if the first of the two consecutive measurements falls within the on-treatment period, irrespective of whether the confirmatory eGFR value falls within the on-treatment period or not.

2.4.1.2 CV death

Time from randomisation to CV death is analysed using a Cox proportional hazards model as described for the primary endpoint and addressing the primary estimand.

2.4.1.3 MALE endpoint

Time from randomisation to first occurrence of MALE, a composite endpoint consisting of

- acute limb ischemia hospitalisation
- chronic limb ischemia hospitalisation

The MALE endpoint is analysed using a Cox proportional hazards model as described for the primary endpoint and addressing the primary estimand.

2.4.1.4 Sensitivity analyses

The two sensitivity analyses with imputation from subjects off treatment will be done for all confirmatory secondary endpoints (section 2.3.2).

Sensitivity analysis for the 5-component composite CKD endpoint

In the analysis for the 5-component composite CKD endpoint, missing data for scheduled central laboratory eGFR values are not imputed. The following sensitivity analysis using multiple imputation is planned. Prior to analysis, missing data are imputed using multiple imputation generating 500 data sets to account for the inherent uncertainty. The imputation is performed separately for each treatment group. In the first step, intermittent missing values are imputed using the Markov Chain Monte Carlo method based on an assumption of multivariate normality. In the second step, imputation of monotone missing values is done within subject groups defined by the treatment group and based on a sequential univariate regression approach. At each scheduled visit starting with the first post-baseline visit the imputation model includes baseline eGFR value and the previous post-baseline scheduled values (observed and imputed) prior to the visit being imputed as covariates. For each eGFR component of the 5-component composite CKD endpoint it is evaluated whether an eGFR event has occurred (yes/no) within the in-trial observation period. Intermittent imputed data are excluded from this evaluation.

After imputation of missing eGFR data, the 5-component composite CKD endpoint is derived, and the 500 multiple-imputed data sets are analysed with the primary Cox proportional hazards model described above. Patients that do not experience an event during the in-trial observation period are censored at the in-trial observation period end date. The resulting estimates of the log(HR) are combined using the methods of Rubin and back transformed to HR scale to draw inference.

2.4.1.5 Supplementary analyses

Supplementary analyses described in sections 2.3.3 for the primary endpoint, will similarly be done for the confirmatory secondary endpoints.

Supplementary analyses described in section 2.3.5 with regards to the impact of the COVID-19 pandemic and section 2.3.6 with regards to the potential impact of co-participation in COVID-19 trials will be done for the primary endpoint and the confirmatory secondary endpoints.

Supplementary analysis using CKD-EPI equation not including race

The equation used for estimating eGFR (CKD-EPI) for the confirmatory secondary endpoint, component composite CKD endpoint, incorporates age, sex and race. To fight racial bias in clinical trials a new equation where race is not incorporated has been introduced, as described in Inker et al. (2021)[3]. A supplementary analysis will be made using this new equation where race is not included to estimate eGFR using a Cox proportional hazards model as for the primary endpoint and addressing the primary estimand.

2.4.2 Supportive secondary endpoints

2.4.2.1 Time-to-event supportive secondary endpoints

Each of the TTE supportive secondary endpoints are analysed using the same Cox proportional hazards model as described for the primary endpoint and addressing the primary estimand. Competing risks for the relevant TTE endpoints can be seen in Table 5.

For the two time-to-event endpoints "Onset of persistent ≥50% reduction in eGFR" and "Onset of persistent eGFR <15 mL/min/1.73 m^2" an event of initiation of chronic renal replacement therapy acts as competing risk. For these two endpoints subject will be censored in the Cox model at time of initiation of chronic renal replacement therapy. In case of one eGFR measurement fulfilling the criteria and no available confirmatory test, the data handling rules are as described for the confirmatory secondary CKD endpoint in section 2.4.1.1

For the time-to-events endpoints involving eGFR, the analyses will exclude patients who already have met relevant renal components at baseline, except for the composite CKD endpoint where if eGFR at baseline is persistent below 15 ml/min/1.73m2 the subject will still be included in the analysis as the subject still can experience one of the other four component events.

For the endpoint "Onset of persistent ≥50% reduction in eGFR" only subjects with a valid baseline value will be included in the analysis.

Supplementary analyses

All-cause death: In addition, all-cause death is analysed using FAS and an extended in-trial observation period including the follow-up for vital status for subjects who withdraw consent or are LFTU. The relative risk for the binary endpoint (death/alive) will be compared between the two treatment groups using the likelihood ratio method. The model is chosen because it doesn't depend on the observation time which is only extended for subjects withdrawn or LTFU.

5-component MACE and 2-component HF: For the two endpoints 5-component expanded MACE and 2-component HF supplementary analyses will be done by replacing the CV death component with all-cause death.

MI and stroke: In the analyses of MI and stroke supplementary analyses including fatal MI and fatal stroke are performed. Thus, the supplementary analysis will analyse endpoints defined as:

- Time from randomisation to first MI (fatal or non-fatal)
- Time from randomisation to first stroke (fatal or non-fatal)

2.4.2.2 Continuous supportive secondary endpoints

The continuous supportive secondary endpoints (change from baseline to 2 years) are analysed using multiple imputation for missing values.
An imputation model (linear regression) is estimated separately for each treatment group including baseline value as a covariate and fitted to subjects having an observed data point (irrespective of adherence to randomised treatment) at year 2. Subjects without a baseline measurement will not be a part of the model. The fitted model is used to impute values for all subjects with missing data at 2 years to create 500 complete data sets. The complete data sets are analysed by an ANCOVA with treatment as fixed factor and baseline value as covariate. Rubin's rule is used to combine the results.

Additionally, change from baseline in hsCRP at year 2 is analysed using the above model. hsCRP is logarithmic transformed and the mean difference on the logarithmic scale is back-transformed to original scale and reported as geometric mean ratio.

2.4.2.3 Annual rate of change in eGFR

The annual rate (slope) of change in eGFR is compared between treatment groups based on a linear random regression model on eGFR values with treatment, time (as a continuous variable) and treatment time interaction as fixed effects, and including subject effect as a random intercept and time as a random slope. The random intercept and slope are assumed to be bivariate normal distributed with mean zero and an unstructured covariance matrix. The independent error term is assumed to be identical univariate normal distributed with mean zero. The model is fitted to observed scheduled eGFR data at baseline and post-baseline. The parameter of interest is the regression coefficient for the treatment and time interaction term, which measures the slope difference between oral semaglutide and placebo.

2.4.2.4 Analysis of recurrent events

Repeated occurrence of the same type of event over time for the same patient may happen. The following recurrent event endpoints are compared between the treatment arms from randomisation to end of trial:

- Number of MACE events
- Number of MI events (fatal or non-fatal)
- Number of stroke events (fatal or non-fatal)
- Number of MI and stroke events (fatal or non-fatal)
- Number of heart failure events (heart failure requiring hospitalisation or urgent heart failure visit)

Mean number of events is plotted as a function of study time and analysed using a marginal mean regression model for recurrent events accounting for competing risk of dying as described by Ghosh & Lin[4, 5]. Treatment effect is reported as a mean ratio and corresponding 95% robust CI to account for the dependency of within-subject of recurrent events.

