Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
NCT number	NCT03989232
Sponsor trial ID:	NN9535-4506
Official title of study:	Efficacy and Safety of Semaglutide 2.0 mg s.c. Once-weekly Compared to Semaglutide 1.0 mg s.c. Once-weekly in Subjects With Type 2 Diabetes
Document date*:	08 December 2020

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

Note: The date in the header from Page 2 is the date of compilation of the documents and not of an update to content.

16.1.1 Protocol and protocol amendments

List of contents

Redacted protocol
Includes redaction of personal identifiable information only.

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Protocol

Protocol title: Efficacy and safety of semaglutide 2.0 mg s.c. once-weekly compared to semaglutide 1.0 mg s.c. once-weekly in subjects with type 2 diabetes

Substance : Semaglutide

Universal Trial Number: U1111-1224-5162

EUdraCT Number: **2018-004529-96**

Trial phase: 3b

Protocol amendment summary of changes table

DOCUMENT HISTORY		
Document version	**Date**	**Applicable in country (-ies) and/or sites**
Protocol version 4.0	15 June 2020	All
Protocol version 3.0	05 March 2020	All
Protocol version 2.0	05 July 2019	All
Original protocol version 1.0	21 March 2019	All

Protocol version 4 (15 June 2020)

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

Overall rationale for preparing protocol, version 4:

Primary statistical analysis for the treatment policy estimand has been revised.

Section # and name	Description of change	Brief Rationale
10.3.1 Analyses addressing the treatment policy estimand Primary analysis	Revision of the primary analysis for the treatment policy estimand.	To revise the imputation method for missing data.

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1 Synopsis

Rationale:

Glucagon–like peptide-1 receptor agonists (GLP-1 RAs) are recommended for the treatment of patients with type 2 diabetes (T2D) who cannot reach their target HbA_{1c} and need to lose weight or minimise weight gain. It has been consistently demonstrated that weight loss in patients with T2D has a beneficial impact on glycaemic control.

Currently, there are two doses of semaglutide available for treatment of subjects with T2D (0.5 mg and 1.0 mg). Although these are effective, results across the phase 3a trials in the clinical development program showed that ~20−30% of patients treated with semaglutide 1.0 mg did not achieve the treatment target of HbA_{1c} of <7%.

Dose-dependent effects of semaglutide at doses exceeding the currently maximum approved dose for the treatment of T2D (1.0 mg once-weekly), have been demonstrated in relation to glycaemic control and body weight.

The present trial has been designed to investigate the effects of semaglutide 2.0 mg on glycaemic control, weight loss and safety in subjects with T2D.

Objectives and endpoints

Primary Objective

To establish the superior effect of semaglutide s.c. 2.0 mg once-weekly versus semaglutide s.c. 1.0 mg once-weekly on glycaemic control in subjects with T2D, on a background of metformin with or without sulphonylurea (SU) treatment.

Secondary Objective

To compare the effect of semaglutide s.c. 2.0 mg once-weekly versus semaglutide s.c. 1.0 mg once-weekly in subjects with T2D on a background of metformin with or without SU treatment, on:

- Body weight
- Vital signs
- Hypoglycaemia
- General safety and tolerability

Hypothetical estimand for the primary objective

The hypothetical estimand for the primary objective will be estimated as the absolute treatment difference in mean change from baseline to week 40 in HbA_{1c} (%-point) of semaglutide 2.0 mg versus semaglutide 1.0 mg, both as an add-on to metformin with or without SU, in all randomised

subjects with T2D, regardless of change in treatment dose and had they not discontinued treatment due to adverse events (AEs) or initiated any rescue medication (anti-diabetic medications).

Hypothetical estimand for the secondary objective regarding body weight

This estimand will be similar to the hypothetical estimand for the primary objective, however, with "HbA_{1c} (%-point)" replaced by "body weight (kg)".

Treatment policy estimand for the primary objective

The treatment policy estimand for the primary objective will be estimated as the absolute treatment difference in mean change from baseline to week 40 in HbA_{1c} (%-point) of semaglutide 2.0 mg versus semaglutide 1.0 mg, both as an add-on to metformin with or without SU, in all randomised subjects with T2D, regardless of change in treatment dose, discontinuation of treatment due to AEs and initiation of rescue medication (anti-diabetic medications).

Treatment policy estimand for the secondary objective regarding body weight

This estimand will be similar to the treatment policy estimand for the primary objective, however, with "HbA_{1c} (%-point)" replaced by "body weight (kg)".

The hypothetical estimand will be considered the primary estimand except in the US, where FDA specifically has requested the treatment policy estimand to be the primary.

Primary Endpoint

- Change from baseline (week 0) to week 40 in HbA_{1c} (%-point)

Confirmatory Secondary Endpoint

- Change from baseline (week 0) to week 40 in body weight (kg)

Supportive Secondary Endpoints

Change from baseline (week 0) to week 40 in:

- Fasting plasma glucose (FPG) (mmol/l)
- Body mass index (BMI) (kg/m^2)
- Waist circumference (cm)
- $HbA_{1c} < 7\%$ at week 40 (yes/no)
- $HbA_{1c} \leq 6.5\%$ at week 40 (yes/no)
- Weight loss $\geq 5\%$ at week 40 (yes/no)
- Weight loss $\geq 10\%$ at week 40 (yes/no)

Supportive Secondary Safety Endpoints

- Number of treatment emergent severe or blood glucose confirmed symptomatic hypoglycaemic episodes from first dose to week 40
- Change from baseline (week 0) to week 40 in pulse rate (bpm)

Overall design:

This is a 40-week, randomised, double blind, active comparator, two-armed, multi-centre, multinational clinical trial comparing semaglutide s.c. 2.0 mg once-weekly with semaglutide s.c.1.0 mg once-weekly in subjects with T2D, on a background of metformin with or without SU treatment.

Key Inclusion Criteria

- Male or female, age ≥18 years at the time of signing informed consent
- Diagnosed with T2D ≥180 days prior to the day of screening
- HbA_{1c} of 8-10% (64−86 mmol/mol) (both inclusive)
- Stable daily dose(s) for 90 days prior to the day of screening of:
  - Any metformin formulations (≥1500 mg or maximum tolerated or effective dose) alone or in combination with sulfonylureas (SU) (≥half of the maximum approved dose according to local label or maximum tolerated or effective dose)

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, as is prior insulin treatment for gestational diabetes
- 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:

Approximately 1377 subjects will be screened to achieve 964 randomised subjects. Number of subjects expected to complete the trial will be 867. Subjects will be followed for the planned duration of the trial.

Treatment groups and duration:

The total trial duration for the individual subject will be approximately 49 weeks. The trial includes a screening period of approximately 2 weeks followed by randomisation. Eligible subjects fulfilling all eligibility criteria at visit 2 (V2) will be randomised in a 1:1 manner to receive either:

- Semaglutide s.c. 2.0 mg once-weekly
- Semaglutide s.c. 1.0 mg once-weekly

Randomisation will be stratified based on country (Japan/other).

Dose escalation to the target maintenance doses of semaglutide 1.0 mg or 2.0 mg once-weekly should take place during the first 12 weeks after randomisation.

