Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
NCT number	NCT04707469
Sponsor trial ID:	NN9924-4635
Official title of study:	Efficacy and safety of once-daily oral semaglutide 25 mg and 50 mg compared with 14 mg in subjects with type 2 diabetes
Document date:	16 September 2022

*Document date refers to the date on which the document was most recently updated.

Protocol
PIONEER PLUS

NN9924-4635

Including:
Amendment 1, dated 09 November 2020
Amendment 2, dated 04 March 2021
Amendment 3, Croatia and Germany, dated 28 April 2021
Amendment 4, dated 04 June 2021
Amendment 5, dated 01 February 2022
Amendment 6, dated 16 September 2022

Protocol title:

Efficacy and safety of once-daily oral semaglutide 25 mg and 50 mg compared with 14 mg in subjects with type 2 diabetes

Substance: Semaglutide

Universal Trial Number: U1111-1247-0210

EudraCT Number: 2020-000299-39

Trial phase: 3b

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

Protocol amendment summary of changes table

DOCUMENT HISTORY		
Document version	Date	Applicable in country(-ies) and/or site(s)
Protocol version 7.0 (including protocol amendment no. 1, 2, 3, 4, 5 and 6)	16 September 2022	Global
Protocol version 6.0 (including protocol amendment no. 1, 2, 3, 4 and 5)	01 February 2022	Global
Protocol version 5.0 (including protocol amendment no. 1, 2, 3 and 4)	04 June 2021	Global
Protocol version 4.0 (including protocol amendment no. 1, 2 and 3)	28 April 2021	For Croatia and Germany only
Protocol version 3.0 (including protocol amendment no. 1 and 2)	04 March 2021	Global
Protocol version 2.0 (including protocol amendment no. 1)	09 November 2020	Global
Original protocol version 1.0	08 July 2020	Global

Protocol version 7.0 (16 September 2022)

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

Overall rationale for preparing protocol, version 7.0:

The overall rationale for the changes implemented in the amended protocol is to add a description of the existing possibility to go back and evaluate previous ECG data in case of unforeseen or abnormal observations that could indicate safety findings and specify content and impact of the planned partial database lock. Furthermore, a numerical error has been corrected in Table 9-2.

Section # and name	Description of change	Brief rationale
8.2.3 Electrocardiograms	Reason for central storage of ECG data has been provided. **Bold** text added in below paragraph: 'The ECGs will be collected for central storage for potential future assessment. **This is to have the possibility to go back and evaluate previous ECG data in case of unforeseen or abnormal observations that could indicate safety findings or for future scientific purposes related to semaglutide, T2D, CV outcome or related diseases.**'	To clarify and describe the purpose of the ECG collection with the possibility of future evaluation.
9.2 Sample size determination	The treatment difference (TD) for HbA_{1c} (%-point) for the 50 mg dose has been corrected in the first five rows of the first column of Table 9-2.	To accommodate feedback from FDA: The TD was incorrectly stated here as -0.53
9.5 Interim analyses	Added reference to Section 9.7.	To accommodate feedback from FDA.
9.7 Reporting of the main part of the trial	Content and impact of the planned partial database lock have been specified before unblinding of data.	To accommodate feedback from FDA.

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1 Protocol summary

1.1 Synopsis

Rationale

The currently approved oral semaglutide maintenance doses are 7 mg and 14 mg[2], and the approval was based on the comprehensive global clinical phase 3a development programme (the PIONEER programme). Although oral semaglutide provided clinically relevant benefits for subjects with type 2 diabetes (T2D) at all disease stages in the PIONEER programme, approximately 20-40% of the subjects did not achieve the recommended level of glycaemic control (HbA_{1c} <7%). Oral semaglutide dose levels higher than 14 mg may enable such subjects to achieve adequate glycaemic control.

Dose-dependent effects of oral semaglutide at doses exceeding the currently maximum approved dose for the treatment of T2D (14 mg once daily), have been demonstrated in relation to glycaemic control and body weight (NN9924-3790). The 40 mg dose level reduced HbA_{1c} by 1.9 %-points and body weight by 7 kg.

To support the approval of higher dose levels of oral semaglutide in T2D, the present randomised controlled clinical trial is designed to compare the efficacy, safety and tolerability of oral semaglutide 14 mg, 25 mg and 50 mg in subjects with T2D.

Objectives and endpoints

Primary objective	To confirm superiority of oral semaglutide 25 mg and 50 mg once daily versus oral semaglutide 14 mg once daily on HbA_{1c} reduction in subjects with T2D on stable dose of 1-3 OADs.
Secondary objectives	To confirm superiority of oral semaglutide 25 mg and 50 mg once daily versus oral semaglutide 14 mg once daily on body weight reduction in subjects with T2D on a stable dose of 1-3 OADs.
	To compare the efficacy of oral semaglutide 25 mg and 50 mg once daily versus oral semaglutide 14 mg once daily on parameters related to glycaemic control in subjects with T2D on a stable dose of 1-3 OADs.
	To compare the efficacy of oral semaglutide 25 mg and 50 mg once daily versus oral semaglutide 14 mg once daily on parameters related to weight-related outcomes in subjects with T2D on a stable dose of 1-3 OADs.
	To compare the safety and tolerability of oral semaglutide 25 mg and 50 mg once daily versus oral semaglutide 14 mg once daily in subjects with T2D on stable dose of 1-3 OADs.

Estimands

For the primary and the confirmatory secondary objective, estimands of primary interest and additional estimands are defined. The estimands are used to address the trial objectives in terms of two different aspects of the treatment effect of oral semaglutide 14, 25 and 50 mg.

The primary and secondary estimands address the primary questions of interest: What is the efficacy of oral semaglutide 25 and 50 mg versus oral semaglutide 14 mg on change from baseline to week 52 in HbA_{1c} (primary objective) and body weight (confirmatory secondary objective) in

subjects with T2D on stable dose of 1-3 OADs regardless of treatment discontinuation, changes in dose and initiation of additional anti-diabetic medication.

The additional estimands address additional questions of interest: What is the efficacy of oral semaglutide 25 and 50 mg versus oral semaglutide 14 mg on change from baseline to week 52 in HbA_{1c} (primary objective) and body weight (confirmatory secondary objective) in subjects with T2D on stable dose of 1-3 OADs regardless of change in dose of trial treatment and if all subjects had remained on trial treatment without use of rescue medication.

Similar estimands are defined for the other secondary efficacy objectives.

Primary endpoint

Endpoint title	Timeframe	Unit
Change in glycated haemoglobin (HbA_{1c})	From baseline (week 0) to week 52	%-point

Secondary confirmatory endpoint

Endpoint title	Timeframe	Unit
Change in body weight	From baseline (week 0) to week 52	kg

Supportive secondary endpoints

Endpoint title	Timeframe	Unit
Change in fasting plasma glucose (FPG)	From baseline (week 0) to week 52	mmol/l
Achievement of HbA_{1c} <7% (Yes/No)	At week 52	Count of subjects
Achievement of HbA_{1c} ≤6.5% (Yes/No)	At week 52	Count of subjects
Relative change in body weight	From baseline (week 0) to week 52	Percentage (%)
Change in waist circumference	From baseline (week 0) to week 52	cm
Achievement of weight loss ≥5% (Yes/No)	At week 52	Count of subjects
Achievement of weight loss ≥10% (Yes/No)	At week 52	Count of subjects
Adverse events	From baseline (week 0) to follow-up visit (week 73)	Count of events

Overall design

This is a 68-week, randomised, active-controlled, double-blinded, three-armed, multi-centre, multinational clinical trial comparing the efficacy, safety and tolerability of once-daily oral semaglutide 25 mg, 50 mg and 14 mg (the current maximum maintenance dose) in subjects with T2D, on stable doses of 1-3 oral anti-diabetic drugs (OADs) (metformin, sulfonylureas, SGLT2 inhibitors, DPP-4 inhibitors).

Subjects will be randomised to receive maintenance doses of either 14 mg, 25 mg or 50 mg oral semaglutide once daily. Randomisation will be stratified on baseline oral anti-diabetic medication and will include a total of 8 strata for combinations of sulfonylureas, SGLT2 inhibitors, and terminated DPP-4 inhibitors. Metformin is not included in the stratification.

Key inclusion criteria

- Male or female, age above or equal to 18 years at the time of signing informed consent.
- Diagnosed with type 2 diabetes mellitus ≥ 180 days prior to the day of screening.
- HbA_{1c} of 8.0-10.5% (64−91 mmol/mol) (both inclusive).

- BMI ≥ 25 kg/m^2.
- Stable daily dose(s) for 90 days prior to the day of screening of: any of the following treatment regimens:
    - No more than 3 of the following oral anti-diabetic drugs and at least 1 marked with a *:
        - * Metformin (≥1500 mg or maximum tolerated or effective dose).
        - * Sulfonylureas (SU) (≥half of the maximum approved dose according to local label or maximum tolerated or effective dose).
        - * SGLT2 inhibitors (maximum tolerated dose).
        - DPP-4 inhibitors (maximally indicated dose as per local label).
- Subjects, on treatment with stable dose of DPP-4 inhibitors at inclusion, must be willing to terminate DPP-4 inhibitor treatment at randomisation (with no wash-out).

Key exclusion criteria

- Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria within the past 90 days prior to the day of screening. However, short term insulin treatment for a maximum of 14 days prior to the day of screening is allowed.
- Renal impairment measured as estimated glomerular filtration rate (eGFR) value of <30 mL/min/1.73 m^2 according to Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation as defined by KDIGO 2012 classification.
- 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.

Number of subjects
1620 subjects will be randomly assigned to trial treatment.

Treatment groups and duration
The planned total duration for each subject will be approximately 75 weeks. The trial includes a screening period of approximately two weeks followed by randomisation. Oral semaglutide will be dosed once daily starting with a dose escalation period of up to 16 weeks followed by a maintenance period of minimum 52 weeks. The duration of dose escalation period will depend on the maintenance dose to be reached, but the total dose escalation and maintenance period comprises 68 weeks for all three treatment arms. All subjects will enter a 5-week follow-up period after the end-of-treatment visit.

Tablets of oral semaglutide (3 mg, 7 mg, 14 mg, 25 mg, 50 mg) in dose packs and/or HDPE bottles will be provided by Novo Nordisk A/S.

The trial products will not be available to subjects after the end of trial.

Trial data monitoring committee: No

1.2 Flowchart

	Protocol sections	Screening	Randomisation	Dose escalation/ maintenance period					Maintenance period								End of treatment	Follow-up
Visit		V1	V2	V3	V4	V5	P6	V7	P8	V9	V10	V11	V12	V13	V14	V15	V16	V17
Timing of Visit		-2W	0W	4W	8W	12W	14W	16W	18W	20W	26W	32W	38W	44W	52W	60W	68W	73W
Visit Window (Days)		±7	±0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3
Informed Consent and Demography [a]	10.1.3	X																
Eligibility Criteria	5.1,5.2	X	X															
Randomisation			X															
Discontinuation Criteria	7.1			X	X	X	X	X	X	X	X	X	X	X	X	X		
Concomitant Medication	6.5	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medical History/Concomitant Illness	8.2	X																
Tobacco Use [b]		X																
Pregnancy Test [c]	8.3.5,10.4	X															X	X
Height	8.2.1	X																
Body Weight	8.1.2	X	X	X	X	X		X		X	X	X	X	X	X	X	X	
Waist circumference	8.1.3		X								X				X		X	
ECG	8.2.3		X								X						X	
Adverse Event	8.3,10.3	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hypoglycaemic Episodes	10.6		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments	10.2	X	X	X	X	X		X		X	X	X	X	X	X	X	X	X
Attend Visit Fasting	5.3.1		X	X		X		X			X				X		X	
PK Sampling	8.5			X		X		X			X				X		X	
Eye Examination	8.2.4	X													X		X	
Physical Examination	8.2.1	X													X		X	
Vital Signs	8.2.2	X	X	X	X	X		X		X	X	X	X	X	X		X	
Dispensing Visit	6.1, 6.3, 5.3.1		X	X	X	X		X		X	X	X	X	X	X	X		

	Protocol sections	Screening	Randomisation	Dose escalation/ maintenance period					Maintenance period								End of treatment	Follow-up
Visit		V1	V2	V3	V4	V5	P6	V7	P8	V9	V10	V11	V12	V13	V14	V15	V16	V17
Timing of Visit		-2W	0W	4W	8W	12W	14W	16W	18W	20W	26W	32W	38W	44W	52W	60W	68W	73W
Visit Window (Days)		±7	±0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3
Drug Accountability	6.4		X	X	X	X		X		X	X	X	X	X	X	X	X	
IWRS Session		X	X	X	X	X		X		X	X	X	X	X	X	X	X	
Hand Out ID Card		X																
Hand Out and Instruct in Diary	8	X	X	X	X	X		X		X	X	X	X	X	X	X	X	
Hand Out and Instruct in BG-meter	10.6		X															
Hand Out of Urine Kit [d]	10.2	X			X					X				X		X		
Hand Out of Pregnancy Test	8.3.5, 10.4		X															

Footnotes:

a: Demography consists of year of birth, sex, race and ethnicity (according to local regulation)

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

c: For women of childbearing potential only. In addition to the planned assessment at screening, end of treatment and follow-up, urine dipstick pregnancy test should be performed at any time during the trial if a menstrual period is missed, or if pregnancy is suspected, or as required by local law.

d: This urine kit can be handed out at an earlier visit for subjects who discontinue trial treatment prematurely and do not attend the V15 visit.

2 Introduction

Semaglutide is a potent glucagon-like peptide-1 receptor agonist (GLP-1 RA) with a high degree of homology to human GLP-1. GLP-1 RAs are recommended for the treatment of patients with type 2 diabetes (T2D) with inadequate glycaemic control and a need to minimize weight gain, promote weight loss or minimize hypoglycaemia.[3] Guidelines have recently been updated to recommend GLP-1 RAs for patients with T2D and high cardiovascular (CV) risk, established cardiovascular disease (CVD), or chronic kidney disease (CKD).[4]

Oral semaglutide (Rybelsus®) is the first peptide-based anti-diabetic therapy available for oral administration. Based on a comprehensive global clinical development programme (PIONEER), once-daily oral semaglutide at dose levels 3, 7 and 14 mg was recently approved as an adjunct to diet and exercise to improve glycaemic control in adults with T2D.

In addition, semaglutide is approved as a subcutaneous (s.c.) formulation (Ozempic®, NN9535, based on the global clinical phase 3a programme SUSTAIN) for once-weekly administration for the treatment of T2D and reduction of CV risk in patients with T2D and established CV disease.

2.1 Trial rationale

The currently approved oral semaglutide maintenance doses are 7 mg and 14 mg[2]. Although oral semaglutide provided clinically relevant benefits for subjects with T2D at all disease stages, approximately 20-40% of the subjects in the PIONEER programme did not achieve the recommended level of glycaemic control (HbA_{1c} <7%). Oral semaglutide dose levels higher than 14 mg may enable such subjects to achieve adequate glycaemic control.

Dose-dependent effects of oral semaglutide, at doses exceeding the currently maximum maintenance dose for the treatment of T2D, have been demonstrated in relation to glycaemic control and body weight (trial NN9924-3790).

To support the approval of higher dose levels of oral semaglutide in T2D, the present randomised controlled clinical trial is designed to compare the efficacy, safety and tolerability of oral semaglutide 14 mg, 25 mg and 50 mg in subjects with T2D. See Section 4.3 for details on the justification of dose.

2.2 Background

The PIONEER programme was a comprehensive clinical programme and including 10 phase 3a trials comprising 9,543 subjects with T2D, of whom 5,707 were exposed to oral semaglutide. The programme confirmed a favourable benefits/risk profile of oral semaglutide in a broad and representative population of subjects with T2D, ranging from treatment-naïve to insulin-requiring subjects, subjects with micro- and macrovascular disease and subjects with moderate renal impairment. Clinically relevant and sustained improvements in glycaemic control and reductions in body weight were demonstrated with the approved maintenance doses of oral semaglutide, and the safety and tolerability profiles of oral semaglutide were consistent with those of other GLP-1 RAs.[5]

By week 26 in the PIONEER phase 3a programme, oral semaglutide 14 mg had reduced HbA_{1c} by up to 1.4% and body weight by 4.4 kg and enabled around 60-80% of the subjects to achieve HbA_{1c} <7%[5]. At week 52, the proportion of subjects who had achieved HbA_{1c} <7% was similar to

that at week 26. Hence, 20-40% of subjects had not achieved the recommend glycaemic goal by week 26 or 52.