2.4.2.5 Number of severe hypoglycaemic episodes

Number of severe hypoglycaemic episodes is analysed using the same marginal recurrent event regression model described above.

2.5 Exploratory endpoints

Change from baseline to year 2 and 3 in cognitive function: Montreal Cognitive Assessment (MoCA) score is compared between oral semaglutide and placebo using the same analysis as outlined above for continuous endpoints. If the trial is terminated earlier than planned (stopping after interim testing) change from baseline to 3 years may not be evaluated.
Refer to Table 8 for more details on the MoCA score.

The smoking endpoint is analysed at year 2 using a logistic regression model with treatment (oral semaglutide, placebo) and baseline smoking status (yes/no) as fixed factors. Missing data are handled by multiple imputation. The imputation model (logistic regression) is done separately for each treatment arm and includes baseline smoking status as a fixed factor and fitted to subjects having an observed data point (irrespective of adherence to randomised treatment) at year 2. The fitted model is used to impute values for all subjects with missing data (see section 2.2) at year 2.

Change from baseline to year 2 for the PROTECT endpoints are compared between oral semaglutide and placebo using the same analysis as outlined above for continuous endpoints.
Refer to Table 9 and Table 10 for more details on the PROTECT endpoints.

Table 7 gives an overview of planned analyses for all endpoints.

2.6 Other assessments

All systematically collected AEs, i.e. serious AEs and non-serious events requiring additional data collection as well as COVID-19 related AEs are summarised as number of subjects with events, proportion of subjects with events, number of events and rate of events according to treatment group. Summaries of SAEs are categorised by severity, relation to treatment, and outcome.

3 Interim testing

The trial design includes *one* pre-planned interim testing for superiority of the primary endpoint. The planned timing is when 817 events (two thirds of the planned total events) of the primary endpoint have been accrued. The interim testing is performed based on a locked snapshot of the study database. The date of the snapshot defines the interim analysis cut-off date for the interim testing.
Subjects without an EAC-confirmed primary endpoint event prior to the date of analysis cut-off are considered censored with the censoring date defined as the first of:

- in-trial observation period end-date
- analysis cut-off date

The same Cox model as described in section 2.3 is used for the interim testing addressing the primary estimand.

3.1 Role of DMC

Blinded and un-blinded data analyses during trial conduct are evaluated by the DMC, as described in the DMC charter. Trial integrity is ensured by using an external independent statistical service provider (independent of trial conduct and external to Novo Nordisk) to prepare these data and analyses for the DMC.

The DMC will evaluate the interim result and make recommendation to terminate the trial early for superiority if appropriate. The DMC evaluates the un-blinded interim results using the group sequential stopping boundary as guidance. Stopping the trial early for superiority is only allowed if the stopping boundary is crossed and the DMC makes the decision to recommend early trial termination based on this and other considerations as specified in the DMC charter.

Recommendations from the DMC back to Novo Nordisk and any other party will exclude any details of the interim results as to maintaining trial integrity.

3.2 Stopping boundary for superiority at interim

The exact number of primary endpoint events used for the interim testing is only known at the time of analysis, and the exact boundary is re-calculated using the Lan-DeMets alpha spending function.

3.3 Analysis on termination

If the trial is terminated early for superiority following the interim testing, definitive evaluation of superiority for the primary endpoint is performed based on all the available data at the end-of-trial, including overrun data. Overrun data include events happening between the cut-off date for the DMC interim testing and end-of-trial as well as additional confirmed events that were undergoing adjudication at the analysis cut-off time point. If the trial is not terminated early for superiority following the interim testing, the analysis at scheduled termination is performed when the planned number of 1,225 events has been accrued. The exact number of primary endpoint events used for the analysis on termination is only known at the time of analysis, and nominal significance level is updated based on the exact number of total accrued events and the Lan-DeMets alpha spending function. Similarly, the significance levels for the confirmatory secondary endpoints are updated

based on the exact number of events and all available data at end-of-trial are used for analyses of both secondary and exploratory endpoints.

For reporting of results for the primary endpoint (p-value, HR and 95% CI), the analysis on termination (either early or at scheduled termination) are adjusted for the group sequential design using the likelihood ratio ordering.

4 Changes to the statistical analyses planned in the protocol

In general, this SAP describes in more details the statistical analyses planned in the protocol.

SAP version 1.0 dated 12-MAR-2019

For the confirmatory secondary endpoint 5-component composite CKD the primary analysis is changed not to include multiple imputation for missing values of eGFR. Instead multiple imputation is done in a sensitivity analysis (section 2.4.1).

Sensitivity analysis for the primary endpoint updated to a 2-way tipping point analysis (section 2.3.2).

Additional analyses added in the SAP and not described in the protocol (section 2.3.3 and 2.4.2):

- Supplementary analyses for primary endpoint and confirmatory secondary endpoints:
  - Risk difference at year 3
  - Secondary estimand (on-treatment)
- Supplementary analyses for 5-component MACE and 2-component HF by replacing CV death component with all-cause death
- Analyses of MI and stroke using both fatal and non-fatal events
- Analysis of all-cause death using an extended in-trial observation period
- Recurrent event analyses for selected endpoints

SAP version 2.0 dated 14-DEC-2022

- Author has been deleted from front page
- It has been clarified that the independent statistician confirming the confirmatory analyses will also be blinded until DBL.
- The definition of baseline value has been updated, see Section 2.2.
- It has been clarified how missing data from subjects who are withdrawn or lost to follow-up are handled, see Section 2.2.
- Assessments of eGFR taken after initiation of chronic renal replacement therapy will not be used for analyses or summary tables (section 2.2)
- It has been clarified how subjects randomised more than once will contribute to the FAS, see Section 2.2.1.
- A definition of the first on-treatment observation period has been added, see Section 2.2.2. The use of it has been added in Sections 2.2.3 and 2.3.3.
- Figure 3 has been added illustrating the in-trial observation period used in analysis of time-to-event endpoints (section 2.2.5)
- It has been clarified that tied event times are handled using the exact method and risk limits are based on the profile likelihood, see section 2.2.5

- It has been specified that the absolute risk difference analysis will be based on the Aalen-Johansen estimator (section 2.3.3).

- Two sensitivity analyses have been added. The analyses impute event times for those that are lost to follow-up or withdrawn, based on the observed event rates for subjects that either go permanently off treatment (first analysis) or at least go off treatment once. (Section 2.3.2 and 2.4.1.5)

- Analyses added in the SAP version 2 that is not described in the protocol

  - Analysis of change from baseline in hsCRP, see Section 2.4.2.2.

  - Subgroup analysis based on peripheral artery disease (yes/no); age: <65, 65≤ to <75, ≥75 years; eGFR: < 30, 30 ≤ to < 45, 45 ≤ to < 60, ≥ 60 mL/min/1.73m^2 (CKD-EPI); EU has been changed to Europe and it has been clarified which region each country belongs to see Section 2.3.4.

  - A supplementary analysis of non-CV death has been added to evaluate the effect of competing risk on the primary endpoint, see Section 2.3.3.

  - Supplementary analyses evaluating the impact of the COVID-19 pandemic on the primary and confirmatory secondary endpoints have been added (section 2.3.5. 2.4.1.5).