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

Trial products

- Semaglutide 1.34 mg/mL, solution for 1.5 mL pre-filled PDS290 pen injector. One pre-filled pen contains 2.0 mg of semaglutide
- Semaglutide placebo, solution for injection, 1.5 mL pre-filled PDS290 pen injector

2 Flowchart

Trial Periods	Protocol section	Screening	Randomisation	Treatment							End of treatment[b]	Follow up[b]	Treatment discontinuation	
													End of treatment[b]	Follow up[b]
Site visit (V)/ phone contact (P)		**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**P9**	**V10**	**P11**	**V10A**	**P11A**
Timing of visit (weeks)		**-2**	**0**	**4**	**8**	**12**	**16**	**20**	**28**	**34**	**40**	**End of treatment + 7 weeks**		**End of treatment + 7 weeks**
Visit window (days)		**±7**		**±7**	**±7**	**±7**	**±7**	**±7**	**±14**	**±14**	**±7**	**+7**		
SUBJECT RELATED INFO/ASSESSMENTS														
Informed consent	Appendix 3	X												
In/exclusion criteria	6.1 6.2	X	X											
Randomisation			X											
Discontinuation criteria	8.1			X	X	X	X	X	X	X				
Concomitant illness	9.4	X												

Trial Periods	Protocol section	Screening	Randomisation	Treatment							End of treatment[b]	Follow up[b]	Treatment discontinuation	
													End of treatment[b]	Follow up[b]
Site visit (V)/ phone contact (P)		**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**P9**	**V10**	**P11**	**V10A**	**P11A**
Timing of visit (weeks)		**-2**	**0**	**4**	**8**	**12**	**16**	**20**	**28**	**34**	**40**	**End of treatment + 7 weeks**		**End of treatment + 7 weeks**
Visit window (days)		**±7**		**±7**	**±7**	**±7**	**±7**	**±7**	**±14**	**±14**	**±7**	**+7**		
Concomitant medication	7.7	X	X	X	X	X	X	X	X	X	X	X	X	X
Demography[a]		X												
Diagnosis of diabetes		X												
Diabetes history and diabetes complications		X												
Medical history	9.4	X												
Tobacco use[c]		X												
Childbearing potential	Appendix 5	X												
EFFICACY														

Trial Periods	Protocol section	Screening	Randomisation	Treatment							End of treatment[b]	Follow up[b]	Treatment discontinuation	
													End of treatment[b]	Follow up[b]
Site visit (V)/ phone contact (P)		**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**P9**	**V10**	**P11**	**V10A**	**P11A**
Timing of visit (weeks)		**-2**	**0**	**4**	**8**	**12**	**16**	**20**	**28**	**34**	**40**	**End of treatment + 7 weeks**		**End of treatment + 7 weeks**
Visit window (days)		**±7**		**±7**	**±7**	**±7**	**±7**	**±7**	**±14**	**±14**	**±7**	**+7**		
Body weight	9.1.2	X	X	X	X	X	X	X	X		X		X	
Height	9.1.2	X												
Waist circumference	9.1.2		X					X			X		X	
Systolic blood pressure	9.4.2		X	X		X	X	X	X		X		X	
Diastolic blood pressure	9.4.2		X	X		X	X	X	X		X		X	
FPG	Appendix 2		X			X		X			X		X	
HbA_{1c}	Appendix 2	X	X			X	X	X	X		X		X	

Trial Periods	Protocol section	Screening	Randomisation	Treatment							End of treatment[b]	Follow up[b]	Treatment discontinuation	
													End of treatment[b]	Follow up[b]
Site visit (V)/ phone contact (P)		**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**P9**	**V10**	**P11**	**V10A**	**P11A**
Timing of visit (weeks)		**-2**	**0**	**4**	**8**	**12**	**16**	**20**	**28**	**34**	**40**	**End of treatment + 7 weeks**		**End of treatment + 7 weeks**
Visit window (days)		**±7**		**±7**	**±7**	**±7**	**±7**	**±7**	**±14**	**±14**	**±7**	**+7**		
Semaglutide plasma concentration	9.5			X				X	X		X		X	
SAFETY														
Hypoglycaemic episodes	9.2.6 Appendix7		X	X	X	X	X	X	X	X	X	X	X	X
Eye examination	9.4.3	X									X		X	
Physical examination	9.4.1	X									X		X	
Pulse	9.4.2		X	X		X	X	X	X		X		X	
Biochemistry	Appendix 2	X						X			X		X	

Trial Periods	Protocol section	Screening	Randomisation	Treatment							End of treatment[b]	Follow up[b]	Treatment discontinuation	
													End of treatment[b]	Follow up[b]
Site visit (V)/ phone contact (P)		**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**P9**	**V10**	**P11**	**V10A**	**P11A**
Timing of visit (weeks)		**-2**	**0**	**4**	**8**	**12**	**16**	**20**	**28**	**34**	**40**	**End of treatment + 7 weeks**		**End of treatment + 7 weeks**
Visit window (days)		**±7**		**±7**	**±7**	**±7**	**±7**	**±7**	**±14**	**±14**	**±7**	**+7**		
Creatinine (including eGFR)	Appendix 2	X						X			X		X	
Haematology	Appendix 2	X						X			X		X	
Pregnancy test	Appendix 2 Appendix 5	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	9.2 Appendix 4		X	X	X	X	X	X	X	X	X	X	X	X
Calcitonin	Appendix 2	X												

Trial Periods	Protocol section	Screening	Randomisation	Treatment							End of treatment[b]	Follow up[b]	Treatment discontinuation	
													End of treatment[b]	Follow up[b]
Site visit (V)/ phone contact (P)		**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**P9**	**V10**	**P11**	**V10A**	**P11A**
Timing of visit (weeks)		**-2**	**0**	**4**	**8**	**12**	**16**	**20**	**28**	**34**	**40**	**End of treatment + 7 weeks**		**End of treatment + 7 weeks**
Visit window (days)		**±7**		**±7**	**±7**	**±7**	**±7**	**±7**	**±14**	**±14**	**±7**	**+7**		
TRIAL MATERIAL														
Dispensing visit			X		X	X	X	X	X					
Drug accountability	7.5		X		X	X	X	X	X		X		X	
IWRS session	7.3 7.4	X	X		X	X	X	X	X		X		X	
REMINDERS														
End of treatment											X		X	
End of trial												X		
Attend visit fasting	6.3.1		X			X		X			X		X	

Trial Periods	Protocol section	Screening	Randomisation	Treatment							End of treatment[b]	Follow up[b]	Treatment discontinuation	
													End of treatment[b]	Follow up[b]
Site visit (V)/ phone contact (P)		**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**P9**	**V10**	**P11**	**V10A**	**P11A**
Timing of visit (weeks)		**-2**	**0**	**4**	**8**	**12**	**16**	**20**	**28**	**34**	**40**	**End of treatment + 7 weeks**		**End of treatment + 7 weeks**
Visit window (days)		**±7**		**±7**	**±7**	**±7**	**±7**	**±7**	**±14**	**±14**	**±7**	**+7**		
Directions for use (DFU)			X											
Training in trial product and pen handling	7.1.1		X	X		X								
Handout ID card		X												
Handout and instruct in diary	9.2.6		X											
Handout and instruct in BG meter	7.1 9.2.6		X											

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

[b] Please refer to Section 8 for details on discontinuation and withdrawal.