Dose-dependent reductions in HbA_{1c} and body weight with oral semaglutide at dose levels up to 40 mg (i.e. around 3 times the currently approved maximum dose level) were demonstrated in the oral semaglutide dose-finding phase 2 trial (NN9924-3790). The 40 mg dose level reduced HbA_{1c} by 1.9 %-points and body weight by 7 kg.

The proportion of subjects with adverse events (AEs) and the number of AEs increased with increasing oral semaglutide dose in trial NN9924-3790. The proportion of subjects who discontinued treatment prematurely due to an AE was higher with oral semaglutide compared to placebo and appeared to increase with increasing dose of oral semaglutide. The AEs were mainly gastrointestinal (GI) AEs; however, most were transient and mild to moderate in severity. A low starting dose of oral semaglutide and slow dose escalation were associated with lower rates of GI AEs during dose escalation and hence lower treatment discontinuation – initiating treatment with a low dose of oral semaglutide had a greater effect on mitigating GI AEs than a slow dose escalation, which is why dose escalation at a starting dose of 3 mg was implemented in the PIONEER programme. The rate of SAEs was low across oral semaglutide groups, and no fatal events were reported in any treatment group in the NN9924-3790 trial. Thus, although the frequency of GI AEs also appeared to be dose dependent, all dose levels investigated in trial NN9924-3790 (including 40 mg) were found to be safe and well tolerated, and no unexpected safety concerns were identified.

A comprehensive review of results from the nonclinical and clinical studies of oral semaglutide can be found in the current edition of the investigator's brochure[5], and any updates hereof.

2.3 Benefit-risk assessment

Main benefits and risks are described in the below sections. More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of oral semaglutide may be found in the investigator's brochure[5], prescribing information[2] or summary of product characteristics.[6]

2.3.1 Risk assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Trial treatment (semaglutide)		
Gastrointestinal (GI) disorders	Consistent with other GLP-1 RAs, the most frequent AEs with semaglutide are GI (nausea, vomiting and diarrhoea). In general, these reactions are mild or moderate in severity, of short duration, and dose dependent. In subjects treated with GLP-1 RAs, nausea, vomiting and diarrhoea may lead to significant dehydration. This should be considered when treating subjects with impaired renal function as it may cause a deterioration of renal function.	Clinical trials have shown that a low starting dose and gradual dose escalation mitigate the risk of developing GI symptoms. Subjects with GI symptoms are recommended to drink plenty of fluids to avoid volume depletion.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Trial treatment (semaglutide)		
Hypoglycaemia	There is a low risk of hypoglycaemic episodes when semaglutide is used as monotherapy. Subjects treated with semaglutide in combination with sulfonylurea or insulin may have an increased risk of hypoglycaemia.	The risk of hypoglycaemia can be lowered by reducing the dose of sulfonylurea or insulin when initiating treatment with semaglutide.
Diabetic retinopathy complications	A 2-year clinical trial with s.c. semaglutide (NN9535-3744) investigating 3,297 subjects with T2D, high CV risk, long duration of diabetes and poorly controlled blood glucose. In this trial, adjudicated events of diabetic retinopathy complications occurred in more subjects treated with s.c. semaglutide (3.0%) compared to placebo (1.8%). This was observed in insulin-treated subjects with known diabetic retinopathy. The treatment difference appeared early and persisted throughout the trial. Systematic evaluation of diabetic retinopathy complication was only performed in the CV outcomes trial with s.c. semaglutide. In clinical trials with oral semaglutide of up to 18 months duration involving 6,352 subjects with T2D, adverse event related to diabetic retinopathy were reported in similar proportions in subjects treated with semaglutide (4.2%) and comparators (3.8%).	Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy, but other mechanisms cannot be excluded. Long-term glycaemic control decreases the risk of diabetic retinopathy. These subjects should be monitored closely and treated according to clinical guidelines. Subjects with uncontrolled and potentially unstable diabetic retinopathy or maculopathy will not be enrolled in this trial.
Allergic reactions	As with all protein-based pharmaceuticals, treatment with semaglutide may evoke allergic reactions, including serious allergic reactions such as angioedema and anaphylactic reactions.	As a precaution, subjects with known or suspected hypersensitivity to semaglutide or related products will not be enrolled in this trial. In addition, subjects will be instructed to contact the site staff as soon as possible for further guidance if suspicion of a hypersensitivity reaction to the trial product occurs.
Acute pancreatitis	Acute pancreatitis has been observed with the use of GLP-1 RAs. In the completed phase 3 trials with s.c. semaglutide and oral semaglutide, both the event rate and the proportion of subjects experiencing confirmed pancreatitis were similar with semaglutide and comparator. Few events were confirmed; the events occurred throughout the trial periods and the overall rates were similar to the rates reported in background populations.	Subjects should be informed of the characteristic symptoms of acute pancreatitis and if pancreatitis is suspected, semaglutide should be discontinued. If confirmed, semaglutide should not be restarted.
Neoplasms (malignant and non-malignant)	Patients with T2D, as well as patients with overweight or obesity, have an increased risk of certain types of cancer. There is no evidence from clinical trials that GLP-1-based therapies increase the risk of neoplasms. However, in the s.c. semaglutide as well as oral semaglutide phase 3a trials, the proportion of subjects with neoplasms (malignant and non-	Subjects with presence or history of malignant neoplasm within 5 years prior to the day of screening will not be enrolled in this trial. Basal and squamous cell skin cancer and any carcinoma in-situ is allowed

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Trial treatment (semaglutide)		
	malignant) were slightly higher with semaglutide than with comparator. The number of subjects exposed to s.c. semaglutide or oral semaglutide for a longer period is considered insufficient for a thorough assessment of the risk of neoplasms.	
Pancreatic cancer	Patients with T2D have an increased risk of certain types of cancer such as pancreatic cancer. There is currently no support from non-clinical studies, clinical trials or post-marketing data that GLP-1 based therapies increase the risk of pancreatic cancer. However, pancreatic cancer has been classified as a potential class risk for all marketed GLP-1 RAs by regulatory agencies. There is no indication of an increased relative risk in the semaglutide treatment groups vs. comparator, including placebo. The rates of EAC-confirmed events of pancreatic cancer were consistently low across trials.	Subjects with presence or history of malignant neoplasm within 5 years prior to the day of screening will not be enrolled in this trial.
Medullary thyroid cancer	Thyroid C-cell tumours were seen in mouse and rat carcinogenicity studies after daily exposure to semaglutide for 2 years. The rodent C-cell tumours are caused by a non-genotoxic, specific GLP-1 receptor mediated mechanism to which rodents are particularly sensitive. No C-cell tumours were observed in monkeys after 52 weeks exposure up to 52-fold above the clinical plasma exposure at 14 mg/day. The GLP-1 receptor is not expressed in the normal human thyroid, and therefore the clinical relevance of the findings is considered to be low.	To mitigate this risk, subjects with a family or personal history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2 (MEN2) are excluded from clinical trials with semaglutide.
Risk of COVID-19 infection in relation to trial treatment	Available data does not suggest an increased risk of infection or a more severe progression of infection when treated with oral semaglutide.	More detailed information about the known risks for oral semaglutide may be found in the investigator's brochure[5], Prescribing information[7] or Summary of product characteristics.[6]

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Trial treatment (semaglutide)		
Trial procedures		
Risk of COVID-19 infection in relation to participation in trial	Subjects may be exposed to the risk of COVID-19 transmission and infection in relation to site visits if an outbreak is ongoing in the given country.	The risk of COVID-19 transmission in relation to site visits is overall considered to be low, however this may vary between geographical area. To minimize the risk as much as possible, the following measures have been taken: • Cautious subject recruitment planning ensures controlled subject enrolment in countries where the COVID-19 pandemic is evaluated to be sufficiently under control, and at sites where health care resources are evaluated to be adequate. • The number of physical on-site visits has been limited to the extent possible. Phone visits have to the extent possible replaced on-site visits. • On-site visits will be well-prepared and as short as possible. Physical contact between subjects and site staff will be limited to the extent possible, and protective measures will be implemented. • A COVID-19 mitigation plan has been developed for this trial which lists the additional actions to consider in case a site or country are locked down and subjects cannot attend on-site visits.
Other		
Pregnancy and fertility	Studies in animals have shown reproductive toxicity. There are limited data from the use of semaglutide in pregnant women.	Semaglutide should not be used during pregnancy. Women of childbearing potential are required to use highly effective contraceptive methods when participating in this trial (Appendix 4 (Section 10.4), Table 10-3). If a subject wishes to become pregnant, or pregnancy occurs, semaglutide should be discontinued (please refer to Section 8.3.5 for further guidance). The effect of semaglutide on fertility in humans is unknown.

2.3.2 Benefit assessment

Oral semaglutide has demonstrated clinically relevant and dose-dependent improvements in glycaemic control and body weight reduction in subjects with T2D. Also, the reduction in HbA_{1c} was consistently greater with higher baseline HbA_{1c}.[8] Consequently, it is expected that oral semaglutide 25 mg and 50 mg will provide improved glycaemic and body weight control in subjects with T2D as compared to semaglutide 14 mg, the current maximum maintenance dose approved.

All subjects will therefore be treated with a regimen expected to be more efficacious compared to the treatment they receive at trial entry.

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

Investigators will ensure that subjects are treated according to recommended standard-of-care for T2D management. Safety and efficacy will be monitored regularly, and acceptable glycaemic control will be reinforced at all times during the trial.

All subjects in this trial will receive trial product and auxiliary supplies free of charge.

2.3.3 Overall benefit-risk conclusion

Necessary precautions have been implemented in the design and planned conduct of the trial in order to minimise the risks and inconveniences of participation in the trial. The safety profile for semaglutide generated from the clinical and non-clinical development programme has not revealed any safety issues that would prohibit administration of oral semaglutide doses up to 50 mg once daily. The results of the phase 2 trial (NN9924-3790) indicate a dose-dependent reduction of HbA_{1c} and body weight following treatment with oral semaglutide.

It is therefore concluded that the potential benefits from the trial will outweigh the potential risks for the subjects. More detailed information about the known and expected benefits and risks and reasonably expected AEs of oral semaglutide may be found in the Investigator's Brochure (IB)[5] and any updates hereof.

3 Objectives and endpoints

3.1 Primary and secondary objectives, and estimands

Primary objective	To confirm superiority of oral semaglutide 25 mg and 50 mg once daily versus oral semaglutide 14 mg once daily on HbA_{1c} reduction in subjects with T2D on stable dose of 1-3 OADs.
Secondary objectives	To confirm superiority of oral semaglutide 25 mg and 50 mg once daily versus oral semaglutide 14 mg once daily on body weight reduction in subjects with T2D on a stable dose of 1-3 OADs.
	To compare the efficacy of oral semaglutide 25 mg and 50 mg once daily versus oral semaglutide 14 mg once daily on parameters related to glycaemic control in subjects with T2D on a stable dose of 1-3 OADs.
	To compare the efficacy of oral semaglutide 25 mg and 50 mg once daily versus oral semaglutide 14 mg once daily on parameters related to weight-related outcomes in subjects with T2D on a stable dose of 1-3 OADs.
	To compare the safety and tolerability of oral semaglutide 25 mg and 50 mg once daily versus oral semaglutide 14 mg once daily in subjects with T2D on stable dose of 1-3 OADs.

Estimands

For the primary and the confirmatory secondary objective, estimands of primary interest and additional estimands are defined. The estimands are used to address the trial objectives in terms of two different aspects of the treatment effect of oral semaglutide 14, 25 and 50 mg. Three intercurrent events are considered: Premature trial treatment discontinuation (due to any reason), change in dose and initiation of additional anti-diabetic medication. Intercurrent events are events occurring after treatment initiation that affect the interpretation or the existence of the measurements associated with the questions of interest.

The estimands for the primary objective are introduced below and the attributes of the estimands are summarised in Table 3-1. Additional details are available in Section 9.

Similar estimands are applied to the objective related to superiority in change in body weight.

The primary estimand addresses the main question of interest: What is the efficacy of oral semaglutide 25 and 50 mg versus oral semaglutide 14 mg on change from baseline to week 52 in HbA_{1c} in subjects with T2D on stable dose of 1-3 OADs regardless of premature trial treatment discontinuation, changes in dose and initiation of additional anti-diabetic medication.

For this estimand, the treatment policy strategy is applied for all intercurrent events (Section 9.3 and Table 9-3). Data collection will continue after an intercurrent event and the collected data will be included in analyses regardless of the occurrence of the event.

Results based on the primary estimand are expected to mirror the clinical practice scenario because the estimand considers both the efficacy and tolerability of oral semaglutide. In addition, a similar estimand is represented in the label for Rybelsus®.

The additional estimand addresses an additional question of interest: What is the efficacy of oral semaglutide 25 and 50 mg versus oral semaglutide 14 mg on change from baseline to week 52 in HbA_{1c} in subjects with T2D on stable dose of 1-3 OADs regardless of change in dose of trial treatment and if all subjects had remained on trial treatment without use of rescue medication.

For this estimand, a hypothetical strategy is applied for two of the intercurrent events (premature trial treatment discontinuation and initiation of rescue medication). The treatment policy strategy is used to handle any changes in trial treatment dose level because this intercurrent event is part of the pre-specified treatment regimen.

The additional estimand is considered relevant because it quantifies the achievable treatment effect without potentially confounding effects of any rescue medication. Further, results obtained with the additional estimand allows for comparison with results from the oral semaglutide phase 3a programme (PIONEER), which applied a similar additional estimand.

Table 3-1 Estimands

Objective	Estimand category	Attributes				
		Treatment condition	**Variable / endpoint**	**Population of interest**	**Intercurrent events and strategy**	**Population-level summary measure**
Primary objective: To confirm superiority of oral semaglutide 25 mg and 50 mg once daily versus oral semaglutide 14 mg once daily on HbA_{1c} reduction in subjects with T2D on stable dose of 1-3 OADs	Primary	The effect of high doses of oral semaglutide with or without additional anti-diabetic medication versus the effect of oral semaglutide 14 mg with or without additional anti-diabetic medication, both as add-on to stable dose of 1-3 OADs	Change in HbA_{1c} from baseline to week 52	T2D subjects as defined by the protocol inclusion and exclusion criteria	**Treatment policy** strategy for: • Premature trial treatment discontinuation • Dose change • Initiation of additional anti-diabetic medication	Difference in means
	Additional*	The effect of high doses of oral semaglutide without rescue medication versus the effect of oral semaglutide 14 mg without rescue medication, both as add-on to stable dose of 1-3 OADs			**Hypothetical** strategy for: • Premature trial treatment discontinuation • Initiation of rescue medication **Treatment policy** strategy for: • Dose change	

Objective	Estimand category	Attributes				
		Treatment condition	**Variable / endpoint**	**Population of interest**	**Intercurrent events and strategy**	**Population-level summary measure**
Secondary objective: To confirm superiority of oral semaglutide 25 mg and 50 mg once daily versus oral semaglutide 14 mg once daily on body weight reduction in subjects with T2D on stable dose of 1-3 OADs	Secondary	The effect of high doses of oral semaglutide with or without additional anti-diabetic medication versus the effect of oral semaglutide 14 mg with or without additional anti-diabetic medication, both as add-on to stable dose of 1-3 OADs	Change in body weight from baseline to week 52	T2D subjects as defined by the protocol inclusion and exclusion criteria	**Treatment policy** strategy for: • Premature trial treatment discontinuation • Dose change • Initiation of additional anti-diabetic medication	Difference in means
	Additional*	The effect of high doses of oral semaglutide without rescue medication versus the effect of oral semaglutide 14 mg without rescue medication, both as add-on to stable dose of 1-3 OADs			**Hypothetical** strategy for: • Premature trial treatment discontinuation • Initiation of rescue medication **Treatment policy** strategy for: • Dose change	

* Not related to the confirmatory hypotheses

Similar estimands are defined for the other efficacy objectives.