  - Supplementary analyses evaluating the impact of co-participation in COVID-19 trials on the confirmatory endpoints have been added (section 2.3.6, 2.4.1.5).

  - A supplementary analysis using a new equation (CKD-EPI) where race is not included to estimate eGFR has been added (section 2.4.1.5)

  - Recurrent event analysis for MACE (section 2.4.2.4)

- For confirmatory secondary endpoints, the significance level used in the hierarchical testing procedure has been changed to follow a alpha spending function in order to control the type 1 error, see Section 2.4.1.

- The definition of eGFR components of confirmatory secondary endpoint in case of competing events (section 2.4.1.1) has been adjusted and a description of on-treatment for eGFR components has been added.

- The supplementary analysis for all cause death has been changed to be a comparison of relative risks for the binary endpoint death/alive (section 2.4.2.1).

- Clarification as to how the ANCOVA for continuous supportive secondary endpoints should be done has been added (section 2.4.2.2).

- For the analysis of MOCA it has been clarified when year 3 will be used (section 2.5)

- For the analysis of smoking, details of the imputation model has been added (section 2.5)

- Section 2.6 has been added
- It has been added that the significance level for the confirmatory secondary endpoints will be updated based on the exact number of events and that all available data at end-of-trial are used for both secondary and exploratory endpoints (section 3.3).
- The part describing that Novo Nordisk will replicate the interim analysis has been removed (section 3.3).
- Details on the endpoints MoCA and PROTECT have been added in Appendix 6.5 6.6.
- In general, editorial changes for alignment with SAPs for trials EX9536-4388 (SELECT) and NN9535-4321 (FLOW) has been made.

5 References

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6 Appendix

6.1 Handling of intercurrent events for the confirmatory endpoints

Table 4 Handling of intercurrent events for the confirmatory endpoints

Endpoint	Intercurrent event	Handling
Time to first occurrence of MACE	Treatment discontinuations Medication modifying cardio-renal risk Initiation of chronic renal replacement therapy	Events and follow-up time are collected after intercurrent events and used in the analysis
	Trial discontinuation (withdrawal of consent or lost-to follow-up)	Censoring at time of trial discontinuation
	Non-CV death (competing risk)	Censoring at time of non-CV death in the Cox model
Time to first occurrence of composite CKD	Treatment discontinuations Medication modifying cardio-renal risk	Events and follow-up time are collected after intercurrent events and used in the analysis
	Trial discontinuation (withdrawal of consent or lost-to follow-up)	Censoring at time of trial discontinuation
	Non-renal and Non-CV death (competing risk)	Censoring at time of non-renal or non-CV death in the Cox model
Time to occurrence of CV death	Treatment discontinuations Medication modifying cardio-renal risk Initiation of chronic renal replacement therapy	Events and follow-up time are collected after intercurrent events and used in the analysis
	Trial discontinuation (withdrawal of consent or lost-to follow-up)	Censoring at time of trial discontinuation
	Non-CV death (competing risk)	Censoring at time of non-CV death in the Cox model
Time to first occurrence of MALE	Treatment discontinuations Medication modifying cardio-renal risk Initiation of chronic renal replacement therapy	Events and follow-up time are collected after intercurrent events and used in the analysis
	Trial discontinuation (withdrawal of consent or lost-to follow-up)	Censoring at time of trial discontinuation
	All cause death (competing risk)	Censoring at time of death in the Cox model

6.2 List of time-to-event endpoints

Table 5 List of time-to-event endpoints

Endpoint	Composite order/details*	EAC**	Competing risk
Primary			
3-component MACE	- CV death - Non-fatal MI - Non-fatal stroke	Yes Yes Yes	Non-CV death
Confirmatory secondary			
5-component CKD	- Renal death - CV death - Initiation of chronic renal replacement therapy - Onset of persistent eGFR<15 ml/min/1.73 m2 - Onset of persistent ≥50% reduction in eGFR	Yes Yes Yes No No	Non-CV and non-renal death
CV death	–	Yes	Non-CV death
MALE	- Acute limb ischemia hospitalisation - Chronic limb ischemia hospitalisation	Yes Yes	All cause death
Supportive secondary			
3-component MACE with all cause death	- All-cause death - Non-fatal MI - Non-fatal stroke	Yes Yes Yes	None
5-component MACE	- CV death - Non-fatal MI - Non-fatal stroke - Coronary revascularisation - Unstable Angina hospitalisation	Yes Yes Yes No Yes	Non-CV death
2-component HF	- CV death - HHF or urgent HF Visit	Yes Yes	Non-CV death
4-component CKD	- Renal death - Initiation of chronic renal replacement therapy - Onset of persistent eGFR<15 ml/min/1.73 m2 - Onset of persistent ≥50% reduction in eGFR	Yes Yes No No	Non-renal death
All cause death	–	Yes	None
Non-fatal MI	–	Yes	All-cause death
Non-fatal stroke	–	Yes	All-cause death
HHF or urgent HF Visit	–	Yes	All-cause death
Coronary revascularisation	–	No	All-cause death
Unstable angina hospitalisation	–	Yes	All-cause death
Renal death	–	Yes	Non-renal death
Onset of persistent ≥50% reduction in eGFR	–	No	All-cause death and initiation of chronic renal replacement therapy
Onset of persistent eGFR<15	–	No	All-cause death and initiation of chronic renal replacement therapy
Initiation of chronic renal replacement therapy	–	Yes	All-cause death
Acute limb ischemia hospitalisation	–	Yes	All-cause death
Chronic limb ischemia hospitalisation	–	Yes	All-cause death
First severe hypoglycaemic episodes	–	No	All-cause death
No of severe hypoglycaemic episode	Recurrent events	No	All-cause death

* For composite endpoints this defines the hierarchy of components when reporting events contributing to a composite endpoint in the situation of ties of date of events of the components

** EAC-confirmed event

6.3 List of continuous and binary endpoints

Table 6 List of continuous and binary endpoints

Endpoint	Type	Details
Supportive secondary		
Annual rate of change in eGFR (total eGFR slope)	Continuous	From randomisation to end-of-trial
Change in HbA1c	Continuous	Change from randomisation to year 2
Change in Body weight	Continuous	Change from randomisation to year 2
Exploratory		
Change in MoCa score	Continuous	Change from randomisation to year 2
Change in MoCa score	Continuous	Change from randomisation to year 3
Smoking (yes/no)	Binary	Smoker at year 2
Change in Working Memory Index*	Continuous	Change from randomisation to year 2
Change in Verbal Reasoning*	Continuous	Change from randomisation to year 2
Change in Attentional Intensity Index*	Continuous	Change from randomisation to year 2
Change in Cognitive Reaction Time*	Continuous	Change from randomisation to year 2
Change in Sustained Attention Index*	Continuous	Change from randomisation to year 2

* Only relevant for English and/or Spanish speaking patients in Argentina, Canada, Colombia, Mexico, Spain, United Kingdom and United States