[c] Smoking is defined as smoking at least one cigarette or equivalent daily

3 Introduction

3.1 Trial rationale

Glucagon–like peptide-1 receptor agonists (GLP-1 RAs) are recommended for the treatment of patients with T2D who cannot reach their target HbA_{1c} and need to lose weight or minimise weight gain[2]. It has been consistently demonstrated that weight loss in patients with T2D has a beneficial impact on glycaemic control[3, 4].

Currently, there are two doses of semaglutide available for treatment of subjects with T2D (0.5 mg and 1 mg). Although these are effective, results across the phase 3a trials[5-9] (excluding the cardiovascular outcomes trial[10]) in the clinical development program showed that ~20−30% of patients treated with semaglutide 1 mg did not achieve the treatment target of HbA_{1c} of <7%.

Dose-dependent effects of semaglutide at doses exceeding the currently maximum approved dose for the treatment of T2D (1 mg once-weekly), have been demonstrated in relation to glycaemic control and body weight[11, 12].

The present trial has been designed to investigate the effects of semaglutide 2.0 mg on glycaemic control, weight loss and safety in subjects with T2D.

3.2 Background

Semaglutide s.c. 0.5 mg and 1 mg once-weekly (Ozempic®) is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with T2D[13, 14]. The currently approved indication was based on a comprehensive global phase 3a clinical development programme for semaglutide s.c. once-weekly (the SUSTAIN programme). The present trial will investigate a 3rd maintenance dose of semaglutide s.c. 2.0 mg once-weekly, for additional glycaemic control in subjects with T2D.

In the SUSTAIN programme, semaglutide provided superior long-term glycaemic control in addition to clinically relevant reductions in body weight as compared to commonly used marketed products across the spectrum of patients with T2D, ranging from treatment-naïve to insulin-treated. The safety profile of semaglutide is well-documented based on data from the non-clinical and clinical development programmes, and is consistent with the safety profile of other drugs within the GLP-1 RA drug class[13, 14].

Two recent dose-finding trials have investigated the efficacy and tolerability of semaglutide s.c. at doses higher than previously studied; both for the use in T2D[11] and in weight management[12].

For the dose-finding trial for once-daily semaglutide in T2D, semaglutide at doses up to 0.3 mg once-daily (equivalent to 2.1 mg once-weekly and thereby exceeding the maximum approved dose

of 1 mg once-weekly) were investigated. In this trial, 65 and 63 patients were exposed to doses equivalent to 1.4 mg and 2.1mg, respectively. In subjects with T2D and overweight or obesity, once-daily semaglutide (in doses of 0.05, 0.1, 0.2, or 0.3 mg/day, corresponding to doses of 0.35 to 2.1 mg/week), demonstrated dose-dependent changes in HbA_{1c} from baseline to week 26 ranging from -1.05%-points with semaglutide 0.05 mg to -1.88%-points with semaglutide 0.30 mg. In addition, semaglutide showed dose-dependent changes from baseline to week 26 in body weight, ranging from -2.76 kg with semaglutide 0.05 mg to -8.23 kg with semaglutide 0.30 mg[11]. The rate of AEs increased with increasing semaglutide dose, however, no marked differences across the semaglutide groups were observed in the proportion of subjects with AEs leading to premature treatment discontinuation. The majority of AEs were gastrointestinal (GI) AEs, and for these, a dose-dependency was seen, with an increasing proportion of subjects reporting GI AEs at increasing dose of semaglutide. GI adverse events were typically mild to moderate and no dose-dependency was observed in relation to GI AEs leading to premature treatment discontinuation with few of these events across the semaglutide groups. In conclusion, the safety profile of the doses equivalent to above 1 mg of semaglutide was generally well tolerated in subjects with T2D during 26 weeks of treatment and no unanticipated safety concerns were identified. For further details on efficacy and safety of semaglutide s.c. once-daily please refer to Appendix 8.

In a 52-week dose-finding trial for semaglutide s.c. in overweight or obese subjects without diabetes, treatment with once-daily semaglutide in doses up to 0.4 mg (equivalent to a weekly sum of 2.8 mg/week) resulted in a clear and dose-dependent weight loss, with the semaglutide s.c. 0.4 mg once-daily dose providing a 13.8% reduction in body weight from baseline to week 52, while displaying an acceptable tolerability profile[12]. All semaglutide doses were generally well tolerated, with no new safety concerns. The most common adverse events were dose-related gastrointestinal symptoms, primarily nausea, as seen previously with GLP-1 receptor agonists. A semaglutide s.c. dose of 2.4 mg once-weekly is currently being investigated as the target maintenance dose for semaglutide s.c. in weight management in a large phase 3a development programme.

A comprehensive review of results from the non-clinical and clinical studies of semaglutide can be found in the current edition of the investigator's brochure (IB) and any updates hereof[15].

3.3 Benefit-risk assessment

3.3.1 Risks related to semaglutide

The sections below describe identified and potential risks associated with semaglutide treatment. For further details of the risks, please refer to the current version of the IB or any updates hereof[15]. The identified/potential risks are based on findings in non-clinical studies and clinical trials with semaglutide as well as other GLP-1 RAs. For each of these risks, mitigating actions have been implemented to minimise the risks for subjects enrolled in this trial.

Identified risks

Gastrointestinal disorders	Consistent with findings with other GLP-1 RAs, the most frequently reported adverse events (AE) in clinical trials with semaglutide were gastrointestinal AEs. A dose dependency has been observed for most of the gastrointestinal disorders. A low starting dose and dose escalation steps will be implemented in the trial to mitigate the risk of gastrointestinal AEs. In patients treated with GLP-1 RAs, nausea, vomiting and diarrhoea may lead to significant dehydration. This should be considered when treating patients with impaired renal function as it may cause a deterioration of renal function. Patients with GI AEs are recommended to drink plenty of fluids to avoid volume depletion.
Hypoglycaemia	There is a low risk of hypoglycaemic episodes when semaglutide is used as monotherapy. Subjects treated with semaglutide in combination with SU or insulin have an increased risk of hypoglycaemia. The risk of hypoglycaemia can be lowered by reducing the dose of SU when initiating treatment with semaglutide (or insulin if subjects have been allowed to use insulin as rescue therapy).
Cholelithiasis	In the semaglutide s.c. T2D clinical development programme (NN9535), events of cholelithiasis were reported more frequently with semaglutide s.c. than with comparators. Few events were serious and there was no clear correlation between events of cholelithiasis and weight loss. Events of cholelithiasis did not lead to an increased risk of complications such as cholecystitis or pancreatitis.
Diabetic retinopathy complications	The cardiovascular outcome trial in the semaglutide T2D development programme showed an increased risk of events related to diabetic retinopathy complications in subjects treated with semaglutide compared to placebo, albeit the proportion of subjects with an event of diabetic retinopathy complications was low. The imbalance was driven by subjects with a history of diabetic retinopathy at baseline and subjects who were treated with insulin. Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy. Long-term glycaemic control decreases the risk of diabetic retinopathy. Patients with a history of diabetic retinopathy should be monitored for worsening and treated according to clinical guidelines. As a precaution, subjects with a history of uncontrolled and potentially unstable diabetic retinopathy or maculopathy will be excluded from the trial, and fundus photography or slit-lamp biomicroscopy examination with pharmacologically dilated pupils will be performed according to flowchart.
Other risks	Patients treated with semaglutide may also experience decreased appetite, dizziness, dysgeusia, fatigue, increased heart rate, increased lipase and amylase, injection site reactions and weight decrease.