3.2 Primary and secondary endpoints

3.2.1 Primary endpoint

Endpoint title	Timeframe	Unit
Change in glycated haemoglobin (HbA_{1c})	From baseline (week 0) to week 52	%-point

3.2.2 Secondary endpoints

3.2.2.1 Confirmatory secondary endpoints

Endpoint title	Timeframe	Unit
Change in body weight	From baseline (week 0) to week 52	kg

3.2.2.2 Supportive secondary endpoints

Endpoint title	Timeframe	Unit
Change in fasting plasma glucose (FPG)	From baseline (week 0) to week 52	mmol/l
Achievement of HbA_{1c} <7% (Yes/No)	At week 52	Count of subjects
Achievement of HbA_{1c} ≤6.5% (Yes/No)	At week 52	Count of subjects
Relative change in body weight	From baseline (week 0) to week 52	Percentage (%)
Change in waist circumference	From baseline (week 0) to week 52	cm
Achievement of weight loss ≥5% (Yes/No)	At week 52	Count of subjects
Achievement of weight loss ≥10% (Yes/No)	At week 52	Count of subjects
Adverse events	From baseline (week 0) to follow-up visit (week 73)	Count of events

4 Trial design

4.1 Overall design

This is a 68-week, randomised, active-controlled, double-blinded, three-armed, multi-centre, multinational clinical trial.

Eligible subjects will be randomised in a 1:1:1 manner to receive either:

- oral semaglutide 50 mg once daily
- oral semaglutide 25 mg once daily
- oral semaglutide 14 mg once daily

Randomisation will be stratified by baseline anti-diabetic medication: ± SU, ±SGLT2 inhibitor, ±terminated DPP-4 inhibitor. Consequently, randomisation will comprise 8 strata for combinations of SU, SGLT2 inhibitor, and terminated DPP-4 inhibitor. Metformin is not included in the stratification. A 30% cap on DPP-4 inhibitor users will be implemented to equalise the representation of baseline background anti-diabetic medication across the population.

The trial comprises a 2-week screening period to assess the subject's eligibility followed by a randomisation visit (V2) and a 68-week treatment period. The treatment period is divided into a dose escalation period of 8-16 weeks and a maintenance period of 52-60 weeks. After the end-of-treatment visit (V16), all subjects will enter a follow-up period of 5 weeks, ended by a follow-up visit (V17), which corresponds to the end of the trial. The planned total trial duration for the individual subject is approximately 75 weeks (including screening).

The trial design is illustrated in Figure 4-1

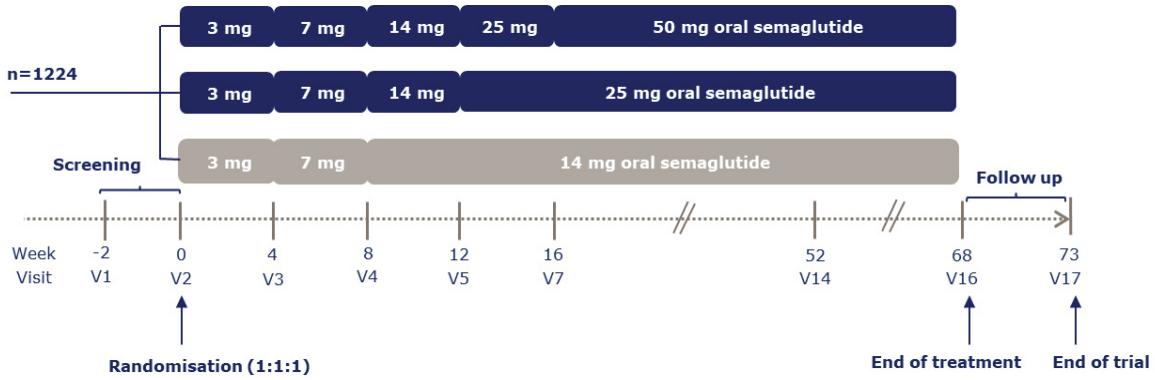


Figure 4-1 Trial design

4.2 Scientific rationale for trial design

The trial has been designed as an active-controlled, double-blinded, parallel, three-armed trial to ensure a direct comparison of oral semaglutide 25 mg, 50 mg, and 14 mg.

A randomised, double-blind trial design was chosen to minimise bias in the assessment of the efficacy and safety of oral semaglutide 25 and 50 mg. The formulation (shape and composition) of the tablets, used for the 25 mg and 50 mg dose levels, has been updated to improve bioavailability

as compared to the formulation of the tablets used for the 14 mg dose level. Consequently, the shape of the tablets will have a minor difference and will not be visually identical. However, the double-blind design is considered justified because: 1) identical primary and secondary packaging is used for all tablets in all treatment arms; 2) a third-party, who is only allowed to be involved in trial product handling will be responsible for drug accountability (see Section 6.3). Of note, a double-dummy design was not considered feasible considering the dosing conditions for oral semaglutide.

The planned treatment duration of the trial is 68 weeks, with an additional 5 weeks of follow-up to account for the exposure and long half-life of semaglutide. An evaluation of the efficacy-related parameters after a 52-week treatment period is considered appropriate and in line with regulatory guidance and with previous trials in T2D, including the PIONEER phase 3a trials. A total treatment duration of 68 weeks will ensure a robust safety and tolerability evaluation.

Predictions based on PIONEER and SUSTAIN exposure-response modelling indicate stabilisation or minimal increase in the effect of semaglutide on HbA_{1c} beyond 26 weeks of treatment. The exposure-response models indicate, however, additional weight benefit at week 52 compared to week 26 based on approximately 30 weeks on maintenance dose. The primary and confirmatory secondary endpoints are therefore defined after 52 weeks of treatment.

Evaluation of the 20-40% of subjects failing to reach the glycaemic target of HbA_{1c} <7% after 26 weeks on oral semaglutide 14 mg in the PIONEER phase 3a programme suggests that the population likely to particularly benefit from a dose of oral semaglutide higher than 14 mg is characterised by high baseline HbA_{1c} (>8%) and high baseline BMI (>25 kg/m^2). Such patients with T2D in need of treatment intensification are very likely to receive a broader range of anti-diabetic medication at baseline; therefore, treatment with stable dose of 1-3 oral anti-diabetic drugs (OADs) at baseline is allowed (see Section 5.1).

This population is considered to be clinically relevant, because it is likely to benefit both from the better glycaemic control and the additional body weight loss anticipated to be achievable with the higher doses of oral semaglutide.

4.3 Justification for dose

The oral semaglutide doses of 25 mg and 50 mg are chosen to ensure that the increments between the doses provide clinically meaningful differentiation between their effects on glycaemic control while displaying a satisfactory safety and tolerability profile.

Relative to formulation used for the currently approved doses of Rybelsus®, the formulation for oral semaglutide 25 mg and 50 mg has been changed with regards to excipient composition. This change in formulation is based on results from trial NN9924-4427, as it is anticipated that the new formulation will lead to improved bioavailability relative to the formulation for the currently approved doses of Rybelsus®. In trial NN9924-4427, exposure of healthy male subjects to once daily dosing of the new formulation of oral semaglutide (5 days on 3 mg and 5 days on 7 mg) resulted in an increase in semaglutide exposure by approximately 25% compared to the formulation of the currently marketed doses of oral semaglutide (Rybelsus®).

Using pharmacokinetic (PK) simulations and assuming dose-proportionality, 25 mg and 50 mg semaglutide are expected to result in C_{avg} of 36.5 (90% range:11.4-92.3) nmol/L and 72.9 (90%

range:22.8-184.7) nmol/L, respectively. The simulated oral semaglutide concentrations are based on a population PK model developed on a trial population matching subjects on 14 mg oral semaglutide from PIONEER 1, 2, 8 and 9 (trials NN9924-4233, 4223, 4280 and 4281).

An exposure level higher than the one potentially reached with steady-state treatment of 25 mg oral semaglutide has already been tested in previous trials with oral and s.c. semaglutide. In the oral semaglutide phase 2 trial (NN9924-3790), subjects with T2D received up to 40 mg oral semaglutide. In this trial, the highest C_{avg} observed in the highest dose arm (40 mg) was 185 nmol/L.

The semaglutide exposure level potentially reached with steady-state treatment of 50 mg oral semaglutide (C_{avg} of 72.9 [90% range: 22.8-184.7] nmol/L) are similar to or may be higher than dose levels previously tested. Approximately 5% of subjects on 50 mg are likely to achieve an exposure level above the maximum exposure level observed with oral semaglutide in trial NN9924-3790 (highest C_{avg} observed was 185 nmol/L) where subjects were treated with doses up to 40 mg. In addition, s.c. semaglutide 0.3 mg and 0.4 mg once daily (corresponding to a weekly dose of 2.1 mg and 2.8 mg, respectively) have been dosed to subjects with T2D or obesity in trials NN9535-4191 and NN9536-4153, respectively. In the obese population, the highest observed C_{avg} for s.c. semaglutide 0.4 mg was 128 nmol/L (trial 4153). No unexpected safety or tolerability findings were observed in either of the trials.

Based on prior experience with oral semaglutide (NN9924-3790 and the PIONEER programme) and other GLP-1 RAs, low starting dose and gradual dose escalation of oral semaglutide is expected to mitigate the risk of developing GI symptoms. To increase GI tolerability, possible dose reductions and extensions of dose-escalation periods will be introduced based on clinical evaluation made by the investigator (see Section 6.6).

4.4 End of trial definition

A subject is considered to have completed the trial if he/she has completed all phases of the trial, including the follow-up visit (V17).

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

5 Trial population

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

5.1 Inclusion criteria

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

1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial.
2. Male or female, age above or equal to 18 years at the time of signing informed consent.
3. Diagnosed with type 2 diabetes mellitus ≥ 180 days prior to the day of screening.
4. HbA_{1c} of 8.0-10.5% (64−91 mmol/mol) (both inclusive).
5. BMI ≥ 25.0 kg/m^2.
6. Stable daily dose(s) for 90 days prior to the day of screening of: any of the following treatment regimens:
   - No more than 3 of the following oral anti-diabetic drugs and at least 1 marked with a *:
     - * Metformin (≥1500 mg or maximum tolerated or effective dose).
     - * Sulfonylureas (SU) (≥half of the maximum approved dose according to local label or maximum tolerated or effective dose).
     - * SGLT2 inhibitors (maximum tolerated dose).
     - DPP-4 inhibitors (maximally indicated dose as per local label).
7. Subjects, on treatment with stable dose of DPP-4 inhibitors at inclusion, must be willing to terminate DPP-4 inhibitor treatment at randomisation (with no wash-out).

Taiwan: for country-specific requirements, please see Appendix 8 (Section 10.8).

5.2 Exclusion criteria

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

1. Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria within the past 90 days prior to the day of screening. However, short-term insulin treatment for a maximum of 14 days prior to the day of screening is allowed.
2. Anticipated initiation or change in concomitant medications (for more than 14 consecutive days) known to affect body weight or glucose metabolism (e.g. treatment with orlistat, thyroid hormones, or systemic corticosteroids).
3. Renal impairment measured as estimated glomerular filtration rate (eGFR) value of <30 mL/min/1.73 m^2 according to CKD-EPI creatinine equation as defined by KDIGO 2012 classification.
4. 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.
5. History of major surgical procedures involving the stomach potentially affecting absorption of drugs and/or nutrients, as judged by the investigator.
6. Personal or first-degree relative(s) history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma.

7. Presence or history of pancreatitis (acute or chronic).
8. Myocardial infarction, stroke, hospitalization for unstable angina pectoris or transient ischaemic attack within 180 days prior to the day of screening.
9. Presently classified as being in New York Heart Association (NYHA) Class IV.
10. Planned coronary, carotid or peripheral artery revascularisation.
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. Known or suspected hypersensitivity to trial products or related products.
13. Previous participation in this trial. Participation is defined as signed informed consent.
14. 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.
15. Participation in any clinical trial of an approved or non-approved investigational medicinal product within 3 months before screening*.
16. Other subject(s) from the same household participating in any oral semaglutide trial
17. Any disorder, unwillingness or inability, which in the investigator's opinion might jeopardise subject's safety or compliance with the protocol.

*Simultaneous participation in a trial with the primary objective of evaluating an approved or non-approved investigational medicinal product for prevention or treatment of COVID-19 disease or COVID-19 postinfectious conditions is allowed if the last dose of the investigational medicinal product has been received more than 30 days before screening.

Croatia and Germany: for country-specific requirements, please see Appendix 8 (Section 10.8).

5.3 Lifestyle considerations

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

5.3.1 Meals and dietary restrictions

The trial product must:

- be taken on an empty stomach in the morning at least 30 minutes before intake of food, liquids or other oral medicinal products.
- waiting less than 30 minutes, or taking with food, beverages (other than water) or other oral medication will lessen the effect of oral semaglutide.
- waiting more than 30 minutes might increase the absorption of oral semaglutide.
- be taken with no more than a half a glass of water equivalent to 120 ml (4 ounces).
- be swallowed whole.
- not be split, crushed or chewed.

Subjects must attend visits fasting according to the flowchart (Section 1.2). Fasting is defined as:

- no food or liquid, except for water, for at least 6 hours prior to the visit.
- no water 2 hours prior to the visit.

Trial product and any medication which should be taken with or after a meal should be withheld on the day of the visit until blood samples have been obtained.

If the subject is not fasting as required, the subject must be called in for a new visit within the visit window to have the fasting procedures performed.

5.4 Screen failures

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

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

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

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

Not applicable for this trial.

6 Treatments

6.1 Treatments administered

Investigational medicinal products

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

Table 6-1 Investigational medicinal products provided by Novo Nordisk

Description	Trial product (IMP) name	Dosage form	Route of administration	Dosing instruction	Packaging [1]
Semaglutide	Semaglutide 3 mg	Tablet	Oral	1 tablet in the morning as described in Section 5.3.1	Dose pack
Semaglutide	Semaglutide 7 mg	Tablet	Oral	1 tablet in the morning as described in Section 5.3.1	Dose pack
Semaglutide	Semaglutide 14 mg	Tablet	Oral	1 tablet in the morning as described in Section 5.3.1	Dose pack
					HDPE bottle
Semaglutide	Semaglutide C 25 mg	Tablet	Oral	1 tablet in the morning as described in Section 5.3.1	HDPE bottle
Semaglutide	Semaglutide C 50 mg	Tablet	Oral	1 tablet in the morning as described in Section 5.3.1	HDPE bottle

[1]: A dose pack contains one blister card with 7 tablets. A high density polyurethane (HDPE) bottle contains 30 tablets.

Directions for use

The investigator must document that directions for use (DFU) are given to the subject orally at the first dispensing visit (as specified in the flowchart in Section 1.2). The investigator should remind subjects of dosing instructions (as described in Section 5.3.1) ongoing throughout the trial, as applicable.

Participants must be instructed to take oral semaglutide at least 30 min before the first food, beverage or other oral medications of the day with no more than 120 mL or 4 ounces of plain water. Waiting less than 30 minutes, or taking food, beverages (other than plain water) or other oral medications will lessen the effect of oral semaglutide. Waiting more than 30 minutes to eat may increase the absorption of oral semaglutide. The tablet must be swallowed whole. The tablet must not be cut, crushed or chewed.

Dose escalation

Dose escalation of oral semaglutide should take place during the first 8-16 weeks after randomisation as illustrated in Table 6-2. All subjects should aim at reaching the randomised target dose of oral semaglutide once daily.

Table 6-2 Treatment overview

		Dose escalation/maintenance				Maintenance	Follow-up
Trial periods	**Screening**	**Randomisation/ Treatment-period 1**	**Treatment-period 2**	**Treatment-period 3**	**Treatment-period 4**	**Treatment- period 5**	**End of treatment**
Duration of each period	2 weeks	4 weeks	4 weeks	4 weeks	4 weeks	52 weeks	5 weeks
Treatment arm							
Oral semaglutide 50 mg	Screening	Oral semaglutide 3 mg Dose pack	Oral semaglutide 7 mg Dose pack	Oral semaglutide 14 mg Dose pack	Oral semaglutide 25 mg HDPE bottle	Oral semaglutide 50 mg HDPE bottle	Follow-up
Oral semaglutide 25 mg	Screening	Oral semaglutide 3 mg Dose pack	Oral semaglutide 7 mg Dose pack	Oral semaglutide 14 mg Dose pack	Oral semaglutide 25 mg HDPE bottle	Oral semaglutide 25 mg HDPE bottle	Follow-up
Oral semaglutide 14 mg	Screening	Oral semaglutide 3 mg Dose pack	Oral semaglutide 7 mg Dose pack	Oral semaglutide 14 mg Dose pack	Oral semaglutide 14 mg HDPE bottle	Oral semaglutide 14 mg HDPE bottle	Follow-up

HDPE = High density polyurethane.