6.4 Overview of planned analyses for all endpoints

Table 7 Overview of planned analyses for all endpoints

Endpoint	**Model/method**	**Summary measure**	**Sensitivity analysis**	**Supplementary analysis**
Primary				
3-component MACE	Cox	Hazard ratio	2-way tipping point Analysis with imputations from subjects permanently off treatment Analysis with imputations from subjects off treatment	-Risk difference -First on-treatment -Subgroup analyses -Non-CV death - Excluding MACEs concurrent with COVID-19 SAE -Excluding MACEs concurrent with COVID-19 AE -Including non-CV deaths with concurrent COVID-19 SAE -censoring subjects who co-participate in COVID-19 trials
Confirmatory secondary				

	5-component CKD	Cox	Hazard ratio	Imputation of missing eGFR Analysis with imputations from subjects permanently off treatment Analysis with imputations from subjects off treatment	-Risk difference -First on-treatment - Excluding CKDs concurrent with COVID-19 SAE -Excluding CKDs concurrent with COVID-19 AE -Including non-CV, non-renal deaths with concurrent COVID-19 SAE -censoring subjects who co-participate in COVID-19 trials -Using eGFR equation where race was taken out of the equation
	CV deaths	Cox	Hazard ratio	Analysis with imputations from subjects permanently off treatment Analysis with imputations from subjects off treatment	-Risk difference -First on-treatment - Excluding CV deaths concurrent with COVID-19 SAE -Excluding CV deaths concurrent with COVID-19 AE -Including non-CV deaths with concurrent COVID-19 SAE -censoring subjects who co-participate in COVID-19 trials
	MALE	Cox	Hazard ratio	Analysis with imputations from subjects permanently off treatment Analysis with imputations from subjects off treatment	-Risk difference -First on-treatment - Excluding MALEs concurrent with COVID-19 SAE -Excluding MALEs concurrent with COVID-19 AE -Including all-cause deaths with concurrent COVID-19 SAE -censoring subjects who co-participate in COVID-19 trials
Supportive secondary					
	3-component MACE with all cause death	Cox	Hazard ratio	–	–
	5-component MACE	Cox	Hazard ratio	–	Including all-cause death
	2-component HF	Cox	Hazard ratio	–	Including all-cause death
	4-component CKD	Cox	Hazard ratio	–	

	All cause death	Cox	Hazard ratio	–	Relative risk extended in-trial period
	Non-fatal MI	Cox	Hazard ratio	–	-Including fatal MI -Recurrent events analysis (including fatal MI)
	Non-fatal stroke	Cox	Hazard ratio	–	-Including fatal stroke -Recurrent events analysis (including fatal stroke)
	MI and stroke (fatal or non-fatal)	Marginal mean regression	Mean ratio		
	HHF or urgent HF Visit	Cox	Hazard ratio	–	Recurrent events analysis
	Coronary revascularisation	Cox	Hazard ratio	–	–
	Unstable angina hospitalisation	Cox	Hazard ratio	–	–
	Renal death	Cox	Hazard ratio	–	–
	Onset of persistent ≥50% reduction in eGFR	Cox	Hazard ratio	–	–
	Onset of persistent eGFR<15	Cox	Hazard ratio	–	–
	Initiation of chronic renal replacement therapy	Cox	Hazard ratio	–	–
	Acute limb ischemia hospitalisation	Cox	Hazard ratio	–	–
	Chronic limb ischemia hospitalisation	Cox	Hazard ratio	–	–
	First severe hypoglycaemic episodes	Cox	Hazard ratio	–	–
	No of severe hypoglycaemic episodes	Marginal mean regression	Mean ratio	–	–
	Annual rate of change in eGFR (total slope)	Random regression model	Mean slope difference	–	–
	Change in HbA_{1c} to year 2	ANCOVA w MImp	Mean difference	–	–
	Change in body weight to year 2	ANCOVA w MImp	Mean difference	–	–
	Change in hsCRP at year 2*	ANCOVA w MImp, logarithmic scale	Mean difference		
Exploratory					
	Change in Montreal Cognitive Assessment score	ANCOVA w MImp	Mean difference	–	–
	Smoker at 2 years	Logistic regression and multiple imputation	Odds ratio	–	–
	Change in Working Memory Index**	ANCOVA w MImp	Mean difference	–	–
	Change in Verbal Reasoning**	ANCOVA w MImp	Mean difference	–	–
	Change in Attentional Intensity Index**	ANCOVA w MImp	Mean difference	–	–
	Change in Cognitive Reaction Time**	ANCOVA w MImp	Mean difference	–	–

	Change in Sustained Attention Index**	ANCOVA w MImp	Mean difference	–	–

ANCOVA w MImp = Analysis of covariance with multiple imputation. *Change from hsCRP at year 2 is not a defined endpoint in the protocol, but analysis is added in SAP.

** Only relevant for English and/or Spanish speaking patients in Argentina, Canada, Colombia, Mexico, Spain, United Kingdom and United States

6.5 MoCA

The MoCA is a cognitive test used for early detection of mild cognitive impairment.
The test checks different types of cognitive/thinking abilities: orientation, short-term memory, executive function/visuospatial ability, language, abstraction, animal naming, attention and clock-drawing test.
The endpoint used is the total score which is the sum of the score breakdowns specified in Table 8.
One point is added to the total score if the participant have 12 years or less of formal education (at baseline).
Lower MoCA score indicates greater cognitive impairment.

Table 8 MoCA score

Score breakdown	**Range**
Visuospatial and executive functioning	0-5
Animal naming	0-3
Attention	0-6
Language	0-3
Abstraction	0-2
Delayed recall (short-term memory)	0-5
Orientation	0-6
Total score	**0-30**

6.6 PROTECT

The PROTECT Cognitive Test Battery consists of 6 tests which produce 12 individual data points. Details can be seen in Table 9.
Based on the PROTECT tests 5 clinical endpoints are defined. More details on the 5 endpoints can be seen in Table 10.

Table 9 PROTECT tests and individual data points

Tests and data points	Unit	Outcome	Range
Self-ordered search			
Self Ordered Search	count	Total correct responses	0 to 40
Paired associate learning			
Paired Associate Learning	count	Total correct responses	0 to 16
Verbal reasoning			
Verbal reasoning score	count	Total correct responses minus total incorrect responses	-88 to 88
Simple Reaction Time			
Simple Reaction Time Median	msec	Median speed of individual correct responses	100 to 30000
Simple Reaction Time SD	msec	Standard Deviation of individual correct responses	0 to 30000
Digit vigilance			
Digit Vigilance Accuracy	%	Percentage of targets responded to within time window	0 to 100
Digit Vigilance Speed	msec	Mean speed of individual responses to targets within time window	150 to 1500
Digit Vigilance False Alarms	count	Number of responses falling outside of specified time window	0 to 999
Digit Vigilance Standard Deviation	msec	Standard Deviation of individual responses to targets within time window	0 to 1500
Choice reaction time			
Choice Reaction Time Accuracy	%	Percentage of stimuli responded to correctly	0 to 100
Choice Reaction Time Median	msec	Median speed of individual correct responses	150 to 30000
Choice Reaction Time SD	msec	Standard Deviation of individual correct responses	0 to 30000

Table 10 PROTECT endpoints

Endpoint	Derivation	Interpretation
Working memory index score	Self Ordered Search + Paired Associate Learning	• *Recalling the position of hidden objects* • A higher score indicates better cognitive function
Verbal reasoning score (count)	Verbal reasoning score	• *Understand and provide an answer* • A higher score indicates better cognitive function
Attentional intensity index (msec)	Simple Reaction Time Median + Digit Vigilance Speed + Choice Reaction Time Median	• *Intensity of concentration* • A lower score indicates better cognitive function
Cognitive reaction Time (msec)	Choice Reaction Time Median - Simple Reaction Time Median	• *Decision making time* • A lower score indicates better cognitive function
Sustained attention index (%-points)	((Choice Reaction Time Accuracy – 50) * 2 + (Digit Vigilance Accuracy* 0.45 - Digit Vigilance False Alarms) * 100/45) / 2	• *Stay focused* • A higher score indicates better cognitive function

6. Summary of changes to the statistical analysis plan

4 Changes to the statistical analyses planned in the protocol

In general, this SAP describes in more details the statistical analyses planned in the protocol.