In a phase 2 trial in doses of up 0.4mg/day in non-diabetic patients with obesity, early satiety, insomnia, dry mouth, and alopecia were also reported more with semaglutide.

Potential risks

Allergic reactions	As is the case with all protein-based pharmaceuticals, subjects treated with semaglutide are at risk of developing immunogenic and allergic reactions. As a precaution, subjects with known or suspected hypersensitivity to semaglutide or related products will not be enrolled in this trial.
Acute pancreatitis	Acute pancreatitis has been observed with the use of GLP-1 RAs. Patients should be informed of the characteristic symptoms of acute pancreatitis and if pancreatitis is suspected, semaglutide should be discontinued. If confirmed, semaglutide should not be restarted.
Malignant neoplasms	There is no indication of a causal relationship between semaglutide and malignant neoplasm based on the available data. However, it is not possible to draw any firm conclusions due to very low numbers. As a precaution, subjects with a history of malignant neoplasms within the past 5 years prior to screening will be excluded from the trial.
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 RA-based therapies increase the risk of pancreatic cancer, but pancreatic cancer has been classified as a potential class risk of GLP-1 RAs by European Medicines Agency. As a precaution, subjects with a history of malignant neoplasms within the past 5 years prior to screening will be excluded from the trial.
Medullary thyroid cancer	Expected proliferative thyroid C-cell changes were seen in the mouse and rat carcinogenicity studies after daily exposure to semaglutide for 2 years. No hyperplasia was observed in monkeys after 52 weeks exposure up to 13-fold above the clinical plasma exposure at 2.4 mg/week. In clinical trials with semaglutide, there have been no clinically relevant changes in calcitonin levels. The C-cell changes in rodents are mediated by the GLP-1 receptor, which is not expressed in the normal human thyroid. Accordingly, the risk of GLP-1 receptor-mediated C-cell changes in humans is considered to be low. However, as a precaution an exclusion criterion related to medical history of multiple endocrine neoplasia type2 (MEN 2) or medullary thyroid cancer (MTC) and elevated plasma levels of calcitonin (biomarker for MTC) have been implemented in the trial.

Other safety considerations

Drug interactions	Semaglutide delays gastric emptying and has the potential to impact the rate of absorption of concomitantly administered oral medicinal products. The potential effect of semaglutide on the absorption of co-administered oral medications was studied in trials at semaglutide 1 mg/week steady state exposure. No clinically relevant drug-drug interactions with semaglutide were observed based on the evaluated medications. Semaglutide did not change the overall pharmacodynamics of warfarin as measured by the international normalised ratio (INR). However, upon initiation of semaglutide treatment in patients on warfarin and/or coumarin derivatives, frequent monitoring of INR is recommended.
Pregnancy, lactation and fertility	Studies in animals have shown reproductive toxicity. There are limited data from the use of semaglutide in pregnant women. Therefore, semaglutide should not be used during pregnancy. If a patient wishes to become pregnant, or pregnancy occurs, semaglutide should be discontinued. Semaglutide should be discontinued at least 7 weeks before a planned pregnancy due to the long half-life. In lactating rats, semaglutide was excreted in milk. As a risk to a breast-fed child cannot be excluded, semaglutide should not be used during breast-feeding. The effect of semaglutide on fertility in humans is unknown. Semaglutide did not affect male fertility in rats. In female rats, an increase in oestrous length and a small reduction in number of ovulations were observed at doses associated with maternal body weight loss.

3.3.2 Benefits

Semaglutide s.c. once-weekly in doses of 0.5 mg and 1 mg has demonstrated clinically relevant and dose-dependent improvements in glycaemic control and body weight in subjects with T2D. Also, the reduction in HbA_{1c} was consistently greater with higher baseline HbA_{1c}[16]. Further dose-dependent reductions in HbA_{1c} and body weight have been observed in phase 2 trials with semaglutide doses exceeding 1 mg/week, both for the use in T2D[11] and in weight management[12]. Consequently, it is expected that semaglutide 2.0 mg will provide equal or better glycaemic and body weight control as compared to semaglutide 1.0 mg in subjects with T2D. All subjects will therefore be treated with a more efficacious regimen 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.

3.3.3 Risk-benefit conclusion

Necessary precautions have been implemented in the design and planned conduct of the trial in order to minimise the risks and inconveniences of participation in the trial. The safety profile for semaglutide generated from the clinical and non-clinical development programme has not revealed any safety issues that would prohibit administration of semaglutide 2.0 mg once-weekly. The results of the two phase 2 trials indicate that semaglutide provides dose-dependent reductions in HbA_{1c} and weight[11, 12].

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 adverse events (AEs) of semaglutide s.c. may be found in the Investigator's Brochure (IB) and any updates hereof[15], and in Appendix 8.

4 Objectives and endpoints

4.1 Objectives

4.1.1 Primary objective

To establish the superior effect of semaglutide s.c. 2.0 mg once-weekly versus semaglutide s.c. 1.0 mg once-weekly on glycaemic control in subjects with T2D, on a background of metformin with or without SU treatment.

4.1.2 Secondary objective

To compare the effect of semaglutide s.c. 2.0 mg once-weekly versus semaglutide s.c. 1.0 mg once-weekly in subjects with T2D, on a background of metformin with or without SU treatment, on:

- Body weight
- Vital signs
- Hypoglycaemia
- General safety and tolerability

4.2 Estimands

Hypothetical estimand for the primary objective

The hypothetical estimand for the primary objective will be estimated as the absolute treatment difference in mean change from baseline to week 40 in HbA_{1c} (%-point) of semaglutide 2.0 mg versus semaglutide 1.0 mg, both as an add-on to metformin with or without SU, in all randomised subjects with T2D, regardless of change in treatment dose and had they not discontinued treatment due to AEs or initiated any rescue medication (anti-diabetic medications).

Hypothetical estimand for the secondary objective regarding body weight

This estimand will be similar to the hypothetical estimand for the primary objective, however, with "HbA_{1c} (%-point)" replaced by "body weight (kg)".

Treatment policy estimand for the primary objective

The treatment policy estimand for the primary objective will be estimated as the absolute treatment difference in mean change from baseline to week 40 in HbA_{1c} (%-point) of semaglutide 2.0 mg versus semaglutide 1.0 mg, both as an add-on to metformin with or without SU, in all randomised subjects with T2D, regardless of change in treatment dose, discontinuation of treatment due to AEs and initiation of rescue medication (anti-diabetic medications).