Missed doses

If a dose is missed, the missed dose should be skipped, and the next dose should be taken the following day.

If consecutive doses of trial treatment are missed, the subject should be encouraged to re-commence the treatment if considered safe as per the investigator's discretion and if the subject does not meet any of the discontinuation criteria (Section 7.1). The trial treatment should be continued as early as the situation allows. If the subject has been off treatment for more than 10 consecutive days, the investigator should consult Novo Nordisk global medical experts for guidance regarding continuation of trial medication.

Auxiliary supplies

The following auxiliary supplies will be provided by Novo Nordisk:

- Blood glucose (BG) meter and related auxiliaries

Subjects will be instructed in how and when to use the BG meter and the instructions will be repeated during the trial as needed.

Shipment of trial product to subject's home

For selected countries and if permitted by local regulations, the investigator may offer to send trial product and auxiliaries from the trial site or pharmacy to the subject's home by courier service.

The process for sending trial product from the trial site or pharmacy to a subject's home is described in the "Trial site/pharmacy instruction for shipment of trial product to patients' homes" document. 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 subject. The process for returning trial product to the trial site or pharmacy by courier is also described in this document.

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

Please note that the drug dispensing and accountability are handled by the third-party, as described in Section 4.2 and 6.3.

6.2 Preparation/handling/storage/accountability

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

- Each site will be supplied with sufficient trial products for the trial on an ongoing basis. Trial products will be distributed to the sites according to screening and randomisation.
- The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all trial products received, and that any discrepancies are reported and resolved before use of the trial products.
- All trial products must be stored in a secure, controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and delegated site staff.
- The investigator must inform Novo Nordisk immediately if any trial product has been stored outside specified conditions. The trial product must not be dispensed to any subject before it has been evaluated and approved for further use by Novo Nordisk. Additional details regarding handling of temperature deviations can be found in the trial materials manual (TMM).
- The investigator or designee is responsible for drug accountability and record maintenance (i.e. receipt, accountability and final disposition records).
- The investigator or designee must instruct the subject in what to return at next visit.
- Drug accountability must be performed in the IWRS by registering tablets as returned either un-used or as lost.
- Destruction of trial products can be performed on an ongoing basis and will be done according to local procedures after accountability is finalised by the site.
  Destruction of trial product must be documented in the IWRS.
- All returned, un-used, expired or damaged trial products (for technical complaint samples, see Section 10.5) must be stored separately from non-allocated trial products. No temperature monitoring is required.
- Non-allocated trial products including expired or damaged products must be accounted as unused, at the latest at closure of the site.

6.3 Measures to minimise bias: Randomisation and blinding

All subjects will be centrally screened and randomised using an IWRS and assigned to the next available treatment according to randomisation schedule. Trial treatment will be dispensed/allocated at the trial visits summarised in the flowchart (Section 1.2).

Subjects will be randomly assigned in a 1:1:1 ratio to receive trial treatment.

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

Dose reduction to lower doses than 14 mg is not allowed (see Section 6.6). Consequently, the allowed dose reduction steps will not induce change of trial product packaging and therefore not compromise the double-blinded trial design.

Investigators and site personnel are to remain blinded throughout the trial. Due to the minor differences in tablet shapes, the primary and secondary packaging are identical in all treatment arms to maintain the blinding (see Section 4.2). Further, a third-party will be responsible for drug accountability of all trial products and an unblinded monitor will be responsible for drug reconciliation (see Section 10.1.8.2). It will not be possible for the third-party or the unblinded monitor to see the actual treatment. The third-party will also be allowed to handle trial product arrival and temperature monitoring of trial product including handling of potential temperature deviations. The unblinded monitor will also be allowed to check documentation regarding potential temperature deviations. The unblinded monitor will also be allowed to check documentation regarding above tasks and be involved in trial product destruction according to local procedures.

It is recommended that the third-party also is responsible for dispensing of all trial products, but in case site personnel and/or investigator needs to be responsible for dispensing of trial products, they are only allowed to handle trial product in its original packaging material (unbroken packaging). The third-party and the unblinded monitor will not be involved in any other trial procedures.

The IWRS is used for blind-breaking. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a subjects' treatment is warranted. Subject safety must always be the first consideration in making such a determination.

If the investigator decides that unblinding is warranted, the investigator should make every effort to contact Novo Nordisk prior to unblinding a subjects' treatment unless this could delay emergency treatment of the subject. If a subject's treatment is unblinded, Novo Nordisk (Global Safety department) must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation.

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

6.4 Treatment compliance

Drug treatment compliance

Throughout the trial, the investigator will remind the subjects to follow the trial procedures and requirements to encourage subject compliance. Compliance is defined as taking between 80%-120% of the dose as prescribed between visits.

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

- Drug accountability information; counting returned trial product
- Questioning of subjects about missed doses

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

6.5 Concomitant medication

Any medication (including over-the-counter (OTC) or prescription medicines) other than the trial treatment that the subject is receiving at the time of the first visit or receives during the trial must be recorded along with:

- Trade name or generic name
- Indication
- Dates of administration including start and stop dates
- Dose (only to be recorded for anti-hyperglycaemic medication and levothyroxine)
- Time of dosing (only to be recorded for levothyroxine)
- Medication administered in relation to a clinical trial for COVID-19 prevention or treatment
- Approved COVID-19 vaccine

After signing the informed consent, subjects must continue their OADs (with the exception of DPP-4 inhibitors – see Section 4.1 and 5.1) at the same dose level and with the same dosing frequency throughout the entire treatment period unless safety concerns related to the use their OADs arise.

To mitigate SU-induced hypoglycaemia, subjects treated with SU should, at the discretion of the investigator, reduce the SU dose at randomisation by approximately 50%.

Apart from the initial dose reduction of SU, background medication dose should remain at the same dose level and with the same frequency during the entire treatment period unless glycaemic rescue treatment is needed (as described in Section 7.1.2) or safety concern related to the use of background medications arises.

Investigators can switch OAD treatment within the same drug class, e.g. in case specific drugs become unavailable.

Changes in concomitant medication, including switch of OAD treatment within the same drug class, must be recorded at each visit. If a change is due to an AE, then this must be reported according to Section 8.3.

Croatia and Germany: for country-specific requirements, please see Appendix 8 (Section 10.8).

6.5.1 Rescue medication

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

Rescue medication should be selected according to American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) guideline[4] (excluding GLP-1 RAs, DPP-4 inhibitors and amylin analogues).

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

Rescue medication should be documented in medical records and reported on the concomitant medication form in the electronic case report form (eCRF).

Rescue medication will not be supplied by Novo Nordisk.

6.6 Dose modification

Subjects should be dose escalated as indicated in Table 6-2 and Figure 4-1. However, if treatment with oral semaglutide 25 mg and 50 mg are associated with unacceptable GI AEs (moderate to severe), dose reduction or extension of dose escalation intervals are allowed in treatment period 4 and 5 (see Table 6-2) if the GI AEs are causally related to the trial treatment as judged by the investigator. This is to accommodate subject tolerability and safety. In these specific, expected rare cases dose adjustments are at the discretion of the investigator. It is recommended that the subject makes at least one attempt to re-escalate to the recommended target dose.

Dose reduction to lower doses than 14 mg is not allowed.

It is mandatory that the investigator consults Novo Nordisk in case of persistent deviations from the planned escalation regimen.

6.7 Treatment after end of trial

When discontinuing trial treatment, the subject should be transferred to a suitable marketed product at the discretion of the investigator.

Considering the long half-life of semaglutide and to avoid over-exposure to GLP-1 RAs and interference with safety data collection, initiating GLP-1 RA or DPP-4 inhibitor should be avoided between the end-of-treatment visit (V16) and the follow-up visit (V17).

7 Discontinuation of trial treatment and subject discontinuation/withdrawal

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

Efforts must be made to have subjects attend and complete all scheduled visit procedures. Only subjects who withdraw consent will be considered as withdrawn from the trial. Subjects must be educated about the continued scientific importance of their data, even if they discontinue trial treatment.

7.1 Discontinuation of trial treatment

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

Subjects who discontinue trial treatment should continue with the scheduled visits and assessments to ensure continued counselling and data collection.

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

*Simultaneous participation in a trial with the primary objective of evaluating an approved or non-approved investigational medicinal product for prevention or treatment of COVID-19 disease or COVID-19 postinfectious conditions is allowed at the investigator discretion without discontinuing trial product.

The subjects should continue with the remaining scheduled visits and assessments until the time of the originally scheduled end-of-treatment visit (V16) and follow-up visit (V17).

All efforts should be made to have the subject attend at least visit V10, V14, the end-of-treatment visit (V16) and the follow-up visit (V17). If the subject does not wish to attend the scheduled clinic visits, efforts should be made to have the remaining visits converted to phone contacts. If a subject is unwilling to attend any of the remaining visits, information about the attempts to follow up with the subject must be documented in the subject's medical record.

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

Croatia and Germany: for country-specific requirements, please see Appendix 8 (Section 10.8).

7.1.1 Temporary discontinuation of trial treatment

If a subject has discontinued trial treatment due to temporary safety concern not related to trial product and treatment with trial product is allowed to be resumed, the guide for missed doses (Section 6.1) should be followed. In such cases a treatment discontinuation session should not be made in the IWRS.

In case of suspicion of acute pancreatitis, the trial treatment should promptly be interrupted (treatment discontinuation session should not be made in IWRS before diagnosis of acute pancreatitis is confirmed). Appropriate actions should be initiated, including local measurement of amylase and lipase (see Appendix 3 (Section 10.3) for reporting).

If acute pancreatitis is confirmed, treatment with trial product should not be restarted, and a treatment discontinuation session should be made in IWRS. If the Atlanta criteria[9] are not fulfilled and thus, the suspicion of acute pancreatitis is not confirmed, treatment with trial product may be resumed.

7.1.2 Rescue criteria

Subjects with persistent and unacceptable hyperglycaemia should be offered treatment intensification. To allow time for dose escalation to maximum dose and to observe the expected effect of treatment on glycaemic parameters, rescue criteria will be applied at week 26 and onwards.

If the HbA_{1c} exceeds the value described below, and no unexpected discrepancies are found in the trend of the subjects previous HbA_{1c} values, then the subject should be offered treatment intensification (rescue medication) at the discretion of the investigator and in accordance with the ADA/EASD guidelines[10] (excluding GLP-1 RAs, DPP-4 inhibitors and amylin analogues).

Rescue medication should be offered from week 26 (V10) to week 68 (V16) to:

- subjects with persistent poor glycaemic control, as expressed by a stable HbA_{1c} value above 8.5% (69 mmol/mol) and considered unacceptably high according to investigator's assessment.

Refer to Section 6.5.1 for description of rescue medication.

7.2 Subject discontinuation/withdrawal from the trial

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

If a subject withdraws consent, the investigator must make every effort to collect AEs from last visit to withdrawal.

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

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

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

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

7.2.1 Replacement of subjects

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

7.3 Lost to follow-up

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

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

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

8 Trial assessments and procedures

- The following sections describe the assessments and procedures, while their timing is summarised in the flowchart (Section 1.2) and in Appendix 2 (Section 10.2).
- Informed consent must be obtained before any trial related activity, see Section 10.1.3.
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all inclusion criteria and none of the exclusion criteria.
- The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reason for screen failure, as applicable.
- At screening, subjects will be provided with a card stating that they are participating in a trial and giving contact details of relevant site staff that can be contacted in case of emergency.
- Adherence to the trial design requirements, including those specified in the flowchart, is essential and required for trial conduct.
- The investigator must ensure to keep regular contact with each subject throughout the entire trial, and always have updated contact information. Even if a visit is missed and it is not possible to reschedule, every effort must be made to have all subjects followed for the primary endpoint and AEs.
- It is the responsibility of the investigator to schedule the visits and contacts as per the protocol flowchart (Section 1.2) and to ensure they take place. See Section 6.4 for treatment compliance.
- Suggested order of assessments:
- electrocardiogram (ECG) and vital signs
- blood samples
- other assessments
- Diaries will include the following in relation to the visit they support:
- Reminders:
    - to attend visit fasting (see flowchart in Section 1.2)
    - to collect first morning urine on day prior to visit and on the day of the visit (see Table 10-1)
    - to return trial product at next site visit
    - to return diary at next site visit
- Instruction on how to use the diary
- Information to be collected:
    - date of first dose of trial product
    - date and time of last dose prior to PK visit
    - hypoglycaemic events (according to Appendix 6 in Section 10.6)
    - health issues
- Review of diaries, ECG and laboratory reports must be documented either on the documents or in the subject's source documents. If clarification of entries or discrepancies in the diary is needed, the subject must be questioned, and a conclusion made in the subject's source documents. Care must be taken not to bias the subject.
- Repeat samples may be taken for technical issues and unscheduled samples or assessments may be taken for safety reasons. Please refer to Appendix 2 (Section 10.2) for further details on laboratory samples.
- Source data of clinical assessments performed and recorded in the CRF must be available and will usually be the subject’s medical records. Additional recordings to be considered source data

include but are not limited to laboratory reports, ECG, diary recordings and clinical outcome assessments. Ensure to transcribe the following into the CRF:

- All information from the diary
- Evaluations of ECGs

8.1 Efficacy assessments

Planned time points for all efficacy assessments are provided in the flowchart (Section 1.2) and in Appendix 2 (Section 10.2).

8.1.1 Clinical efficacy laboratory assessments

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

8.1.2 Body weight

Body weight will be measured and recorded as specified in the flowchart (Section 1.2).

Body weight should be measured without shoes and only wearing light clothing and recorded in the eCRF in kilogram [kg] or pound [lb] with a precision of 1/10 unit (e.g. 62.2 / 137.2 lb). BMI will be calculated in the eCRF.

8.1.3 Waist circumference

Waist circumference will be measured and recorded as specified in the flowchart (Section 1.2).

Waist circumference is defined as the minimal abdominal circumference located midway between the lower rib margin and the iliac crest and will be measured using a non-stretchable measuring tape. The measurement of waist circumference should be performed and recorded in the eCRF to the nearest ½ cm or ¼inch. The waist circumference should be measured in a standing position with an empty bladder and wearing light clothing with accessible waist. The subject should be standing with arms down their side and feet together. The measuring tape should touch the skin but not compress soft tissue. The subject should be asked to breathe normally, and the measurement should be taken when the subject is breathing out gently.

8.2 Safety assessments

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

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

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

Only relevant and significant medical history including COVID-19 as judged by the investigator should be recorded in the eCRF at the screening visit. Findings of specific medical history (diabetes

history, comorbidities and history of cardiovascular disease) should de described in designated forms.

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

Any new finding fulfilling the AE definition (see Appendix 3 (Section 10.3)) during the trial and any clinically significant worsening from baseline must be reported as an AE (see Section 8.3).

8.2.1 Physical examinations

- A physical examination will include assessments of the following: General appearance, thyroid gland, cardiovascular system, respiratory system, gastrointestinal system incl. mouth, central and peripheral nervous system, and musculoskeletal system.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- Height will be measured and recorded as specified in the flowchart (Section 1.2).
- Height should be measured without shoes in centimetres or inches and recorded to nearest ½ cm or ¼ inch.

8.2.2 Vital signs

- Pulse rate as well as systolic and diastolic blood pressure will be assessed as specified in the flowchart (Section 1.2).
- Blood pressure and pulse rate measurements should be preceded by at least 5 minutes of rest for the subject in a quiet setting without distractions (e.g. no use of television, cell phones).
- Blood pressure and pulse rate measurements will be assessed sitting with a completely automated device. Manual techniques must be used only if an automated device is not available.
- Blood pressure will consist of 3 systolic and diastolic blood pressure measurements with intervals of at least 1-2 minutes. An additional fourth blood pressure measurement must be performed if the first two readings on systolic or diastolic blood pressure differ by >10 mmHg. Only the last 2 systolic and last 2 diastolic blood pressure readings must be recorded in the eCRF. The eCRF will then calculate the mean for systolic and diastolic blood pressure.
- Pulse rate will be measured in connection to the blood pressure measurements. Record the pulse rate for the last 2 blood pressure measurements in the eCRF. The pulse rate is to be recorded as the mean of the last 2 measurements.