SAP version 1.0 dated 12-MAR-2019

For the confirmatory secondary endpoint 5-component composite CKD the primary analysis is changed not to include multiple imputation for missing values of eGFR. Instead multiple imputation is done in a sensitivity analysis (section 2.4.1).

Sensitivity analysis for the primary endpoint updated to a 2-way tipping point analysis (section 2.3.2).

Additional analyses added in the SAP and not described in the protocol (section 2.3.3 and 2.4.2):

- Supplementary analyses for primary endpoint and confirmatory secondary endpoints:
  - Risk difference at year 3
  - Secondary estimand (on-treatment)
- Supplementary analyses for 5-component MACE and 2-component HF by replacing CV death component with all-cause death
- Analyses of MI and stroke using both fatal and non-fatal events
- Analysis of all-cause death using an extended in-trial observation period
- Recurrent event analyses for selected endpoints

SAP version 2.0 dated 14-DEC-2022

- Author has been deleted from front page
- It has been clarified that the independent statistician confirming the confirmatory analyses will also be blinded until DBL.
- The definition of baseline value has been updated, see Section 2.2.
- It has been clarified how missing data from subjects who are withdrawn or lost to follow-up are handled, see Section 2.2.
- Assessments of eGFR taken after initiation of chronic renal replacement therapy will not be used for analyses or summary tables (section 2.2)
- It has been clarified how subjects randomised more than once will contribute to the FAS, see Section 2.2.1.
- A definition of the first on-treatment observation period has been added, see Section 2.2.2. The use of it has been added in Sections 2.2.3 and 2.3.3.
- Figure 3 has been added illustrating the in-trial observation period used in analysis of time-to-event endpoints (section 2.2.5)
- It has been clarified that tied event times are handled using the exact method and risk limits are based on the profile likelihood, see section 2.2.5

- It has been specified that the absolute risk difference analysis will be based on the Aalen-Johansen estimator (section 2.3.3).

- Two sensitivity analyses have been added. The analyses impute event times for those that are lost to follow-up or withdrawn, based on the observed event rates for subjects that either go permanently off treatment (first analysis) or at least go off treatment once. (Section 2.3.2 and 2.4.1.5)

- Analyses added in the SAP version 2 that is not described in the protocol

  - Analysis of change from baseline in hsCRP, see Section 2.4.2.2.

  - Subgroup analysis based on peripheral artery disease (yes/no); age: <65, 65≤ to <75, ≥75 years; eGFR: < 30, 30 ≤ to < 45, 45 ≤ to < 60, ≥ 60 mL/min/1.73m^2 (CKD-EPI); EU has been changed to Europe and it has been clarified which region each country belongs to see Section 2.3.4.

  - A supplementary analysis of non-CV death has been added to evaluate the effect of competing risk on the primary endpoint, see Section 2.3.3.

  - Supplementary analyses evaluating the impact of the COVID-19 pandemic on the primary and confirmatory secondary endpoints have been added (section 2.3.5. 2.4.1.5).

  - Supplementary analyses evaluating the impact of co-participation in COVID-19 trials on the confirmatory endpoints have been added (section 2.3.6, 2.4.1.5).

  - A supplementary analysis using a new equation (CKD-EPI) where race is not included to estimate eGFR has been added (section 2.4.1.5)

  - Recurrent event analysis for MACE (section 2.4.2.4)

- For confirmatory secondary endpoints, the significance level used in the hierarchical testing procedure has been changed to follow a alpha spending function in order to control the type 1 error, see Section 2.4.1.

- The definition of eGFR components of confirmatory secondary endpoint in case of competing events (section 2.4.1.1) has been adjusted and a description of on-treatment for eGFR components has been added.

- The supplementary analysis for all cause death has been changed to be a comparison of relative risks for the binary endpoint death/alive (section 2.4.2.1).

- Clarification as to how the ANCOVA for continuous supportive secondary endpoints should be done has been added (section 2.4.2.2).

- For the analysis of MOCA it has been clarified when year 3 will be used (section 2.5)

- For the analysis of smoking, details of the imputation model has been added (section 2.5)

- Section 2.6 has been added
- It has been added that the significance level for the confirmatory secondary endpoints will be updated based on the exact number of events and that all available data at end-of-trial are used for both secondary and exploratory endpoints (section 3.3).
- The part describing that Novo Nordisk will replicate the interim analysis has been removed (section 3.3).
- Details on the endpoints MoCA and PROTECT have been added in Appendix 6.5 6.6.
- In general, editorial changes for alignment with SAPs for trials EX9536-4388 (SELECT) and NN9535-4321 (FLOW) has been made.

5 References

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Category: Other **Description:** I am a Deputy Editor for Diabetes Care and receive a quarterly honorarium for that activity **Additional Information:**		
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Category: Consultant **Description:** **Additional Information:**		
Bayer	Grant / Contract	Self
Recipient Name: Oregon Health and Science University **Grant / Contract Description:** site PI for FineOne trial **Additional Information:**	**Recipient Type:** Institution **Grant / Contract Purpose:** Research	
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Category: Consultant **Description:** **Additional Information:**		
Biogen	Data And Safety Monitoring	Self
Category: Data And Safety Monitoring **Description:** **Additional Information:**		
Lexicon Pharmaceuticals, Inc.	Grant / Contract	Self
Recipient Name: University of Michigan **Grant / Contract Description:** site PI for the RELIEF interventional trial **Additional Information:**	**Recipient Type:** Institution **Grant / Contract Purpose:** Research	
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Novo Nordisk	Consultant	Self
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Category: Consultant **Description:** Consulting **Additional Information:** Consulting		
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Boehringer Ingelheim (Phil.) Inc.	Grant / Contract	Other - Contract held by UNC. No salary support to PI
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   No.

Certification

I certify that the information provided in this disclosure is complete and accurate.