Treatment policy estimand for the secondary objective regarding body weight

This estimand will be similar to the treatment policy estimand for the primary objective, however, with "HbA_{1c} (%-point)" replaced by "body weight (kg)".

The hypothetical estimand will be considered the primary estimand except in the US, where FDA specifically has requested the treatment policy estimand to be the primary.

4.3 Endpoints

4.3.1 Primary endpoint

- Change from baseline (week 0) to week 40 in HbA_{1c} (%-point)

4.3.2 Secondary endpoints

4.3.2.1 Confirmatory secondary endpoint

- Change from baseline (week 0) to week 40 in body weight (kg)

4.3.2.2 Supportive secondary endpoints

Supportive secondary effect endpoints
Change from baseline (week 0) to week 40 in:

- Fasting plasma glucose (FPG) (mmol/l)
- Body mass index (BMI) (kg/m^2)
- Waist circumference (cm)
- $HbA_{1c} < 7\%$ at week 40 (yes/no)
- $HbA_{1c} \leq 6.5\%$ at week 40 (yes/no)
- Weight loss $\geq 5\%$ at week 40 (yes/no)
- Weight loss $\geq 10\%$ at week 40 (yes/no)

Supportive secondary safety endpoints

- Number of treatment emergent severe or blood glucose confirmed symptomatic hypoglycaemic episodes from first dose to week 40
- Change from baseline (week 0) to week 40 in pulse rate (bpm)

5 Trial design

5.1 Overall design

- This is a 40-week, randomised, double-blind, active comparator, two-armed, multi-centre, multinational clinical trial.
- Subjects will be randomised in a 1:1 manner to receive either:
  - Semaglutide s.c. 2.0 mg once-weekly
  - Semaglutide s.c. 1.0 mg once-weekly

- Randomisation will be stratified based on country (Japan/other).

- There is a 2-week screening period followed by a randomisation visit and a 40-week treatment period. The treatment period is divided into a dose escalation period of 12 weeks and a maintenance period of 28 weeks. After the end of treatment visit (V10), all subjects will enter a follow-up period of 7 weeks, ended by a follow up phone contact, which corresponds to the end of trial (P11). Total trial duration for the individual subject will be approximately 49 weeks.

- The trial population will consist of subjects with T2D using metformin with or without SU, with an HbA_{1c} of 8-10% (both inclusive)

A schematic illustration of the trial design is provided in Figure 5-1.

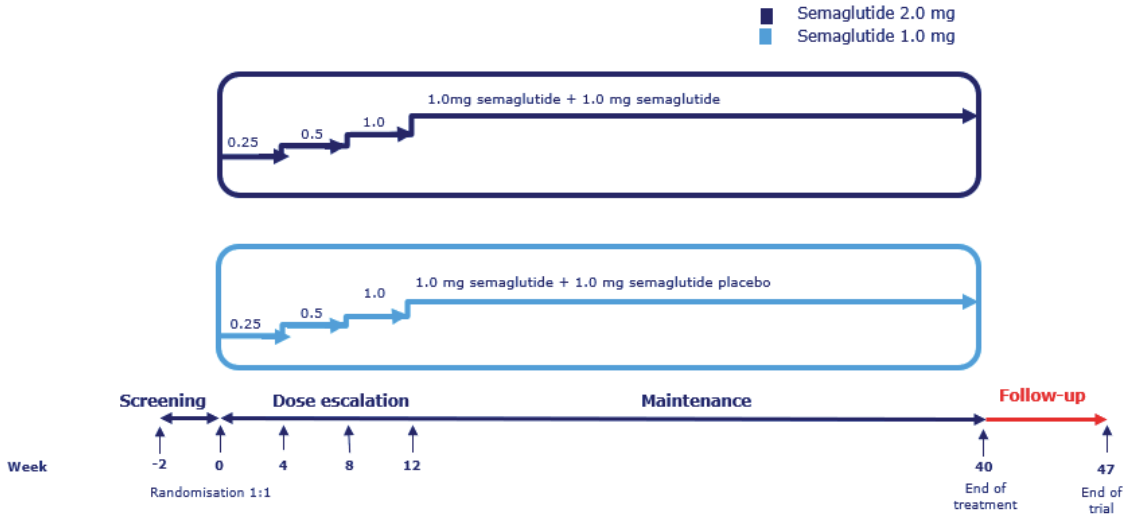

Figure 5-1 A schematic diagram of the trial design, with the duration of the trial periods. As outlined in the figure, all subjects in the trial will receive one injection per week during a 12-week dose escalation period, until the target dose for semaglutide 2.0 mg is reached. Starting week 13 to end of treatment, all subjects in the trial will receive two injections using two pens per week to ensure blinding of the target maintenance dose of semaglutide 2.0 mg (Table 7-2)

5.2 Subject and trial completion

Approximately 1377 subjects will be screened in order to achieve 964 subjects to be randomly assigned to trial product. The number of subjects expected to complete the trial will be 867 subjects (see Section 10.1 for further details on the sample size considerations). Subjects will be followed for the planned duration of the trial.

Trial period completion for a subject:

Trial period completion is defined as when the randomised subject has completed the final scheduled visit ‘end of trial’ according to the flowchart in Section 2).

'Date of trial completion' is the date the subject completed the final scheduled visit, as mentioned above.

Treatment period completion for a subject:

Treatment period completion is defined as when the randomised subject has received the required treatment and attended the 'end of treatment' visit according to the flowchart in Section 2.

5.3 End of trial definition

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

5.4 Scientific rationale for trial design

The treatment duration of the trial is 40 weeks, with an additional 7 weeks of follow-up. A follow up phone contact, that will take place 7 weeks after the end of treatment, is included to account for the exposure and long half-life of semaglutide. A 40-week treatment duration (including 28 weeks on target doses) will provide robust data for the evaluation of efficacy and safety parameters.

A randomised, double blind, active comparator, two armed, multicentre, multinational trial design is chosen to minimise bias in the assessment of the effect and safety of semaglutide 2.0 mg and semaglutide 1.0 mg.

The trial includes a screening visit to assess the subject's eligibility. After randomisation visit, visits are scheduled every 4 weeks to support the subject during dose escalation. To mimic usual clinic practice, from week 20, a visit is planned at week 28, a phone contact at week 34 and the end of treatment visit at week 40. A follow-up visit ('end of trial') for safety assessments is scheduled 7 weeks after end of treatment to account for the exposure and the long half-life of semaglutide.

The trial population will consist of subjects with T2D treated with stable doses of metformin only or metformin in combination with sulphonylurea, in need of the treatment intensification. Subjects with an HbA_{1c} of 8-10% are included as they are anticipated to particularly benefit from advancing to a higher dose of semaglutide. Further, this population represents a clinically relevant population, as it is likely to benefit both from the better glycaemic control, as well as from the anticipated body weight loss.