8.2.3 Electrocardiograms

12-lead ECG will be obtained as outlined in the flowchart (Section 1.2) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT and QTc intervals.

The ECGs will be collected for central storage for potential future assessment. This is to have the possibility to go back and evaluate previous ECG data in case of unforeseen or abnormal observations that could indicate safety findings or for future scientific purposes related to semaglutide, T2D, CV outcome or related diseases.

Local review for clinically significant abnormal findings must be performed by the investigator.

ECG must be performed according to the manual from the supplier.

8.2.4 Eye examination

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

Results of an eye examination performed by an ophthalmologist or another suitably qualified health care provider (e.g. optometrist) must be available and evaluated by the investigator before randomisation to assess eligibility. The eye examination should be performed as a fundus photography (e.g. 2-field 60 degree or better, colour or red-free) or by slit-lamp biomicroscopy examination (e.g. using a pre-corneal or corneal contact lens examination). Pharmacological pupil-dilation is a requirement unless using a digital fundus photography camera specified for non-dilated examination.

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

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

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

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

Germany and United States of America: for country-specific requirements, please see Appendix 8 (Section 10.8).

8.2.5 Clinical safety laboratory assessments

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

8.3 Adverse events and serious adverse events

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

*including 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.

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

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

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

Event type
Diabetic retinopathy
Gallbladder disease
Hepatic Event
Neoplasm
Acute pancreatitis
Acute kidney injury
Medication error, misuse and abuse

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

Hypoglycaemic episodes

Hypoglycaemic episodes require additional data collection on a hypoglycaemic episode form. As opposed to AEs requiring additional data collection (Table 8-1), non-serious hypoglycaemic episodes do not require an AE form to be filled in. If the hypoglycaemic episode fulfils the criteria for an SAE, then, in addition to the hypoglycaemic episodes form, an AE form and a safety information form must be filled in, please refer to Appendix 3 (Section 10.3). For more information on hypoglycaemic episodes, please refer to Appendix 6 (Section 10.6).

8.3.1 Time period and frequency for collecting AE and SAE information

All AEs and SAEs must be collected from the screening visit and until the follow-up visit (V17) at the time points specified in the flowchart (Section 1.1).

Medical occurrences that take place or have onset prior to the time point from which AEs are collected will be recorded as concomitant illness/medical history. AE and SAE reporting timelines can be found in Appendix 3 (Section 10.3). All SAEs must be recorded and reported to Novo Nordisk or designee within 24 hours, and the investigator must submit any updated SAE data to Novo Nordisk or designee within 24 hours of it being available.

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

8.3.2 Method of detecting AEs and SAEs

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

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

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs should be followed until final outcome of the event or the subject is lost to follow-up as described in Section 7.3. Further information on follow-up and final outcome of events is given in Appendix 3 (Section 10.3).

8.3.4 Regulatory reporting requirements for SAEs

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

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

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

8.3.5 Pregnancy

Details of pregnancies in female subjects will be collected after first exposure to trial product and until pregnancy outcome.

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

8.3.6 Cardiovascular and death events

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

8.3.7 Technical complaints

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

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

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

8.4 Treatment of overdose

There are no specific antidotes to semaglutide. Effects of overdose with semaglutide may be associated with GI disorders.

In the event of an overdose, the investigator should closely monitor the subject for overdose-related AE/SAE and laboratory abnormalities, and appropriate supportive treatment should be initiated according to the subjects' clinical signs and symptoms. A prolonged period of observation and treatment for these symptoms may be necessary, taking into account the long half-life of oral semaglutide of approximately one week.

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

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

8.5 Pharmacokinetics

- Single blood samples for measuring plasma concentration of semaglutide will be drawn on visits specified in the flowchart (Section 1.2) and in Appendix 2 (Section 10.2).
- Subject must be instructed to withhold their trial treatment in the morning of the clinic visit until blood sampling has been performed.
- The exact timing (date and time) of obtaining the pharmacokinetic (PK) sample must be recorded on the laboratory form.
- The exact timing (data and time) of last oral semaglutide dose must be recorded in the eCRF in relation to the PK sample
- The purpose of measuring plasma semaglutide levels is to conduct exposure-response, to evaluate the dose response and the adherence to the treatment.
- Blood samples for PK assessments must be collected, handled and shipped according to the description in the laboratory manual supplied by the central laboratory. The bioanalysis of semaglutide PK will be performed by a special laboratory. Semaglutide PK samples will be stored at the special laboratory responsible for PK until final Clinical Trial Report (CTR) in case Novo Nordisk requests further analysis of the PK samples. Details of the bioanalysis will be outlined in a bioanalytical study plan issued by the special laboratory. Bioanalysis of plasma samples for semaglutide will be carried out using a validated LC-MS/MS assay.

8.6 Pharmacodynamics

Not applicable for this trial.

8.7 Genetics

Not applicable for this trial.

8.8 Biomarkers

Not applicable for this trial.

8.9 Immunogenicity assessments

Anti-semaglutide antibodies

Blood samples for measurements of binding antibodies against semaglutide will be collected at pre-specified time points according to Appendix 2 (see Section 10.2) and must be completed pre-dose at V2. Blood samples will be collected, but anti-semaglutide antibodies will only be analysed by Novo Nordisk or a special lab appointed by Novo Nordisk if deemed necessary for clarification of unexpected drug exposure or other safety issues that may be related to antibody formation. If anti-semaglutide binding antibodies are measured, data as well as assay method description will be reported outside the CTR for this trial.

Procedures for sampling, handling, storage, labelling and shipment of samples must be performed in accordance with the laboratory manual.

Residual antibody samples will be retained (please refer to Appendix 7, Section 10.7).

8.10 Health economics

Not applicable for this trial.

9 Statistical considerations

9.1 Statistical hypotheses

Four confirmatory hypotheses will be evaluated based on the primary and secondary estimand. For the primary endpoint, change in HbA_{1c} from baseline to week 52, the following confirmatory one-sided hypothesis of superiority will be tested for both oral semaglutide 50 mg and 25 mg versus oral semaglutide 14 mg. Let the mean treatment difference (higher dose of oral semaglutide - oral semaglutide 14 mg) be defined as μ. The null (H_0) and alternative (H_A) hypotheses to be tested are:

H_0: $\mu \geq 0$ %-point against H_A: $\mu < 0$ %-point

For the confirmatory secondary endpoint, change in body weight from baseline to week 52, the following confirmatory one-sided hypothesis of superiority will be tested for both oral semaglutide 50 mg and 25 mg versus oral semaglutide 14 mg:

H_0: $\mu \geq 0$ kg against H_A: $\mu < 0$ kg

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

Multiplicity adjustment

Adjustment for multiplicity associated with the testing of the four confirmatory hypotheses will be done using the weighted Bonferroni-based closed testing procedure described in Bretz et al.[11] and outlined in Figure 9-1. The type I error will be preserved in the strong sense at a nominal two-sided 5% level. The first hypothesis to be tested is superiority of oral semaglutide 50 mg vs 14 mg on change from baseline in HbA_{1c}. It will be tested at the overall significance level (5%) while allocating 0% local significance level to the remaining of the hypotheses. For this hypothesis, and in general, if a hypothesis is confirmed, then the significance level will be reallocated according to the weight and the direction of the arrows going from the confirmed hypothesis to the next hypotheses as specified in Figure 9-1. Each of the four hypotheses will be tested at their updated local significance level (α-local). This process will be repeated until no further hypotheses can be confirmed.

Superiority will be considered confirmed if the mean treatment difference is supporting the corresponding alternative hypothesis and the two-sided p-value from the primary analysis is strictly below its local two-sided significance level as defined by the closed testing procedure. This is equivalent to using a one-sided p-value (nominal $\alpha = 0.025$) and a one-sided 2.5% overall significance level in the closed testing procedure.

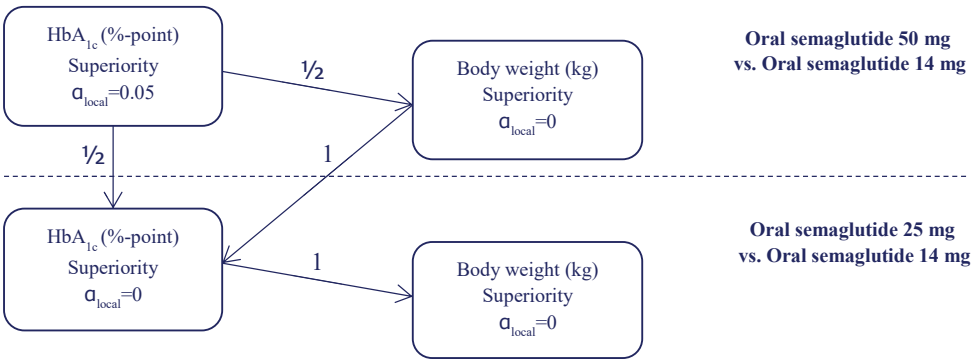


Figure 9-1 Graphical illustration of the closed testing procedure

The overall significance level of α = 0.05 (two-sided) is initially allocated to the hypothesis of superiority of oral semaglutide 50 mg vs 14 mg on change from baseline in HbA_{1c} (top left box). If a hypothesis is confirmed, the local significance level (α-local) will be reallocated according to the weight given by the directed edges between boxes (hypotheses).

9.2 Sample size determination

The sample size calculation was made considering the power for jointly confirming the superiority hypotheses with respect to HbA_{1c} for both oral semaglutide 50 mg and 25 mg versus oral semaglutide 14 mg for the primary estimand and to ensure a sufficient number of subjects will be exposed to assess safety and tolerability of the higher dose levels.

The sample size is calculated using the calcPower function in the R package, gMCP[12] using 10000 simulations. All of the four pre-specified confirmatory tests are assumed to be independent. Because some of the tests are positively correlated, the assumption of independence is viewed as conservative.

For change from baseline in HbA_{1c}, exposure-response modelling indicates a treatment difference vs 14 mg oral semaglutide of -0.52%-point and -0.33%-point for oral semaglutide 50 mg and 25 mg, respectively, in the population with baseline HbA_{1c} between 8.0% and 10.5% and baseline BMI ≥25kg/m^2 assuming that all subjects remain on trial treatment and do not initiate rescue medication. For change from baseline in body weight, treatment differences versus 14 mg oral semaglutide are predicted to be below -3.6 kg and -1.8 kg for oral semaglutide 50 mg and 25 mg, respectively.

In the sample size calculation, the assumed treatment effect will be adjusted for the anticipated premature trial treatment discontinuation, change in dose and use of rescue medication during 52 weeks. Across the PIONEER phase 3a trials, 15% to 20% of the subjects had discontinued trial treatment by week 52 with oral semaglutide 14 mg. Based on data from the PIONEER phase 3a trials for subjects with baseline HbA_{1c} between 8.0% and 10.5% and baseline BMI ≥25kg/m^2, similar to the inclusion criteria in this trial, it is anticipated that approximately 12% of subjects randomised to oral semaglutide 14 mg will prematurely discontinue trial treatment and that 12% will initiate rescue medication. Data from the 20 mg and 40 mg dose arms in the phase 2 trial (NN9924-3790) suggest that with oral semaglutide 25 and 50 mg, an additional 10-15% of the subjects may discontinue trial treatment, however, this was based on another dose escalation approach with a higher initial dose level. The procedures described in Section 6.6 are anticipated to

reduce the proportion of subjects prematurely discontinuing trial treatment with the higher dose levels. The proportion of subjects initiating rescue medication for the higher dose levels is assumed to be less than with the 14 mg dose.

It can be assumed that subjects discontinuing on oral semaglutide 14 mg would also do so if randomised to 25 mg or 50 mg. For the 12% of subjects expected to discontinue already at 14 mg, a treatment difference of zero is therefore assumed. For the remaining subjects discontinuing on 25 mg and 50 mg, a residual benefit of the higher dose could be expected depending on time of discontinuation. On the other hand, if discontinuing, subjects may initiate another treatment inferior to oral semaglutide 14 mg. As described in Section 6.6, dose reduction is allowed to accommodate subject tolerability. Collectively, a treatment difference of zero is assumed for the excess proportion of subjects assumed to reduce dose or prematurely discontinue treatment with the higher dose levels as well. The treatment difference is assumed to be reduced by 75% for subjects initiating rescue medication.

The sample size calculation is based on the assumptions that 20% of the subjects reduce dose or discontinue trial treatment prematurely with the higher dose levels and that 12% initiate rescue medication with 14 mg oral semaglutide. Hereby, the adjusted treatment difference (TD) will be:

$$\text{Adjusted } TD = 0.68 \cdot TD + 0.12 \cdot 0.25 \cdot TD + 0.20 \cdot 0 \cdot TD$$

The adjusted TD are -0.38 %-point and -0.23 %-point for HbA_{1c} and of -2.6 kg and -1.3 kg for body weight for oral semaglutide 50 and 25 mg, respectively. The power to jointly confirm HbA_{1c} superiority for both dose levels will be 89% with 1620 subjects randomised and a randomisation ratio of 1:1:1. The assumed common standard deviations for the change from baseline endpoints are based on data from subjects with baseline HbA_{1c} between 8.0% and 10.5% and baseline BMI ≥25kg/m^2 in PIONEER 2 (trial NN9924-4223) and 3 (trial NN9924-4222). Calculated powers for individual hypotheses are presented in Table 9-1.

Table 9-1 Calculated powers for individual hypotheses

	HbA_{1c} superiority		Body weight superiority	
Treatment dose	50 mg	25 mg	50 mg	25 mg
Power	>99%	89%	>99%	86%

Table 9-2 shows the sensitivity of the power under different deviations from the above assumptions with a fixed sample size of 1620 subjects.

Table 9-2 Power for jointly confirming HbA_{1c} superiority under various assumptions

TD HbA_{1c} (%-point)		TD BW (kg)		Proportion discontinued	Adj. TD HbA_{1c} (%-point)		Adj. TD BW (kg)		Standard deviation		Power
50 mg	25 mg	50 mg	25 mg	Both doses	50 mg	25 mg	50 mg	25 mg	HbA_{1c}	BW	
-0.52	-0.33	-3.6	-1.8	25%	-0.36	-0.22	-2.4	-1.2	1.2	5.5	84 %
-0.52	-0.33	-3.6	-1.8	20%	-0.38	-0.23	-2.6	-1.3	1.25	6.0	87 %
-0.52	**-0.33**	**-3.6**	**-1.8**	**20%**	**-0.38**	**-0.23**	**-2.6**	**-1.3**	**1.2**	**5.5**	**89 %**
-0.52	-0.33	-3.6	-1.8	20%	-0.38	-0.23	-2.6	-1.3	1.15	5.0	92 %
-0.52	-0.33	-3.6	-1.8	18%	-0.39	-0.24	-2.6	-1.3	1.2	5.5	91 %
-0.50	-0.30	-3.3	-1.5	25%	-0.33	-0.20	-2.2	-1.0	1.2	5.5	77 %
-0.50	-0.30	-3.3	-1.5	20%	-0.36	-0.21	-2.3	-1.1	1.2	5.5	83 %
-0.50	-0.30	-3.3	-1.5	18%	-0.37	-0.22	-2.4	-1.1	1.2	5.5	85 %

Assuming 12% on rescue medication with 14 mg oral semaglutide. The highlighted scenario has been chosen for the sample size calculation.

1620 subjects will be randomly assigned to trial treatment.

9.3 Populations for analyses

The following populations are defined:

Population	Description
Full analysis set (FAS)	All subjects randomised. Subjects contribute to a treatment group based on the trial treatment they were randomised to receive.
Safety analysis set (SAS)	All subjects who receive at least 1 dose of trial treatment. Subjects contribute to a treatment group based on the trial treatment they actually received.

The FAS will be used in the evaluation of the efficacy endpoints, the SAS will be used for the evaluation of the safety endpoints, exclusively.

Data selections and observation periods

Unless subjects withdraw their informed consent, data collection will continue for the planned full duration of the trial for the individual subject. The full duration of the trial is defined as up to and including the follow-up visit (V17) for subjects completing trial treatment and subjects who have discontinued trial treatment prematurely.