John Deanfield

Discloser Identifier: 1151616

Disclosure Purpose: 25-01006

Summary of Interests

Company or Organization

Entity	Type	Interest Held By
Aegerion Pharmaceuticals, Inc.	Other	Self
Category: Other **Description:** Received CME honoraria and/or consulting fees **Additional Information:**		
Amgen	Other	Self
Category: Other **Description:** Received CME honoraria and/or consulting fees **Additional Information:**		
AstraZeneca	Consultant	Self
Category: Consultant **Description:** **Additional Information:**		
Bayer	Other	Self
Category: Other **Description:** Received CME honoraria and/or consulting fees **Additional Information:**		
Boehringer Ingelheim	Other	Self
Category: Other **Description:** Received CME honoraria and/or consulting fees **Additional Information:**		
British Heart Foundation	Grant / Contract	Self
Recipient Name: Professor John Deanfield **Grant / Contract Description:** Progression of cardio-renal phenotypes in young people with type 1 diabetes: The AdDIT cohort **Additional Information:**	**Recipient Type:** Institution **Grant / Contract Purpose:** Research	
Merck	Other	Self
Category: Other **Description:** Received CME honoraria and/or consulting fees **Additional Information:**		
Novartis	Other	Self
Category: Other		

Entity	Type	Interest Held By
Description: Received CME honoraria and/or consulting fees **Additional Information:**		
Novo Nordisk	Other	Self
Category: Other **Description:** Received CME honoraria and/or consulting fees Member of SOUL and SELECT Study Steering Committees **Additional Information:**		
Pfizer	Other	Self
Category: Other **Description:** Received CME honoraria and/or consulting fees **Additional Information:**		
Sanofi	Other	Self
Category: Other **Description:** Received CME honoraria and/or consulting fees **Additional Information:**		

Additional Questions

1. **Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?**

   No.

2. **What is the manuscript title?**

   Oral Semaglutide and Cardiovascular Outcomes in Type 2 Diabetes

3. **Are you the corresponding author?**

   No.

Certification

I certify that the information provided in this disclosure is complete and accurate.

Scott Emerson

Discloser Identifier: 755030

Disclosure Purpose: 25-01006

Summary of Interests

Company or Organization

Entity	Type	Interest Held By
AstraZeneca Pharmaceuticals LP	Data And Safety Monitoring	Self
Category: Data And Safety Monitoring **Description:** DMCs in CKD and HTN **Additional Information:**		
Novo Nordisk AS	Consultant	Self
Category: Consultant **Description:** Steering Committees for Cardiovascular Outcome Trials of semaglutide in obesity/overweight (SELECT) and in type 2 diabetes (SOUL) (with earlier role on CVOT of insulin degludec) **Additional Information:**		

Additional Questions

1. **Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?**

   No.

2. **What is the manuscript title?**

   Cardiovascular Outcomes with Oral Semaglutide in People with Type 2 Diabetes

3. **Are you the corresponding author?**

   No.

Certification

I certify that the information provided in this disclosure is complete and accurate.

Feb 12, 2025 05:41:42 EST
New England Journal of Medicine

Mads Engelmann

Discloser Identifier: 999933

Disclosure Purpose: 25-01006

Summary of Interests

Company or Organization

Entity	Type	Interest Held By
Novo Nordisk AS	Employment	Self
Title: International Medical Vice President **Position Description:** Senior specialist with cross function CVD responsibility **Additional Information:** Full time employment		
Novo Nordisk AS	Stock	Self
Additional Information: Shareholder in Novo Nordisk AS		

Additional Questions

1. **Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?**

   No.

2. **What is the manuscript title?**

   Cardiovascular Outcomes with Oral Semaglutide in People with Type 2 Diabetes

3. **Are you the corresponding author?**

   No.

Certification

I certify that the information provided in this disclosure is complete and accurate.

Mette Gislum

Discloser Identifier: 1230608

Disclosure Purpose: 25-01006

Summary of Interests

I do not have any interests to disclose at this time.

Additional Questions

1. **Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?**

   No.

2. **What is the manuscript title?**

   Oral Semaglutide and Cardiovascular Outcomes in High-Risk Type 2 Diabetes

3. **Are you the corresponding author?**

   No.

Certification

I certify that the information provided in this disclosure is complete and accurate.

G. Kees Hovingh

Discloser Identifier: 999934

Disclosure Purpose: 25-01006

Summary of Interests

Company or Organization

Entity	Type	Interest Held By
Novo Nordisk AS	Employment	Self
Title: senior medical officer **Additional Information:**	**Position Description:** responsible for the medical and scientific evaluation of in-house and external development, mainly focused on CVS	
Novo Nordisk AS	Stock	Self
Additional Information:		

Additional Questions

1. **Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?**

   No.

2. **What is the manuscript title?**

   Oral Semaglutide and Cardiovascular Outcomes in Type 2 Diabetes

3. **Are you the corresponding author?**

   No.

Certification

I certify that the information provided in this disclosure is complete and accurate.

Silvio Inzucchi

Discloser Identifier: 9290

Disclosure Purpose: 25-01006

Summary of Interests

Company or Organization

Entity	Type	Interest Held By
AstraZeneca	Consultant	Self
Category: Consultant **Description:** **Additional Information:**		
AstraZeneca	Other	Self
Category: Other **Description:** Lectures supported by company or affiliates **Additional Information:**		
AstraZeneca	Travel	Self
Location(s): **Purpose:** **Additional Information:**		
Bayer	Consultant	Self
Category: Consultant **Description:** **Additional Information:**		
Bayer	Travel	Self
Location(s): **Purpose:** **Additional Information:**		
Boehringer Ingelheim	Other	Self
Category: Other **Description:** Medical writing support (while is reported by this company as 'transfer of value' (TOV)) **Additional Information:**		
Boehringer Ingelheim	Other	Self
Category: Other **Description:** Lectures supported by company or affiliates **Additional Information:**		
Boehringer Ingelheim	Consultant	Self
Category: Consultant		

Entity	Type	Interest Held By
Description: **Additional Information:**		
Boehringer Ingelheim	Travel	Self
Location(s): **Purpose:** **Additional Information:**		
Corcept Therapeutics	Consultant	Self
Category: Consultant **Description:** **Additional Information:**		
Merck	Consultant	Self
Category: Consultant **Description:** **Additional Information:**		
Novo Nordisk	Consultant	Self
Category: Consultant **Description:** **Additional Information:**		
Novo Nordisk	Travel	Self
Location(s): **Purpose:** **Additional Information:**		
PFIZER PHARMA GMBH	Consultant	Self
Category: Consultant **Description:** **Additional Information:**		

Additional Questions

1. **Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?**

   No.

2. **What is the manuscript title?**

   Oral Semaglutide and Cardiovascular Outcomes in Type 2 Diabetes,

3. **Are you the corresponding author?**

   No.

Certification

I certify that the information provided in this disclosure is complete and accurate.

Convey Global Disclosure System | AAMC

Johannes Mann

Discloser Identifier: 710809

Disclosure Purpose: 25-01006

Summary of Interests

Company or Organization

Entity	Type	Interest Held By
Bayer Healthcare	Consultant	Self
Category: Consultant **Description:** **Additional Information:**		
Cytel	End Point Review Committee	Self
Category: End Point Review Committee **Description:** **Additional Information:**		
Hexal AG	Other	Self
Category: Other **Description:** speaking engagement **Additional Information:**		
Idorsia	Data And Safety Monitoring	Self
Category: Data And Safety Monitoring **Description:** **Additional Information:**		
IQVIA	Data And Safety Monitoring	Self
Category: Data And Safety Monitoring **Description:** **Additional Information:**		
Kidney Disease Improving Global Outcomes	Consultant	Self
Category: Consultant **Description:** writing guidelines. chair of guideline committee on high blood pressure **Additional Information:**		
Labcorp	Data And Safety Monitoring	Self
Category: Data And Safety Monitoring **Description:** **Additional Information:**		
Novo Nordisk AS	Consultant	Self
Category: Consultant **Description:**		

Entity	Type	Interest Held By
Additional Information:		
Sanofi	Data And Safety Monitoring	Self
Category: Data And Safety Monitoring **Description:** **Additional Information:**		
UpToDate, Inc.	Other	Self
Category: Other **Description:** writing honoraria **Additional Information:**		

Additional Questions

1. **Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?**

   No.