5.5 Justification for dose

Results from the phase 2 dose-finding trial (NN9536-4191) showed that the semaglutide 0.3 mg once-daily dose was the most effective in terms of both glycaemic control and weight management, while displaying an acceptable tolerability profile (refer to Appendix 8). The daily dose of 0.3mg corresponds to a weekly dose of 2.1mg.

A target dose of 2.0 mg has been selected for this trial and as an intended 3rd maintenance dose of semaglutide s.c. once-weekly for glycaemic control in T2D, in addition to 0.5 mg and 1.0 mg. A single, intuitive dose escalation step is implemented to ensure simplicity when progressing the dose from 1.0 mg to 2.0 mg in clinical practice.

Subjects will therefore be initiated at a once-weekly dose of 0.25 mg and follow a fixed-dose escalation regimen, with dose increases every 4 weeks (to doses of 0.5, 1.0 and 2.0 mg/week), until the target maintenance dose of 2.0 mg is reached after 12 weeks.

Semaglutide s.c. 2.0 mg once-weekly will provide a simpler treatment intensification regimen as compared to advancing treatment with additional anti-hyperglycaemic agents or combination injectable therapy in order to reach glycaemic targets. The added benefit of significant weight loss observed with higher dose would also allow clinicians to further individualise the treatment to meet the needs of the subject with T2D.

A treatment arm with semaglutide 1.0 mg once-weekly is included to be able to compare the effect on glycaemic control, body weight and safety between the two semaglutide doses (1.0 and 2.0 mg).

Please refer to Section 7.1 for more details on treatment doses.

6 Trial population

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

6.1 Inclusion criteria

Subjects are eligible to be included in the trial only if all 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 ≥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 8-10% (64−86 mmol/mol) (both inclusive)
5. Stable daily dose(s) for 90 days prior to the day of screening of: any metformin formulations (≥1500 mg or maximum tolerated or effective dose) alone or in combination with sulfonylureas (SU) (≥half of the maximum approved dose according to local label or maximum tolerated or effective dose).

Japan: For country specific requirements, refer to Appendix 9.

6.2 Exclusion criteria

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

Diabetes related

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, as is prior insulin treatment for gestational diabetes
2. Anticipated initiation or change in concomitant medications (for more than 14 consecutive days) known to affect weight or glucose metabolism (e.g. treatment with orlistat, thyroid hormones, or corticosteroids)
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[17]
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

General safety

5. Personal or first degree relative(s) history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma
6. Calcitonin ≥ 100 ng/L as measured by the central laboratory at screening
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 product(s) or related products
13. Previous participation in this trial. Participation is defined as signed informed consent
14. Receipt of any investigational medicinal product within 30 days before screening
15. 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
16. Any disorder, unwillingness or inability, which in the investigator's opinion, might jeopardise the subject's safety or compliance with the protocol

6.3 Lifestyle restrictions

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

6.3.1 Meals and dietary restrictions

- Subjects must attend the visits fasting according to the flowchart.
- Fasting is defined as at least 6 hours prior to the visit without food or liquids, except for water. Trial product and any medication which should be taken with or after a meal should be withheld on the day of the visit until blood samples have been obtained.
- If the subject is not fasting as required, the subject should be called in for a new visit within the visit window to have the fasting procedures done.

6.4 Screen failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are not eligible for participation according to in/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 date of inform consent, demography, date of visit, screen failure details, eligibility criteria, and any 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. Re-sampling is not allowed if the subject has failed one of the inclusion criteria or fulfilled one of the exclusion criteria related to laboratory parameters. However, in case of technical issues (e.g. haemolysed or lost), re-sampling is allowed for the affected parameters.

7 Treatments

7.1 Treatments administered

The investigational medicinal products (trial products) provided by Novo Nordisk are listed in Table 7-1. Trial product must only be used, if it appears clear and colourless.

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

Trial product name:	semaglutide 1.34 mg/mL	semaglutide placebo
Dosage form:	Solution for injection	Solution for injection
Route of administration:	Subcutaneous	Subcutaneous
Dosing instructions:	Once-weekly	Once-weekly
Packaging	1.5 mL pre-filled PDS290 pen-injector	1.5 mL pre-filled PDS290 pen-injector

Dose escalation

All subjects are to reach the target maintenance dose of semaglutide 1.0 mg or 2.0 mg once-weekly.

Dose escalation to the target maintenance doses of semaglutide 1.0 mg or 2.0 mg once-weekly should take place during the first 12 weeks after randomisation. From V5 (week 12) the treatment will include 2 injections using 2 pens as described in Figure 5-1 and Table 7-2.

If a subject does not tolerate the designated target dose, the subject may stay at a lower dose level. This should only be allowed if the subject would otherwise discontinue trial product completely and if considered safe to continue trial product at a lower dose, as per the investigator's discretion. The subject should make at least one attempt to re-escalate to the designated target dose, as per the investigator's discretion.

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

Table 7-2 Dose escalation and maintenance

Trial periods	Screening	Treatment period 1	Treatment period 2	Treatment period 3	Treatment period 4	Follow-up
Alias for trial period	Screening	Dose escalation	Dose escalation	Dose escalation	Maintenance	Follow-up
Visits in each period	V1	V2	V3	V4	V5-V10	P11
Duration of each period	2 weeks	4 weeks	4 weeks	4 weeks	28 weeks	
Treatment arm						
semaglutide s.c. 1.0 mg	Screening	semaglutide 0.25 mg	semaglutide 0.5 mg	semaglutide 1.0 mg	semaglutide 1.0 mg and semaglutide placebo 1.0 mg	Follow-up
semaglutide s.c. 2.0 mg	Screening	semaglutide 0.25 mg	semaglutide 0.5 mg	semaglutide 1.0 mg	semaglutide 1.0 mg and semaglutide 1.0 mg	Follow-up
All subjects on background medication of metformin with or without sulphonylurea treatment.						

Please refer to Figure 5-1 for more information.

Instructions for the subject

Subjects will be instructed to inject the trial product(s) subcutaneously once weekly in the abdomen, thigh, or upper arm. The injection site can be changed without dose adjustment. Subjects must be trained in handling the pen-injectors when dispensed the first time and training must be repeated during the trial as indicated per flowchart Section 2.The investigator may choose to observe the subject when administering the first dose.

The investigator must document that directions for use (DFU) are given to the subject orally and in writing at the first dispensing visit and again during the trial, if the investigator finds it relevant. The injection can be administered at any time of the day irrespective of meals, but on the same day of the week. The day of weekly administration can be changed if necessary if the time between two doses is at least 2 days (>48 hours) or in accordance with the local label. After selecting a new dosing day, once weekly dosing should be continued.

The investigator should give the dose reminder card at each dispensing visit. At V5 the investigator should also give the pen differentiation guide to the subject.

Missed doses

If a semaglutide dose is missed, it should be administered as soon as noticed, provided the time to the next scheduled dose is at least 2 days (48 hours). If a dose is missed and the next scheduled dose

is less than 2 days (48 hours) away, the subject should not administer the missed dose. A missed dose should not affect the scheduled dosing day of the week.