As described in Section 3.1 the trial objectives relating to efficacy will be addressed using two different types of estimands. The primary and secondary estimands applying a treatment policy strategy to all intercurrent events and the additional supportive estimands applying a hypothetical strategy to the intercurrent events of premature trial treatment discontinuation and initiation of additional anti-diabetic medication. The handling of the intercurrent events with respect to data collection and analysis is specified in Table 9-3.

Table 9-3 Handling of intercurrent events for the estimands

Intercurrent event	Primary and secondary estimands	Additional supportive estimands
Premature trial treatment discontinuation	Data collected after the intercurrent event is used in analysis in line with a treatment-policy strategy, i.e. disregarding the occurrence of the intercurrent event	Data collected after the intercurrent event will be excluded and treated as missing in analysis, i.e. using a hypothetical strategy
Initiation of additional anti-diabetic medication		
Change of dose		Data collected after the intercurrent event and used in analysis in line with a treatment-policy strategy, i.e. disregarding the occurrence of the intercurrent event

Additional anti-diabetic medication is defined as new anti-diabetic medication and/or intensification of anti-diabetic medication initiated at or after randomisation and before planned end of treatment. Rescue medication is used to designate additional anti-diabetic medication initiated while on trial treatment, i.e. before last dose of trial product.

Observation periods will be used to select data for analyses in line with the strategies applied for the intercurrent events. Subjects and data to be used in an analysis will be selected in a two-step manner:

- First, subjects will be selected based on the specified analysis set.
- Second, data points on the selected subjects from the first step will be selected based on the specified observation period.

For the efficacy and safety evaluations, three different observation periods will be defined:

- The **in-trial** observation period – the time period from when a subject is randomised until the final scheduled visit, including any period after initiation of additional anti-diabetic medication or discontinuation of trial treatment.
- The **on-treatment** observation period – the time period when a subject is on trial treatment, including any period after initiation of rescue medication.
- The **on-treatment without rescue medication** observation period – the time period when a subject is on trial treatment, excluding any period after initiation of rescue medication.

The **in-trial** observation period begins at the date of randomisation and ends at the final scheduled visit, which can be one of the below:

- the follow-up visit (V17) for subjects who complete treatment and for subjects who discontinue trial treatment prematurely
- the last contact for subjects who withdraw from trial, are lost to follow-up or die

The **on-treatment** observation period begins at the date of first dose of trial treatment; the end date depends on the assessment being evaluated:

- For all efficacy assessments and certain safety assessments (laboratory assessments, physical examination and vital signs), a plus-3-day window (i.e. the 3-day visit window) is used and the period ends at the first of the following time points:
- last dose of trial treatment plus a 3-day window
- end of the in-trial observation period

- For the remaining safety assessments (eye examination categories, AEs, and hypoglycaemic episodes), a plus-38-day window (i.e. the 5-week follow-up period plus the 3-day visit window) is used and the period ends at the first of the following time points:
- the follow-up visit (V17)
- the last dose of trial treatment +38 days
- end of the in-trial observation period

The **on-treatment without rescue medication** observation period begins at the date of the first dose of trial treatment and ends at the first of the following time points:

- end of the on-treatment observation period
- initiation of rescue medication (if any)

For the efficacy endpoints, the primary and secondary estimands will be evaluated based on data from the in-trial observation period and the additional supportive estimands will be evaluated based on data from the on-treatment without rescue medication observation period thereby selecting data in line with the strategies applied for the intercurrent events as shown in Table 9-3. The safety evaluation will primarily be based on the on-treatment observation period, except for deaths and AE types with potentially long latency between onset and diagnosis, for which the in-trial observation period will be used. The observation period determines what data subjects contributes with to a specific analysis. Baseline values are by definition included in all observation periods; other data points collected outside the observation period used for an analysis will be considered missing.

Before data are locked for statistical analysis, a review of all data will take place. Exclusion of data from analyses should be used restrictively, and normally no data should be excluded from the FAS. The subjects or observations to be excluded, and the reasons for their exclusion must be documented before unblinding. The subjects and observations excluded from analysis sets, and the reason for this, will be described in the clinical trial report.

9.4 Statistical analyses

The statistical analysis plan (SAP) will be finalised prior to database lock or potential partial database lock, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints, including the primary and confirmatory secondary endpoints.

9.4.1 General considerations

Data from all sites will be analysed and reported together.

In statistical analyses where stratification is accounted for, the background medication at screening will be included based on the actual information collected through the eCRF. In case of missing eCRF information, the information collected from the IWRS system will be used.

The latest available measurement, at or prior to the randomisation visit, will be used as the baseline measurement. If no measurement(s) have been obtained, at or prior to randomisation, the baseline value will be left missing.

Results from a statistical analysis will as a minimum be presented by the estimated treatment contrasts for each high dose vs. 14 mg oral semaglutide with associated two-sided 95% confidence intervals and p-values corresponding to two-sided tests of no difference.

Missing data

The amount of missing data when estimating the primary and secondary estimands (i.e. data that are not available even though all efforts were made to ensure that subjects stayed in the trial regardless of premature discontinuation of trial treatment or initiation of additional anti-diabetic treatment) is expected to be low. At week 52, the proportion of subjects with missing data was 5-7% across trials in the PIONEER programme. Missing data will be missing mainly be due to subjects withdrawing consent or being lost to follow-up. In the statistical analyses, missing data will be handled in line with the strategies applied for the pre-defined intercurrent events.

9.4.2 Primary endpoint

The primary endpoint is the change in HbA_{1c} (%-point) from baseline (week 0) to week 52.

Primary analysis for the primary estimand

The primary estimand defined in Section 3.1 will be estimated based on the FAS using week 52 measurements from the in-trial observation period. The primary statistical analysis will be a pattern mixture model using multiple imputation to handle missing data assuming that the missing data mechanism is missing at random (MAR) within the groups used for imputation. Imputation of missing week-52 data will be done within 6 groups of subjects defined by randomised treatment arm, and whether subjects at week 52 (i) are still on treatment and have not initiated rescue medication or (ii) have discontinued treatment or initiated rescue medication. It is hereby assumed that the likely values of what the missing data would have been if available are best described by information from subjects who at week 52 are similar in terms of randomised treatment arm and trial treatment discontinuation/rescue medication status. For each imputation group, an analysis of covariance model (ANCOVA) with stratification factor and region as factors and baseline HbA_{1c} as covariate will be used to impute 1000 values for each subject with missing week 52 data. For the imputation groups where the subjects have discontinued treatment or initiated rescue medication the time (days) from randomisation until discontinuation or initiation of rescue medication will also be included as a covariate. The 1000 complete data sets will be analysed using an ANCOVA with treatment, stratification factor and region as factors and baseline HbA_{1c} as covariate. The results obtained from analysing the datasets will be combined using Rubin's rule[13] to draw inference.

Sensitivity analysis for the primary estimand

In line with ICH E9 (R1), sensitivity analyses will be performed investigating the robustness of the conclusions made on the basis of the primary analyses towards the impact of missing data.

Tipping-point multiple imputation analysis: A two-dimensional tipping point sensitivity analysis will be used to address the assumption of MAR within imputation groups. Subjects with missing data will be assumed to have a worse outcome in the 25 mg and 50 mg treatment arms and a better outcome in the 14 mg arm compared to the imputations in the primary analysis. Missing data will first be imputed as in the primary analysis. Secondly, penalties will be added to or subtracted from the imputed week-52 values. The approach is to gradually increase these penalties independently in

the treatment arms until the confirmed HbA_{1c} conclusion from the primary analysis is changed. For each hypothesis tested, the values of the penalties that changes the conclusion will be used to evaluate the robustness of the primary analysis results.

Return to baseline multiple imputation analysis: subjects with missing data at week 52 will have their change from baseline value imputed as 0 plus a random error. The error is randomly drawn from a normal distribution with a mean of 0 and a variance equal to the residual variance estimated from the MMRM for observed values of change from baseline in HbA_{1c}, adjusted for the same covariates and factors as in the primary analysis. For missing values from patients who are still on treatment, it will be assumed that those data are missing at random and they will be imputed based on the observed data from the subjects who completed the trial on treatment in the same treatment arm.

Analysis for the additional estimand

The additional estimand (Section 3.1) will be estimated based on the FAS using post-baseline measurements up to and including week 52 from the on-treatment without rescue medication observation period. The analysis for the additional estimand will be a Mixed Model for Repeated Measurements (MMRM). A restricted maximum likelihood will be used. The model will include all post baseline HbA_{1c} measurements collected at scheduled visits up to and including week 52 as dependent variables. The independent effects included in the model will be treatment, stratification factor and region as categorical fixed effects and baseline HbA_{1c} as a covariate, all nested within visit. An unstructured covariance matrix for HbA_{1c} measurements within the same subject will be employed, assuming measurements from different subjects are independent.

9.4.3 Secondary endpoints

9.4.3.1 Confirmatory secondary endpoint

The confirmatory secondary endpoint is the change in body weight (kg) from baseline (week 0) to week 52.

Analysis for the secondary estimand

The secondary estimand will be estimated in the same way as for the primary endpoint with baseline HbA_{1c} replaced by baseline body weight as the covariate.

Sensitivity analysis for the secondary estimand

Sensitivity analyses similar to the ones performed for the primary endpoint will be performed.

Analysis for the additional estimand

The additional estimand will be estimated in the same way as for the primary endpoint with baseline HbA_{1c} replaced by baseline body weight as the covariate.

9.4.3.2 Supportive secondary endpoints

For details on analyses of additional supportive secondary endpoints, please refer to the SAP, which will be completed prior to database lock or potential partial database lock.

9.4.4 Other safety analyses

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

9.4.5 Other analyse(s)

For other analyse(s), please refer to the SAP.

9.4.5.1 Pharmacokinetic modelling

Population PK modelling and exposure-response analyses may be included to support dose selection and to explore the benefits of high versus lower doses of semaglutide in subjects with T2D.

The modelling will include data from all randomised subjects that were exposed to semaglutide in this trial and might be performed as a meta-analysis including data from historical trials. Actual dose and date of administration of last dose before PK sampling will be registered in the CRF and used in the analysis, together with actual time point for PK sampling.

A modelling analysis plan will be prepared before database lock or potential partial database lock for the trial, outlining details of the analysis. The results will be reported separately from the CTR.

9.5 Interim analyses

See Section 9.7 for details regarding partial database lock.

9.6 Data monitoring committee

Not applicable for this trial.

9.7 Reporting of the main part of the trial

A partial database lock will be performed at the end of the treatment period for all subjects, i.e., after the date of the last subject last treatment visit. A partial database lock is implemented to support potential earlier access of oral semaglutide 25 and 50 mg to the patient population expected to benefit from higher doses.

All efficacy analyses will be performed based on the data from the partial database lock. No efficacy assessments are collected after last subject last treatment, and so unblinding of Novo Nordisk staff will be after all subjects have completed treatment. Therefore, efficacy results cannot be biased by the early unblinding. Impact on PK and safety evaluation after partial database lock is considered minor as most subjects will have completed the follow-up visit, and subjects and investigators remain blinded. Full analysis of PK and safety will be performed after the full database lock.

The SAP will be finalised prior to partial database lock. A detailed plan for data handling, blinding, data analysis, and operational aspects of the partial database lock and the database update will be finalised before the partial database lock.

The result of the evaluation at partial database lock will not be shared with investigators or subjects before the full database lock, and only a minimum number of Novo Nordisk staff will know the randomisation code at subject level. There will be no change in study design regardless of the outcome of the evaluation at partial database lock.

The database will be updated after the partial database lock to include the remaining data. The full database lock will be performed, as per the usual procedures, after the date of the last subject last visit.

10 Supporting documentation and operational considerations

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

10.1.1 Regulatory and ethical considerations

- This trial will be conducted in accordance with the protocol and with the following:
- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki[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 CTR according to national requirements.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the trial design, except for changes necessary to eliminate an immediate safety hazard to trial subjects.
- Before a site is allowed to start screening subjects, written notification from Novo Nordisk must be received.
- The investigator will be responsible for:
- providing written summaries of the status of the trial annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC and/or regulatory authorities.
- notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
- providing oversight of the conduct of the trial at the site and adherence to requirements of ICH guidelines, the IRB/IEC, and all other applicable local regulations.
- ensuring submission of the CTR synopsis to the IRB/IEC.
- reporting any potential serious breaches to the sponsor immediately after discovery.

10.1.2 Financial disclosure

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

For US sites: Verification under disclosures per Code of Federal Regulations (CFR) of Financial Conflict of Interest.

10.1.3 Informed consent process

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

- The investigator must ensure the subject ample time to come to a decision whether or not to participate in the trial.
- Subjects must be informed that their participation is voluntary.
- Subjects must be informed about their privacy rights.
- Subjects will be required to sign and date a statement of informed consent that meets the requirements of local regulations, ICH guidelines[15], Declaration of Helsinki[14] and the IRB/IEC or site.
- The medical record must include a statement that written informed consent was obtained before any trial related activity and the date when the written consent was obtained. The authorised person obtaining the informed consent must also sign and date the informed consent form before any trial related activity.
- The responsibility of seeking informed consent must remain with the investigator, but the investigator may delegate the task to a medically qualified person, in accordance with local requirements.
- Subjects must be re-consented to the most current version of the informed consent form during their participation in the trial.
- A copy of the informed consent form must be provided to the subject.

10.1.4 Information to subjects during trial

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

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

10.1.5 Data protection

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

10.1.6 Committees structure

10.1.6.1 Novo Nordisk safety committee

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

10.1.7 Dissemination of clinical trial data

Information of the trial will be disclosed at clinicaltrials.gov, clinicaltrialsregister.eu 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)[16], the Food and Drug Administration Amendment Act (FDAAA)[17], European Commission Requirements[1, 18, 19] and other relevant recommendations or regulations. If a subject requests to be included in the trial via the Novo Nordisk e-mail contact at these web sites, Novo Nordisk may disclose the investigator's contact details to the subject. As a result of increasing requirements for transparency, some countries require public disclosure of investigator names and their affiliations.

The primary completion date (PCD) is the last assessment of the primary endpoint, and is for this trial last subject first treatment (LSFT) + 52 weeks corresponding to visit V14. If the last subject is withdrawn early, the PCD is considered the date when the last subject would have completed visit V14. The PCD determines the deadline for results disclosure at clinicaltrials.gov according to FDAAA.

10.1.8 Data quality assurance

10.1.8.1 Case report forms

- Novo Nordisk or designee is responsible for the data management of this trial including quality checking of the data.
- All subject data relating to the trial will be recorded on electronic CRFs unless transmitted electronically to Novo Nordisk or designee (e.g. laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The following will be provided as paper CRFs:
- Pregnancy forms
- The following will be provided as paper CRFs to be used when access to the eCRF is revoked or the eCRF is temporarily unavailable:
- AE forms
- Safety information forms
- Technical complaint forms (also to be used to report complaints on trial product not yet allocated to a subject)
- Corrections to the CRF data may be made by the investigator or the investigator's delegated staff. An audit trail will be maintained in the CRF application containing as a minimum: the old and the new data, identification of the person entering the data, date and time of the entry and reason for the correction. If corrections are made by the investigator's delegated staff after the

date when the investigator signed the CRF, the CRF must be signed and dated again by the investigator.

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

10.1.8.2 Monitoring

- The investigator must permit trial-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents (original documents, data and records). Direct access includes permission to examine, analyse, verify and reproduce any record(s) and report(s) that are important to the evaluation of the trial. If the electronic medical record does not have a visible audit trail, the investigator must provide the monitor with signed and dated printouts. In addition, the relevant site staff should be available for discussions at monitoring visits and between monitoring visits (e.g. by telephone).
- Trial monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorised site personnel are accurate, complete and verifiable from source documents; that the safety and rights of subjects are being protected, to monitor drug accountability and collect completed paper CRF pages, if applicable, and that the trial is being conducted in accordance with the currently approved protocol and any other trial agreements, ICH GCP, and all applicable regulatory requirements.
- Monitoring will be conducted using a risk-based approach including risk assessment, monitoring plans, centralised monitoring (remote assessment of data by Novo Nordisk) and visits to sites.
- Monitors will review the subject's medical records and other source data, e.g. the diaries to ensure consistency and/or identify omissions compared to the CRF.
- An unblinded monitor will be responsible for the reconciliation process set up for this trial.