2. **What is the manuscript title?**

   Oral Semaglutide and Cardiovascular Outcomes in Type 2 Diabetes.

3. **Are you the corresponding author?**

   No.

Certification

I certify that the information provided in this disclosure is complete and accurate.

Nikolaus Marx

Discloser Identifier: 471536

Disclosure Purpose: 25-01006

Summary of Interests

Company or Organization

Entity	Type	Interest Held By
AstraZeneca	Consultant	Self
Category: Consultant **Description:** Partcipation in advisory boards **Additional Information:**		
AstraZeneca	Other	Self
Category: Other **Description:** various lectures within 36 months **Additional Information:**		
Bayer	Consultant	Self
Category: Consultant **Description:** Participation in advisory boards **Additional Information:**		
Bayer	Other	Self
Category: Other **Description:** various lectures within 36 months **Additional Information:**		
Boehringer Ingelheim	Grant / Contract	Self
Recipient Name: University Hospital **Grant / Contract Description:** Independent Research grant **Additional Information:**	**Recipient Type:** Institution **Grant / Contract Purpose:**	
Boehringer Ingelheim	Consultant	Self
Category: Consultant **Description:** Participation in advisory boards **Additional Information:**		
Boehringer Ingelheim	Other	Self
Category: Other **Description:** various lecture within 36 months **Additional Information:**		
Bristol-Myers Squibb	Consultant	Self
Category: Consultant **Description:** Participation in advisory boards		

Entity	Type	Interest Held By
Additional Information:		
Bristol-Myers Squibb	Other	Self
Category: Other **Description:** various lectures within 36 months **Additional Information:**		
Lilly Deutschland	Other	Self
Category: Other **Description:** various lectures within 36 months **Additional Information:**		
Merck Sharp and Dohme	Other	Self
Category: Other **Description:** various lectures within 36 months **Additional Information:**		
Merck Sharp and Dohme	Consultant	Self
Category: Consultant **Description:** Participation in advisory boards **Additional Information:**		
Novo Nordisk	Grant / Contract	Self
Recipient Name: University Hospital Aachen **Grant / Contract Description:** independent research grant **Additional Information:**	**Recipient Type:** Institution **Grant / Contract Purpose:**	
Novo Nordisk	Other	Self
Category: Other **Description:** various lectures within 36 months **Additional Information:**		
Novo Nordisk	Consultant	Self
Category: Consultant **Description:** Participation in advisory boards **Additional Information:**		
Sanofi Aventis	Other	Self
Category: Other **Description:** Various lectures within 36 months **Additional Information:**		
Sanofi Aventis	Consultant	Self
Category: Consultant **Description:** Participation in advisory boards **Additional Information:**		

Additional Questions

1. **Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?**

   No.

2. **What is the manuscript title?**

   Oral Semaglutide and Cardiovascular Outcomes in Type 2 Diabetes

3. **Are you the corresponding author?**

   No.

Certification

I certify that the information provided in this disclosure is complete and accurate.

Darren McGuire

Discloser Identifier: 391260

Disclosure Purpose: 25-01006

Summary of Interests

Company or Organization

Entity	Type	Interest Held By
AbbVie	Other	Self
Category: Other **Description:** Trial leadership **Additional Information:**		
Afimmune	Consultant	Self
Category: Consultant **Description:** Consultant **Additional Information:**		
Alnylam Pharmaceuticals Inc.	Consultant	Self
Category: Consultant **Description:** consultant **Additional Information:**		
Altimmune	Consultant	Self
Category: Consultant **Description:** consultant **Additional Information:**		
Alveus Therapeutics	Consultant	Self
Category: Consultant **Description:** **Additional Information:**		
Alveus Therapeutics	Consultant	Self
Category: Consultant **Description:** consulltant **Additional Information:**		
American Heart Association	Other	Self
Category: Other **Description:** Deputy Editor, Circulation **Additional Information:**		
Amgen Inc.	Consultant	Self
Category: Consultant **Description:**		

Entity	Type	Interest Held By
Additional Information:		
Applied Therapeutics	Consultant	Self
Category: Consultant **Description:** consultant **Additional Information:**		
Arena Pharmaceuticals	Data And Safety Monitoring	Self
Category: Data And Safety Monitoring **Description:** Clinical Trial IDMC member **Additional Information:**		
Arrowhead Pharmaceuticals	Consultant	Self
Category: Consultant **Description:** **Additional Information:**		
AstraZeneca	Other	Self
Category: Other **Description:** Trial Executive Committee **Additional Information:**		
Bayer	Data And Safety Monitoring	Self
Category: Data And Safety Monitoring **Description:** idmc **Additional Information:**		
Bayer Healthcare	Consultant	Self
Category: Consultant **Description:** consultant **Additional Information:**		
Beren Pharmaceutical	Data And Safety Monitoring	Self
Category: Data And Safety Monitoring **Description:** trial IDMC member **Additional Information:**		
Boehringer Ingelheim	Consultant	Self
Category: Consultant **Description:** consultant **Additional Information:**		
Boehringer Ingelheim	Expert Witness	Self
Category: Expert Witness **Description:** Patent Lawsuit; paid by Kirkland & Ellis representing Boehringer Ingelheim **Additional Information:**		
CSL Behring	Data And Safety Monitoring	Self
Category: Data And Safety Monitoring **Description:** trial IDMC member		

Entity	Type	Interest Held By
Additional Information:		
Dynavax	Data And Safety Monitoring	Self
Category: Data And Safety Monitoring **Description:** trial IDMC member **Additional Information:**		
Eidos Pharmaceuticals	Data And Safety Monitoring	Self
Category: Data And Safety Monitoring **Description:** Clnical Trial IDMC member **Additional Information:**		
Eli Lilly and Company	Other	Self
Category: Other **Description:** Trial Executive Committee **Additional Information:**		
Eli Lilly and Company	Consultant	Self
Category: Consultant **Description:** Global Advisory Board **Additional Information:**		
Esperion Therapeutics, Inc.	Other	Self
Category: Other **Description:** national lead investigator **Additional Information:**		
Esperion Therapeutics, Inc.	Consultant	Self
Category: Consultant **Description:** consultant **Additional Information:**		
GlaxoSmithKline	Consultant	Self
Category: Consultant **Description:** **Additional Information:**		
INTERCEPT PHARMACEUTICALS, INC.	Consultant	Self
Category: Consultant **Description:** consultant **Additional Information:**		
Ipsen Bioscience Inc	Consultant	Self
Category: Consultant **Description:** **Additional Information:**		
Kailera	Consultant	Self