If ≥ 2 consecutive doses of trial product are missed, the subject should be encouraged to 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 8.1). The trial product should be continued as early as the situation allows. The missed doses should not affect the scheduled dosing day of the week. The start dose for re-initiation of trial product is at the investigator's discretion. In case of questions related to re-initiation of trial product, the investigator should consult Novo Nordisk global medical experts. If doses are missed blood glucose should be more closely monitored if judged necessary by the investigator.

Auxiliary supplies

The following auxiliary supplies will be provided by Novo Nordisk:

- Needles for the pre-filled PDS290 pen-injectors
- Directions for use (DFU) for the pre-filled PDS290 pen-injector
- Blood glucose (BG) meter and related auxiliaries

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

Only needles provided by Novo Nordisk must be used for administration of trial product. The subject should be advised to discard the injection needle after each injection and store the pen without an injection needle attached. Needles to be used with the trial product should be provided throughout the trial as needed.

7.1.1 Medical devices

Information about the PDS290 pre-filled pen-injector for semaglutide 1.34 mg/mL may be found in the IB and any updates hereof.

Information about the use of the PDS290 pre-filled pen-injector for semaglutide 1.34 mg/mL and semaglutide placebo can be found in the DFU.

Training for the pre-filled PDS290 pen-injector

When training the subjects, the following should be emphasised:

- Always use a new needle for each injection as this will prevent contamination and ensure correct dose.
- Remember to prime the pen-injector the first time it is used to ensure product flow.

- Check the dose counter to see that the correct dose has been dialled.
- The needle should be kept in the skin while counting slowly to 6 after the dose counter has returned to zero after injection. If the needle is removed too early then the full dose may not have been delivered.
- In-use conditions of the pen-injector including in-use time and storage (see Section 7.5).

7.2 Dose modification

Not applicable for this trial. Please refer to Section 7.1 for description of missed dose(s).

7.3 Method of treatment assignment

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

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

7.4 Blinding

The first 12 weeks during escalation all the trial products are packed open-label. From week 13 the subject will receive trial product which is packed open-label as well as trial product which is packed blinded containing either semaglutide 1.34 mg/mL or semaglutide placebo. The active drug and placebo drug are visually identical.

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

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

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

If the blind has been broken by investigator, the subject must discontinue treatment with trial product and a treatment discontinuation session must be completed in IWRS.

7.5 Preparation/Handling/Storage/Accountability

Only subjects enrolled in the trial may receive trial product and only authorised site staff may supply or administer trial product. Each trial site will be supplied with sufficient trial products for the trial on an on-going basis controlled by the IWRS. Trial product will be distributed to the trial sites according to screening and randomisation.

The investigator must confirm that appropriate temperature conditions have been maintained during transit for all trial products received and any discrepancies are reported and resolved before use of the trial products.

All trial products must be stored in a secure, controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff. For the storage and in-use conditions see the trial materials manual (TMM) and the labels of trial product. The investigator must inform Novo Nordisk immediately if any trial product has been stored outside specified conditions. Additional details regarding handling of temperature deviations can be found in the TMM. Trial product that has been stored improperly must not be dispensed to any subject before it has been evaluated and approved for further use by Novo Nordisk.

Subjects must return all used, partly used and unused trial products as instructed by the investigator. The investigator is responsible for drug accountability and record maintenance (i.e. receipt, accountability and final disposition records). Drug accountability must be performed in the IWRS by registering pen-injectors as returned either as used/partly used, unused or as lost.

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

All returned, expired or damaged trial products (for technical complaint samples see Appendix 6) must be stored separately from non-allocated trial products. No temperature monitoring is required. Non-allocated trial products including expired or damaged products must be accounted as unused, at the latest at closure of the trial site.

Japan: For country specific requirements, refer to Appendix 9

7.6 Treatment compliance

Throughout the trial, the investigator will remind the subjects to follow the trial procedures and requirements to ensure subject compliance. If a subject is found to be non-compliant the investigator will remind the subject of the importance of following the instructions given including taking the trial products as prescribed.

Treatment compliance of trial product will be assessed by asking subject about changes in the dose taken or missed doses, and by monitoring of drug accountability. Information about compliance should be described in the subject's source documents.

7.7 Concomitant medication

Any medication (including over-the-counter or prescription medicines) other than the trial product 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)

After signing the informed consent, subjects must continue their anti-diabetic background medication (metformin with or without SU) throughout the entire trial.

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 8.1.2) or safety concern related to the use of background medications arises.

In addition, all background medication(s):

- is considered to be non-investigational medicinal product.
- will not be provided by Novo Nordisk A/S, except if required by local regulations and not in contradiction to local regulations.
- should be used in accordance with standard of care and current approved label in the individual country.
- should not exceed the maximum approved dose in the individual country.

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

Any change 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 9.2.

7.7.1 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 8.1.2.

Rescue medication should be selected according to ADA/EASD guideline[2] (excluding GLP-1 RAs, dipeptidyl peptidase-4 (DPP-4) inhibitors and amylin analogues).

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

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

Rescue medication will not be supplied by Novo Nordisk but reimbursed as long as subject is participating in the trial, if required according to local regulations (Appendix 9).

7.8 Treatment after the end of the trial

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

8 Discontinuation/Withdrawal criteria

The 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 the subjects, who discontinue trial product, to continue in the trial.

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

8.1 Discontinuation of trial treatment

Discontinuation of trial treatment can be decided by either the investigator or the subject.

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

The subject must be discontinued from trial product, if the following applies:

17. Safety concern as judged by the investigator
18. Confirmation of acute pancreatitis
19. Pregnancy
20. Intention of becoming pregnant
21. Simultaneous participation in another clinical trial of an approved or non-approved investigational medicinal product

As soon as possible after the decision to discontinue trial product, the subject should attend the treatment discontinuation visit (V10A), followed by the treatment discontinuation follow-up visit (P11A) 7 weeks after treatment discontinuation. See the flowchart (Section 2) for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

The subjects should continue with the remaining scheduled visits and assessments until the time of the originally scheduled ‘end of treatment’ visit (V10) and “end of trial” visit (phone contact P11). All efforts should be made to have the subject attend at least the ‘end of treatment’ clinic visit containing the final data collection of primary and confirmatory secondary efficacy endpoints, and the “end of trial” visit. 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.

The investigator should discuss with the subject about the continued scientific importance of their data even if they discontinue trial product. If a subject is unwilling to attend any of the 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 product must be specified in the end-of-treatment form in the case report form (CRF), and final drug accountability must be performed. A treatment discontinuation session must be made in the IWRS.

8.1.1 Temporary discontinuation of trial treatment

In case of suspicion of acute pancreatitis, the trial product 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 4 for reporting).

If acute pancreatitis is confirmed, trial product should not be restarted, and a treatment discontinuation session should be made in IWRS. If the Atlanta criteria[18] are not fulfilled and thus, the suspicion of acute pancreatitis is not confirmed, trial product may be resumed.

If a subject has discontinued trial product due to temporary safety concern not related to trial product and is allowed to resume, the subject should follow the guide for missed doses (Section 7.1). Similarly, a subject who discontinues trial product on their own initiative should be encouraged to resume the trial product (Section 7.1).