10.1.8.3 Protocol compliance

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

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

10.1.9 Source documents

- All data entered in the CRF must be verifiable in source documentation other than the CRF.
- If source data is entered directly in a paper CRF, each data entry or clear series of data entries must be signed and dated separately by the trial staff making the entry.
- The original of the completed diaries must not be removed from the site, unless they form part of the CRF and a copy is kept at the site.
- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the site.

- Data reported on the paper CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents, or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records. Also, current medical records must be available.
- It must be possible to verify subject's medical history in source documents, such as subject's medical record.
- The investigator must document any attempt to obtain external medical information by noting the date(s) when information was requested, and who was contacted.
- Definition of what constitutes source data can be found in a source document agreement at each site. There will only be one source document defined at any time for any data element.

10.1.10 Retention of clinical trial documentation

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

Canada: for country-specific requirements, please see Appendix 8 (Section 10.8).

10.1.11 Trial and site closure

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

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

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

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

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

- discontinuation of further trial product development.

10.1.12 Responsibilities

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

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

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

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

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

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

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

10.1.13 Indemnity statement

Novo Nordisk carries product liability for its products, and liability as assumed under the special laws, acts and/or guidelines for conducting clinical trials in any country, unless others have shown negligence.

Novo Nordisk assumes no liability in the event of negligence or any other liability of the sites or investigators conducting the trial or by persons for whom the said site or investigator are responsible.

10.1.14 Publication policy

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

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

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

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

One (or two) investigator(s) will be appointed by Novo Nordisk to review and sign the CTR (signatory investigator) on behalf of all participating investigators. The signatory investigator(s) will be appointed based upon the criteria defined by the International Committee of Medical Journal Editors for research publications.[20]

10.1.14.1 Communication of results

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

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

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

In all cases, the trial results will be reported in an objective, accurate, balanced and complete manner, with a discussion of the strengths and limitations. In the event of any disagreement on the content of any publication, both the investigators' and Novo Nordisk opinions will be fairly and sufficiently represented in the publication.

10.1.14.2 Authorship

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

Authorship of publications should be in accordance with the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals by the International Committee of Medical Journal Editors.[20]

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

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

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

For a multicentre clinical trial, analyses based on single-site data usually have significant statistical limitations and frequently do not provide meaningful information for healthcare professionals or subjects, and therefore may not be supported by Novo Nordisk. Thus, Novo Nordisk may deny a request or ask for deferment of the publication of individual site results until the primary manuscript is accepted for publication. In line with Good Publication Practice, such individual reports should not precede the primary manuscript and should always reference the primary manuscript of the trial.

10.1.14.4 Investigator access to data and review of results

As owner of the trial database, Novo Nordisk has the discretion to determine who will have access to the database.

Individual investigators will have their own research subjects' data and will be provided with the randomisation code after results are available.

10.2 Appendix 2: Clinical laboratory tests

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

Table 10-1 Protocol-required efficacy laboratory assessments

Laboratory assessments	Parameters	Visit
Glucose metabolism	• Fasting plasma glucose[1]	V2, V5, V7, V10, V14, V16
	• HbA_{1c}	V1, V2, V3, V4, V5, V7, V9, V10, V11, V12, V13, V14, V15, V16
Lipids	• High density lipoprotein (HDL) cholesterol • Low density lipoprotein (LDL) cholesterol • Triglycerides • Total cholesterol	V2, V10, V14, V16
Urinanalysis[2]	• Urinary albumin to creatinine ratio (UACR)	V2, V5, V10, V14, V16

NOTES:
[1]An FPG result ≤3.9 mmol/L (70 mg/dL) in relation to planned fasting visits should not be reported as a hypoglycaemic episode but as an AE at the discretion of the investigator (see Appendix 3 (Section 10.3).
[2] Subjects should collect a first morning urine sample both on the day prior to the visit and on the day of the visit. Samples should be stored in the fridge at home and brought to the site

Table 10-2 Protocol-required safety laboratory assessments

Laboratory assessments	Parameters	Visit
Haematology	• Eosinophils • Lymphocytes • Basophils • Monocytes • Neutrophils • Erythrocytes • Haematocrit • Haemoglobin • Leucocytes • Thrombocytes	V1, V10, V14, V16
Biochemistry[1]	• Alanine Aminotransferase (ALT) • Alkaline phosphatase • Aspartate Aminotransferase (AST) • Creatinine • Potassium • Sodium • Amylase • Lipase • Total bilirubin	V1, V10, V14, V16
Hormones	• Calcitonin[2]	V2
Pregnancy Testing	• Urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[3]	V1, V16, V17
Pharmacokinetics	• Semaglutide plasma concentration	V3, V5, V7, V10, V14, V16
Antibodies	• Anti-semaglutide antibodies	V2, V3, V5, V7, V10, V14, V16, V17
Other tests	• eGFR calculated by the central laboratory based on the creatinine value using the CKD-EPI equation	V1, V10, V14, V16

Notes:
[1] Details of required actions and follow-up assessments for increased liver parameters including any discontinuation criteria are given in Appendix 3 (Section 10.3) (Hy's Law) and Section 7.1.
[2] Calcitonin will be measured once at baseline. Not intended for screening. The investigator must evaluate need for further measurements during the trial.
[3] Local urine testing will be standard unless serum testing is required by local regulation or IRB/IEC.

All trial-required laboratory assessments will be performed by a central laboratory, with the exception of:

- urine pregnancy testing, which will be performed locally at site or at home
- semaglutide plasma concentrations, which will be performed at a specialised laboratory
- anti-semaglutide antibodies (if deemed necessary for clarification of unexpected drug exposure or other safety issues that may be related to antibody formation), which will be performed at a specialised laboratory

Laboratory/analyte results that could unblind the trial will not be reported to the sites until the trial has been unblinded.

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

10.3.1 Definition of AE

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

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

10.3.2 Definition of an SAE

An SAE is an AE that fulfils at least one of the following criteria:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalisation or prolongation of existing hospitalisation • Hospitalisation signifies that the subject has been detained at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office

or outpatient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other seriousness criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious.

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

d. Results in persistent or significant disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Important medical event:

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

10.3.3 Description of AEs requiring additional data collection

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

Adverse events requiring additional data collection
AEs requiring additional data collection (Table 8-1) are AEs where the additional data will benefit the evaluation of the safety of the trail product. The selection of these events is based on the non-clinical and clinical data with semaglutide, knowledge from the GLP-1 RA drug class as well as regulatory requirements.

Diabetic retinopathy
New onset or worsening of diabetic retinopathy.

Gallbladder disease
Events of symptomatic gallbladder disease, including gallstones and cholecystitis.

Hepatic event
Hepatic event defined as:
- disorders of the liver including cholestatic conditions and liver related signs and symptoms
- ALT or AST > 3x ULN and total bilirubin > 2x ULN*
- ALT or AST > 3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

* Please note that in case of such a hepatic event where no alternative aetiology exists (Hy's law), the event must be reported as an SAE using the important medical event criterion if no other seriousness criteria are applicable.

Neoplasms
All confirmed neoplasms (both malignant and non-malignant) by histology or other substantial clinical evidence.

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

Acute kidney injury
Event of an abrupt or rapid decline in renal filtration function. This condition is usually marked by a rise in serum creatinine concentration or by azotemia (a rise in blood urea nitrogen (BUN) concentration).

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

Misuse and abuse
- Situations where the IMP is intentionally and inappropriately used not in accordance with the protocol (e.g. overdose to maximise effect)
- Persistent or sporadic, intentional excessive use of an IMP which is accompanied by harmful physical or psychological effects (e.g. overdose with the intention to cause harm)

Medication error, misuse and abuse must always be reported as an AE (e.g. accidental overdose, intentional overdose or other) on a separate AE form, and a medication error, misuse and abuse form must be completed. In case of a medication error and/or misuse and abuse resulting in a clinical consequence (e.g. hypoglycaemia or other), this must be reported on an additional AE form.

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

AE and SAE recording

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

Assessment of severity

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

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

Assessment of causality

- The investigator is obligated to assess the relationship between IMP and the occurrence of each AE/SAE.
- Relationship between an AE/SAE and the relevant IMP(s) should be assessed as:
  - Probable - Good reason and sufficient documentation to assume a causal relationship.
  - Possible - A causal relationship is conceivable and cannot be dismissed.
  - Unlikely - The event is most likely related to aetiology other than the IMP.
- Alternative aetiology, such as underlying disease(s), concomitant medication, and other risk factors, as well as the temporal relationship of the event to IMP administration, will be considered and investigated.
- The investigator should use the investigator's brochure for the assessment. For each AE/SAE, the investigator must document in the medical records that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report. However, **it is important that the investigator**

always makes an assessment of causality for every event before the initial transmission of the SAE data.

- The investigator may change his/her opinion of causality, in light of follow-up information, and update the causality assessment in the CRF.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Final outcome

The investigator will select the most appropriate outcome:

- **Recovered/resolved:** The subject has fully recovered, or by medical or surgical treatment the condition has returned to the level observed when first documented
- **Recovering/resolving:** The condition is improving, and the subject is expected to recover from the event. This term may be applicable in cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE).
- Note: For SAEs, this term is only applicable if the subject has completed the follow-up period and is expected to recover.
- **Recovered/resolved with sequelae:** The subject has recovered from the condition but with lasting effect due to a disease, injury, treatment or procedure. If a sequela meets an SAE criterion, the AE must be reported as an SAE.
- **Not recovered/not resolved:** The condition of the subject has not improved, and the symptoms are unchanged, or the outcome is not known.
  Note: This term may be applicable in cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE).
- **Fatal:** This term is only applicable if the subject died from a condition related to the reported AE. Outcomes of other reported AEs in a subject before he/she died should be assessed as "recovered/resolved", "recovering/resolving", "recovered/resolved with sequelae" or "not recovered/not resolved". An AE with a fatal outcome must be reported as an SAE.
- **Unknown:** This term is only applicable if the subject is lost to follow-up.

Follow-up of AE and SAE

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

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

New or updated information will be recorded in the CRF.

10.3.5 Reporting of SAEs

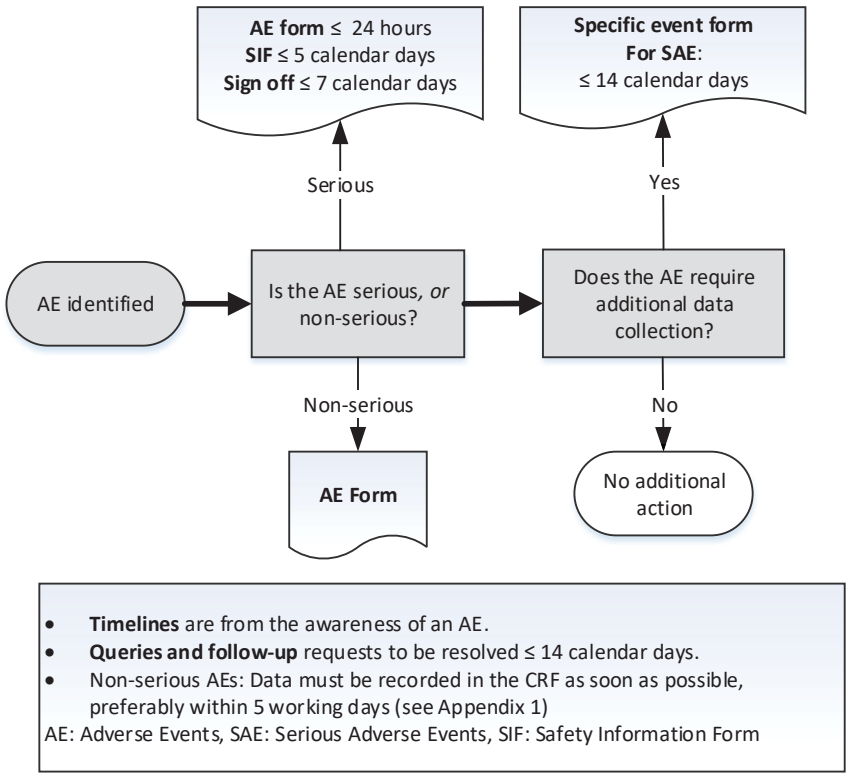
SAE reporting via electronic CRF

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

AE and SAE reporting via paper CRF

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



NOTE: The collection of AEs includes the collection of COVID-19 or suspected COVID-19 AEs.

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

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

10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information

Definitions

Woman of childbearing potential (WOCBP)

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

Females in the following categories are not considered WOCBP

1. Premenarcheal
2. Females with one or more of the following:

- Documented total hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

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

3. Postmenopausal female:

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

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

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

Contraception guidance

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

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

Table 10-3 Highly effective contraceptive methods

CONTRACEPTIVES [a] ALLOWED DURING THE TRIAL INCLUDE:

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

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

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

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

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

Czech Republic, and Germany: For country-specific requirements, please see Appendix 8 (Section 10.8).

Pregnancy testing

- WOCBP should only be included after a negative highly sensitive urine pregnancy test (refer to Appendix 2, Section 10.2)
- Additional pregnancy testing should be performed according to the flowchart (Section 1.2).
- Pregnancy testing should be performed whenever a menstruation is missed or when pregnancy is otherwise suspected.
- Pregnancy testing is advised 5 weeks after premature discontinuation of trial treatment.
- Additional pregnancy testing should be performed during the treatment period, if required locally (Appendix 8, Section 10.8).

Collection of pregnancy information

Female subjects who become pregnant

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

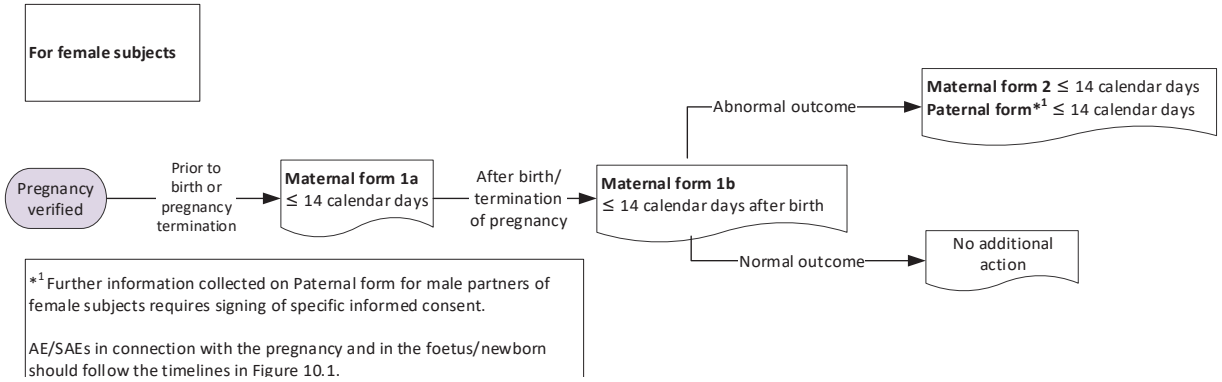


Figure 10-2 Decision tree for determining the forms to complete with associated timelines for pregnancy.

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

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

10.5.1 Definition of technical complaint

Technical complaint definition
• A technical complaint is any written, electronic or oral communication that alleges product (medicine or device) defects. The technical complaint may be associated with an AE but does not concern the AE itself.

Examples of technical complaints:

- Problems with the physical or chemical appearance of trial products (e.g. discoloration, particles or contamination)
- Problems with packaging material including labelling

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

10.5.2 Recording and follow-up of technical complaints

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

Timelines for reporting of technical complaints to Novo Nordisk
The investigator must complete the technical complaint form in the CRF within: • 24 hours if related to an SAE (or could have led to an SAE) • 5 days calendar for all other technical complaints If the CRF is unavailable, or when reporting a technical complaint on a trial product that is not yet allocated to subject , the information must be provided on a paper form to Customer Complaint Center, Novo Nordisk, within the same timelines as stated above. When the CRF becomes available again, the investigator must enter the information on the technical complaint form in the CRF.