Entity	Type	Interest Held By
Category: Consultant **Description:** **Additional Information:**		
Lexicon Pharmaceuticals, Inc.	Consultant	Self
Category: Consultant **Description:** consultant **Additional Information:**		
Merck	Consultant	Self
Category: Consultant **Description:** Global Advisory Board **Additional Information:**		
Merck	Other	Self
Category: Other **Description:** Trial Executive Committee **Additional Information:**		
Metavant	Consultant	Self
Category: Consultant **Description:** consultant **Additional Information:**		
Metsera	Consultant	Self
Category: Consultant **Description:** **Additional Information:**		
neurotronics	Consultant	Self
Category: Consultant **Description:** consultant **Additional Information:**		
new amsterdam	Other	Self
Category: Other **Description:** trial executive committee **Additional Information:**		
Novo Nordisk	Consultant	Self
Category: Consultant **Description:** Global Advisory Board **Additional Information:**		
Novo Nordisk	Other	Self
Category: Other **Description:** Trial Chairperson **Additional Information:**		
Otsuka Pharmaceutical	Data And Safety Monitoring	Self

Entity	Type	Interest Held By
Category: Data And Safety Monitoring **Description:** trial IDMC member **Additional Information:**		
Pfizer	Data And Safety Monitoring	Self
Category: Data And Safety Monitoring **Description:** IDMC **Additional Information:**		
Pfizer	Consultant	Self
Category: Consultant **Description:** consultant **Additional Information:**		
Pfizer	Other	Self
Category: Other **Description:** Trial Executive Committee **Additional Information:**		
Sage Publications	Other	Self
Category: Other **Description:** Clinical Trials Editor; Diabetes and Vascular Disease Research **Additional Information:**		
Sarepta Therapeutics, Inc.	Consultant	Self
Category: Consultant **Description:** consultant **Additional Information:**		
University of Texas Southwestern Medical Center	Employment	Self
Title: Professor of Internal Medicine **Additional Information:**	**Position Description:** faculty cardiologist	
Ventyx	Data And Safety Monitoring	Self
Category: Data And Safety Monitoring **Description:** IDMC **Additional Information:**		

Additional Questions

1. **Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?**

   No.

2. **What is the manuscript title?**

   Oral Semaglutide and Cardiovascular Outcomes in Type 2 Diabetes

3. **Are you the corresponding author?**

   Yes.

a. **Please list the other authors' names here.**

Nikolaus Marx, M.D., Sharon L. Mulvagh, M.D., John Deanfield, M.D., Silvio E. Inzucchi, M.D., Rodica Pop-Busui, M.D., Ph.D., Johannes F. E. Mann, M.D., Scott Emerson, M.D., Ph.D., Neil Poulter, F.Med.Sci., Mads D. Engelmann, M.D., Ph.D., Maria Sejersten Ripa, M.D., M.D.Sc, G. Kees Hovingh, M.D., Ph.D., Kirstine Brown-Frandsen, M.D., Stephen C. Bain, M.D., Matthew A. Cavender, M.D., M.P.H., Mette Gislum, M.Sc., Jens-Peter David, Ph.D., and John B. Buse, M.D., Ph.D., on behalf of the SOUL Study Group*

Certification

I certify that the information provided in this disclosure is complete and accurate.

Feb 11, 2025 06:22:42 EST
New England Journal of Medicine

Sharon Mulvagh

Discloser Identifier: 1230603

Disclosure Purpose: 25-01006

Summary of Interests

Company or Organization

Entity	Type	Interest Held By
Merck	Consultant	Self
Category: Consultant **Description:** **Additional Information:**		
Novo Nordisk	Consultant	Self
Category: Consultant **Description:** Steering Committee SOUL Clinical Trial **Additional Information:**		

Additional Questions

1. **Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?**

   No.

2. **What is the manuscript title?**

   Oral Semaglutide and Cardiovascular Outcomes in Type 2 Diabetes

3. **Are you the corresponding author?**

   No.

Certification

I certify that the information provided in this disclosure is complete and accurate.

Feb 13, 2025 11:18:54 EST
New England Journal of Medicine

Neil Poulter

Discloser Identifier: 335929

Disclosure Purpose: 25-01006

Summary of Interests

Company or Organization

Entity	Type	Interest Held By
AstraZeneca	Other	Self
Category: Other **Description:** Lectures **Additional Information:**		
Servier Affaires Medicales	Grant / Contract	Self
Recipient Name: **Grant / Contract Description:** **Additional Information:**	**Recipient Type:** **Grant / Contract Purpose:**	
Servier Affaires Medicales	Consultant	Self
Category: Consultant **Description:** Servier, Aktiia, Alnylam **Additional Information:**		

Additional Questions

1. **Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?**

   No.

2. **What is the manuscript title?**

   Oral Semaglutide and Cardiovascular Outcomes in Type 2 Diabetes

3. **Are you the corresponding author?**

   No.

Certification

I certify that the information provided in this disclosure is complete and accurate.

Feb 24, 2025 03:12:37 EST
New England Journal of Medicine

Maria Ripa

Discloser Identifier: 1230605

Disclosure Purpose: 25-01006

Summary of Interests

Company or Organization

Entity	Type	Interest Held By
Novo Nordisk AS	Employment	Self
Title: IMD **Position Description:** **Additional Information:**		
Novo Nordisk AS	Stock	Self
Additional Information:		

Additional Questions

1. **Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?**

   No.

2. **What is the manuscript title?**

   Oral Semaglutide and Cardiovascular Outcomes in Type 2 Diabetes

3. **Are you the corresponding author?**

   No.

Certification

I certify that the information provided in this disclosure is complete and accurate.

Data Sharing Statement

McGuire DK, Marx N, Mulvagh SL, et al. Oral Semaglutide and Cardiovascular Outcomes in High-Risk Type 2 Diabetes. N Engl J Med. DOI: 10.1056/NEJMoa2501006.

Question	Authors' Response
Will the data collected for your study be made available to others?	Yes
Would you like to offer context for your decision?	—
Which data?	Complete de-identified patient data set
Additional information about data	Individual participant data will be shared in data sets in a deidentified/anonymized format.
How or where can the data be obtained?	The data will be made available on a specialized SAS data platform.
When will data availability begin?	The data will be available permanently after research completion and approval of product and product use in both EU and US.
When will data availability end?	No end date.
Will any supporting documents be available?	Yes
Which supporting documents?	Other
Additional information about supporting documents	Study protocol and redacted Clinical Study Report (CSR).
How or where can supporting documents be obtained?	The study protocol is submitted together with the manuscript, available at nejm.org.
When will supporting documents availability begin?	At publication of the manuscript.
When will supporting documents availability end?	At publication of the manuscript.
To whom will data be available?	Data will be shared with bona fide researchers submitting a research proposal requesting access to data for use.
For what type of analysis or purpose?	For use as approved by the Independent Review Board according to the IRB Charter (see novonordisk-trials.com).
By what mechanism?	Access request proposal form and the access criteria can be found at novonordisk-trials.com.
Any other restrictions?	-

Additional information	Novo Nordisk is committed to sharing information about Novo Nordisk-sponsored clinical research completed after 2001 for product indications approved in both the EU and US.

This statement was posted on March 29, 2025, at NEJM.org.