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

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

10.5.3 Reporting of technical complaints

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

10.6 Appendix 6: Hypoglycaemic episodes

Table 10-4 Classification of hypoglycaemia

Classification of hypoglycaemia		
Level	**Glycaemic criteria**	**Description**
Hypoglycaemia alert value (level 1)	≤ 3.9 mmol/L (70 mg/dL) and ≥ 3.0 mmol/L (54 mg/dL)	Sufficiently low for treatment with fast-acting carbohydrate and dose adjustment of glucose-lowering therapy
Clinically significant hypoglycaemia (level 2)	< 3.0 mmol/L (54 mg/dL)	Sufficiently low to indicate serious, clinically important hypoglycaemia
Severe hypoglycaemia (level 3)	No specific glucose threshold	[1]Hypoglycaemia associated with severe cognitive impairment requiring external assistance for recovery
Notes: The Novo Nordisk terms are adapted from IHSG[21], ADA[22], ISPAD[23], type 1 diabetes outcomes program[24], ATTD[25]. Severe hypoglycaemia as defined by Seaquist[26] and ISPAD[23].		

Severe hypoglycaemia

[1]Severe hypoglycaemia is an event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.[26]

Nocturnal hypoglycaemia

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

Reporting of hypoglycaemic episodes

Reporting of hypoglycaemic episodes by BG meters:
Plasma glucose (PG) should always be recorded in the diary/eCRF when a hypoglycaemic episode is suspected.
Hypoglycaemic episodes should be reported according to the instructions below. When a subject experiences a hypoglycaemic episode, the subject should record the general information in relation to the hypoglycaemia (timing, PG measurements, symptoms etc.) as described in the diary. The investigator should ensure correct reporting of the hypoglycaemic episode and report the hypoglycaemic episode to the eCRF. In case a subject is not able to fill in the diary (e.g. in case of hospitalisation), the investigator should still report the hypoglycaemic episode on the hypoglycaemic episodes form in the eCRF.

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

Upon onset of a hypoglycaemic episode the subject is recommended to measure PG every 15 minutes until the PG value is >3.9 mmol/L (70 mg/dL) and/or symptoms have been resolved in accordance with current guidelines.[26]

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

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

Regarding the question: "To feel better, did you need help to get a sugary drink, food, or medicine?" the investigator must instruct the subjects to answer "Yes", if the episode was an event that required assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. PG concentrations may not be available during an event, but neurological recovery following the return of PG to normal is considered sufficient evidence that the event was induced by a low PG concentration.[26]

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

Diary review

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

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

- If a hypoglycaemic episode form in the diary is not completed by the subject within 7 calendar days of the PG measurement, the episode should be described in the source documents and reported by the investigator on a hypoglycaemic episode (e)CRF with as much information as possible. If the subject did not need help to get a sugary drink, food, or medicine, Novo Nordisk will only ask for start date due to recall bias.[27, 28]

Re-training of subjects

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

10.7 Appendix 7: Retention of human biosamples

Remaining and residual antibody samples already collected (Sections 8.5 and 8.9) may be retained after end of the trial.

- The samples will be stored at Novo Nordisk or a biorepository assigned by Novo Nordisk after end of trial and until marketing authorisation approval or until the research project terminates, but no longer than 15 years from the end of the trial after which they will be destroyed.
- Samples might be transferred to other countries, to a laboratory assigned by Novo Nordisk.
- The retained samples may be used to:
- evaluate safety or efficacy aspects that address concerns arising during or after the trial.
- further characterise the antibody responses towards the drug, if required by health authorities or for safety reasons.
- conduct further analytical method development and validation of antibody assays.

10.8 Appendix 8: Country-specific requirements

Section 5.1 Inclusion criteria

For Taiwan:
Inclusion criteria 2: ≥ 20 years at the time of signing informed consent.

Section 5.2 Exclusion criteria

For Croatia and Germany:

Exclusion criterion 15: "*Simultaneous participation in a trial with the primary objective of evaluating an approved or non-approved investigational medicinal product for prevention or treatment of COVID 19 disease or COVID-19 postinfectious conditions is allowed if the last dose of the investigational medicinal product has been received more than 30 days before screening." is not applicable for Croatia and Germany.

Section 6.5 Concomitant medication

For Croatia and Germany:

"Medication administered in relation to a clinical trial for COVID-19 prevention or treatment" is not applicable for Croatia and Germany.

Section 7.1 Discontinuation of trial treatment

For Croatia and Germany:

Discontinuation of trial treatment criterion 5: "*Simultaneous participation in a trial with the primary objective of evaluating an approved or non-approved investigational medicinal product for prevention or treatment of COVID-19 disease or COVID-19 postinfectious conditions is allowed at the investigator discretion without discontinuing trial product." is not applicable for Croatia and Germany.

Section 8.2.3 Eye examination

For Germany:

Fundus photography have to be performed by an ophthalmologist. Performance of fundus photography by an optimetrist or another qualified health care provider is not allowed.

For United States of America:

Fundus photography will be performed by the Investigator or a local Ophthalmologist/Optometrist according to local practice.

Appendix 1, Section 10.1.10 Retention of clinical trial documentation

For Canada:

Retention period is 25 years.

Appendix 4 Contraceptive guidance and collection of pregnancy information

For Czech Republic and Germany:

Contraceptive measures considered adequate include highly effective contraceptive methods in accordance with the CTFGs "Recommendations related to contraception and pregnancy testing in clinical trials", as listed in Table 10-3.

10.9 Appendix 9: Abbreviations

ADA	American Diabetes Association
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BG	blood glucose
BMI	body mass index
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CRF	case report form
COVID-19	Coronavirus disease 2019
CTFG	Clinical Trial Facilitation Group
CTR	clinical trial report
CV	cardiovascular
CVD	cardiovascular disease
DFU	directions for use
DPP-4	dipeptyl peptidase-4
DUN	dispensing unit number
EAC	event adjudication committee
EASD	European Association for the Study of Diabetes
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
FAS	full analysis set
FDA	U.S. Food and Drug Administration
FDAAA	FDA Amendments Act
FPG	fasting plasma glucose
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
GLP-1	glucagon-like peptide-1
GLP-1 RA	glucagon-like peptide-1 receptor agonist

HbA_{1c}	glycated haemoglobin
HCG	human chorionic gonadotropin
HDL	high-density lipoprotein
HDPE	High density polyurethane
HF	heart failure
HRT	hormone replacement therapy
ICH	International Council for Harmonisation
IEC	independent ethics committee
IMP	investigational medicinal product
IRB	institutional review board
IUD	Intrauterine device
IUS	Intrauterine device
IWRS	interactive web response system
KDIGO	kidney disease improving global outcomes
LDL	low-density lipoprotein
LSFT	last subject first treatment
MAR	missing at random
MEN2	multiple endocrine neoplasia type 2
MMRM	mixed model for repeated measurement
NYHA	New York Heart Association
OAD	oral anti-diabetic drug
OTC	over-the-counter
PCD	primary completion date
PG	plasma glucose
PK	pharmacokinetic
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Safety analysis set
s.c.	subcutaneous
SGLT2	sodium-glucose co-transporter 2
SU	sulphonylurea
SUSAR	suspected unexpected serious adverse reaction
TD	treatment difference
T2D	type 2 diabetes
TMM	trial materials manual

ULN	upper limit of normal
UACR	urinary albumin to creatinine ratio
WOCBP	woman of child bearing potential

10.10 Appendix 10: Protocol amendment history

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

Protocol version 2.0, including protocol amendment no. 1: 09 November 2020, global

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.

Overall rationale for preparing protocol, version 2.0

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

This amendment also addresses clarifications for missed doses and treatment compliance, as well as administrative changes.

Section # and name	Description of change	Brief rationale
Section 1.2 Flowchart	For V14 and V15, visit window corrected from '+3' to '±3'	For correctness
Section 1.2 Flowchart	For V17, visit window corrected from 0/3 to +3	For correctness
Section 1.2 Flowchart	For Laboratory Assessments, added X under the visit columns	For correctness
Section 5.2 Exclusion criteria	Addition to exclusion criterion 15 *Simultaneous participation in a trial with the primary objective of evaluating an approved or non-approved investigational medicinal product for prevention or treatment of COVID-19 disease or COVID-19 postinfectious conditions is allowed if the last dose of the investigational medicinal product has been received more than 30 days before screening.	To allow for co-participation in COVID-19 trials
Section 6.1 Missed doses	Text modified with regards to guidance on missed doses	To clarify that if the subject has been off treatment for more than 10 consecutive days, the investigator should consult Novo Nordisk global medical experts for guidance regarding continuation of trial medication.
Section 6.4 Treatment compliance	Definition of treatment compliance added	To clarify that compliance is defined as taking between 80%-120% of the dose as prescribed between visits.

Section # and name	Description of change	Brief rationale
Section 6.5 Concomitant medication	Text included for collection of COVID-19 concomitant medication	To specify that medication(s) in relation to a clinical trial for COVID-19 prevention or treatment as well as approved COVID-19 vaccine must be recorded.
Section 7.1 Discontinuation of trial treatment	Text added to discontinuation criterion 5 *Simultaneous participation in a trial with the primary objective of evaluating an approved or non-approved investigational medicinal product for prevention or treatment of COVID-19 disease or COVID-19 postinfectious conditions is allowed at the investigator discretion without discontinuing trial product.	To allow for co-participation in a COVID-19 trial
Section 8.2 Safety assessments	Addition of COVID-19 in text	To include COVID-19 to the concomitant illness/medical history that should be reported in relevant forms
Section 8.3 Adverse events	Text regarding COVID-19 AEs included *including 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.	To describe the procedure for collection of COVID-19 AEs
Appendix 2	Bilirubin removed from the list of Biochemistry test parameters	For correctness
Appendix 3, Figure 10-1	Text regarding COVID-19 AEs included	To describe the procedure for collection of COVID-19 AEs

Protocol version 3.0, including protocol amendment no. 1 and 2: 04 March 2021, global

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.

Overall rationale for preparing protocol, version 3.0

The exposure-response modelling has been updated based on data that have become available after the completion of the first version of the protocol. The new predicted treatment differences for 50 mg and 25 mg compared to 14 mg are less than previously predicted and therefore, the sample size has been increased to maintain the power.

This amendment also addresses few additional changes such as third-party responsibility and user credentials for IT systems.

Section # and name	Description of change	Brief rationale
Protocol amendment summary of changes table	Substantial amendment as per the European Parliament and the Council of the European Union	Reference added for information
Section 1.1 Synopsis	Number of subjects changed from 1224 to 1620.	To ensure sufficient power given the lower expected treatment differences
Section 2.3.1 Risk assessment	Allergic reactions and neoplasms	New information added to align with the current risk assessment of semaglutide
Section 2.3.1 Risk assessment	COVID-19 related mitigation plan	To develop a COVID-19 mitigation plan for this trial
Section 4.2 Scientific rationale for trial design	Third-party responsibility	To clarify that a third-party, who is only allowed to be involved in trial product handling, will be responsible for drug accountability
Section 6.3 Measures to minimise bias: Randomisation and blinding	Blinding and trial product handling	To clarify the third-party responsibilities in relation to trial product handling
Section 6.3 Measures to minimise bias: Randomisation and blinding	Quality Assurance audit at site(s)	To follow GCP advice agreement, text regarding Quality Assurance audit at site(s) and allowing them access to unblinded trial treatment records at the site(s) has been removed
Section 8.2.4 Eye examination	Fundus photography or slit-lamp biomicroscopy	To clarify that fundus photography or slit-lamp biomicroscopy examination should be used for evaluation of retinopathy or maculopathy. Additional examinations (e.g., optical coherence tomography and/or best corrected visual acuity) can be performed as a supplement for further evaluation. However, in this trial, additional eye examinations including the optical coherence tomography and/or best corrected visual acuity, cannot replace the fundus photography or slit-lamp biomicroscopy examination
Section 9.2 Sample size determination	Updated sample size assumption	To ensure sufficient power given the lower expected treatment differences
Section 9.4.2 Primary endpoint	Updated tipping point sensitivity analysis and added an extra sensitivity analysis	To accommodate feedback from FDA
Section 9.4.3.1 Confirmatory secondary endpoint	Updated with similar sensitivity analyses as for the primary endpoint	To accommodate feedback from FDA

Section # and name	Description of change	Brief rationale
Section 10.1.12 Responsibilities	Sharing of user credentials for IT systems	To emphasize that the investigator will ensure that IT equipment will not be shared with others in a way where user credentials have the possibility of being shared
Appendix 2 (Section 10.2) Clinical laboratory tests	In Table 10-1, V15 removed for fasting plasma glucose	For correctness
Appendix 2 (Section 10.2) Clinical laboratory tests	In Table 10-1 footnote, FPG of <3.9 mmol/L changed to ≤3.9 mmol/L	For correctness
Appendix 6 (Section 10.6) Hypoglycaemic episodes	In Table 10-4, Hypoglycaemia alert value (level 1) <3.9 mmol/L changed to ≤3.9 mmol/L	For correctness
Appendix 6 (Section 10.6) Hypoglycaemic episodes	PG value ≥3.9 mmol/L changed to >3.9 mmol/L For repeated PG measurements, succeeding PG value changed from ≥3.9 mmol/L to >3.9 mmol/L	For correctness
Appendix 9 (Section 10.9) Abbreviations	Added COVID-19	For clarification
Section 11 References	The European Parliament and the Council of the European Union	Reference added for information

Protocol version 4.0, including protocol amendment no. 1, 2 and 3: 28 April 2021, Croatia and Germany

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

For Croatia and Germany, 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.

Overall rationale for preparing protocol, version 4.0:

The overall rationale for the changes implemented in the amended protocol is to address local requirements in Croatia and Germany.

Section # and name	Description of change	Brief rationale
5.2 Exclusion criteria	Updated to include a reference to country-specific requirements for Croatia and Germany	Co-participation in COVID-19 trials is not allowed in Croatia and Germany due to local requirements.
6.5 Concomitant medications	Updated to include a reference to country-specific requirements for Croatia and Germany	Co-participation in COVID-19 trials is not allowed in Croatia and Germany due to local requirements.
7.1 Discontinuation of trial treatment	Updated to include a reference to country-specific requirements for Croatia and Germany	Co-participation in COVID-19 trials is not allowed in Croatia and Germany due to local requirements.
10.8 Appendix 8: Country-specific requirements	Requirements for Croatia and Germany updated to disallow co-participation in clinical trials evaluating approved or non-approved investigational medicinal products for the prevention or treatment of COVID-19 disease or COVID-19 postinfectious conditions. Accordingly, exclusion criterion #15, use of concomitant medications related to COVID-19 and discontinuation of trial treatment criterion #5 are not applicable for Croatia and Germany.	Co-participation in COVID-19 trials is not allowed in Croatia and Germany due to local requirements.

Protocol version 5.0, including protocol amendment no. 1, 2, 3 and 4: 04 June 2021, global

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

Overall rationale for preparing protocol, version 5.0:

The overall rationale for the changes implemented in the amended protocol is to include an unblinded monitor.

Section # and name	Description of change	Brief rationale
6.3 Measures to minimise bias: Randomisation and blinding	Addition of an unblinded monitor	To clarify monitoring responsibilities
10.1.8.2 Monitoring	Addition of an unblinded monitor	To clarify monitoring responsibilities

Protocol version 6.0, including protocol amendment no. 1, 2, 3, 4 and 5: 01 February 2022

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

Overall rationale for preparing protocol, version 6.0:

The overall rationale for the changes implemented in the amended protocol is to include the possibility of performing partial DBL and to update the text related to reconciliation process to include risk based reconciliation.

Section # and name	Description of change	Brief rationale
9.4 statistical analysis, 9.4.3.2 supportive secondary endpoints, 9.4.5.1 pharmacokinetic modelling, 9.7 reporting of the main part of the trial	Addition of partial DBL text	The possibility of performing a partial DBL is implemented to support potential earlier access of oral semaglutide 25 and 50 mg to the patient population expected to benefit from higher doses.
6.2 preparation/handling/storage/accountability	Text with respect to reconciliation process is updated as below: "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 product must be documented in the IWRS." Deleted **bold** text from the above bullet point	This text was misleading in relation to the reconciliation process set up for PIONEER PLUS as risk based reconciliation is used for this trial.
10.1.8.2 Monitoring	The last bullet text regarding reconciliation process has been updated i.e. "An unblinded monitor will reconcile trial product accountability" was updated to "An unblinded monitor will be responsible for the reconciliation process set up for this trial."	This text was misleading in relation to the reconciliation process set up for PIONEER PLUS as risk based reconciliation is used for this trial.

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