8.1.2 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 16 and onwards.

If any of the HbA_{1c} values exceeds the limit outlined below and no intercurrent cause of the hyperglycaemia can be identified, a confirmatory HbA_{1c} in the central laboratory should be obtained within 30 days.

If the confirmatory HbA_{1c} exceeds the value described below then the subject should be offered treatment intensification (rescue medication) at the discretion of the investigator and in accordance with the ADA/EASD guidelines[2] (excluding GLP-1RAs, DPP-4 inhibitors and amylin analogues).

Rescue medication should be offered from week 16 to week 40 to:

- subjects with persistent poor glycaemic control, as expressed by a stable HbA_{1c} value above 8.5% (69 mmol/mol) that is confirmed within 30 days by the central laboratory and considered unacceptably high according to investigator's assessment.

Refer to Section 7.7.1 for description of rescue medication.

8.2 Withdrawal from the trial

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

If a subject withdraws consent, the investigator must ask the subject if he/she is willing, as soon as possible, to have assessment performed according to visit 10A. See the flowchart (Section 2) for data to be collected.

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

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.

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

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.

8.2.1 Replacement of subjects

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

8.3 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 trial site.

The following actions must be taken if a subject fails to return to the trial 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 the subject wishes to and/or should continue in the trial.
- Before a subject is deemed lost to follow-up, the investigator 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'.

9 Trial assessments and procedures

- Trial procedures and their timing are summarised in the flowchart.
- Informed consent must be obtained before any trial related activity, see Appendix 3.
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility 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 trial site staff.
- Adherence to the trial design requirements, including those specified in the flowchart, is essential and required for trial conduct.
- A subject who does not fulfil the eligibility criteria must not be randomised. If a subject is randomised in violation of inclusion and exclusion criteria, this will be handled as an important protocol deviation, and the IEC/IRB and regulatory authorities must be notified according to local requirements.
- The investigator must ensure they 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 to have all subjects followed for the primary endpoint and AEs must be made.
- It is the responsibility of the investigator to schedule the visits and contacts as per the protocol flowchart (Section 2) and to ensure they take place.
- Assessments should be carried out according to the clinic's standard of practice unless otherwise specified in the current section. Efforts should be made to limit the bias between assessments.
- Review of completed hypoglycaemic episode diaries 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.
- Review of laboratory reports must be documented either on the documents or in the subject's source documents.
- Repeat samples may be taken for technical issues and unscheduled samples or assessments may be taken for safety reasons. Refer to Appendix 2 for further details on laboratory samples.

US and Canada: For country specific requirements, refer to Appendix 9

9.1 Efficacy assessments

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

9.1.1 Clinical efficacy laboratory assessments

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

9.1.2 Body measurements

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

Height is measured without shoes in centimetres or inches and recorded to nearest ½cm or ¼inch.

Body weight should be measured without shoes and only wearing light clothing and recorded in the eCRF in kilogram or pound [kg/lb], with a precision of 1/10 unit, (e.g. 45.2 kg / 137.2 lb). BMI will be calculated in the eCRF.

The 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 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.

9.2 Adverse events

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

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

9.2.1 Time period and frequency for collecting AE and SAE information

All AEs will be collected from the first trial-related activity after obtaining informed consent and until the follow up phone contact, at the time points specified in the flowchart.

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

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

The method of recording, evaluating and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

Timelines for reporting of AEs are listed in Figure 9-1.

Some AEs require additional data collection via a specific event form. This includes medication errors observed during the trial. The relevant specific events are listed in Table 9-1 and the reporting timelines in Figure 9-1.

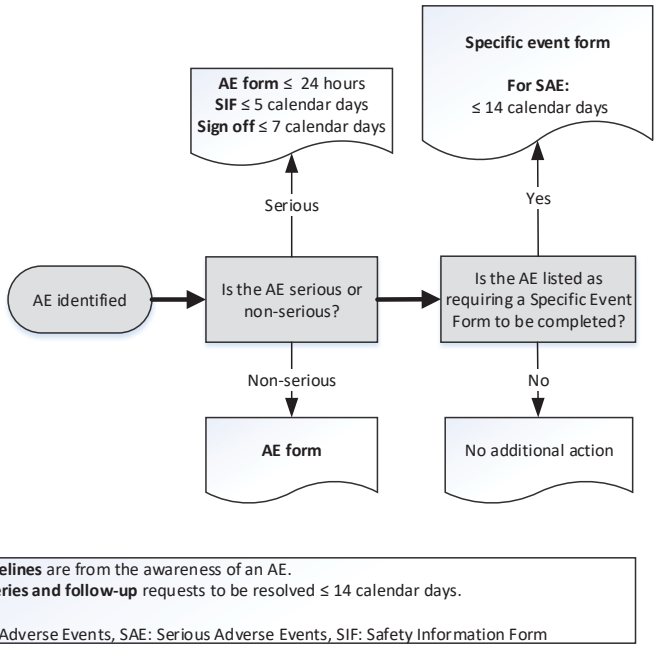

Figure 9-1 Decision tree for determining the event type and the respective forms to complete with associated timelines

Table 9-1 AEs requiring additional data collection (via specific event form)

Event type
Acute gallbladder disease
Acute pancreatitis
Acute renal failure
Diabetic retinopathy
Hepatic event
Malignant neoplasms
Medication error

9.2.2 Method of detecting AEs and SAEs

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

9.2.3 Follow-up on AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, will be followed until resolution, stabilisation, or if the event is otherwise explained (e.g. chronic condition) or the subject is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 4.

9.2.4 Regulatory reporting requirements for SAEs

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

Novo Nordisk has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a trial product under clinical investigation. Novo Nordisk will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

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

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

9.2.5 Cardiovascular and death events

Cardiovascular and death events will be handled and reported according to AE/SAEs description in Section 9.2.1.

9.2.6 Disease-related events and/or disease-related outcomes not qualifying as an AE or SAE

The following Disease-Related Events (DREs) are common in subjects with T2D and can be serious/life threatening:

- Hypoglycaemic episodes

Definitions, classification and reporting requirements are described in Appendix 7.

Hypoglycaemia

Non-serious hypoglycaemia must be reported on a hypoglycaemic episode form.

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.

BG meter and hypoglycaemic episode diary

Subjects will be provided with a blood glucose (BG) meter including auxiliaries as well as instructions for use. The subjects will be instructed in how to use the device and the instruction will be repeated at regular intervals as indicated in the flowchart.

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

The BG meter provided by Novo Nordisk should be used for the measurements required in the protocol as described in Appendix 7.

Subjects will also be provided with a hypoglycaemic episode diary. When subject experiences a hypoglycaemic episode, subject should use the BG meter and record the general information in relation to the hypoglycaemia in a diary as described in Appendix 7.

Relevant data from the diary must be transcribed into the CRF, as specified in Appendix 7, during or following the contact. If obtained via phone and a discrepancy is later detected, the values in the CRF must be corrected.

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

9.2.7 Pregnancies and associated adverse events

Details of pregnancies in female subjects will be collected after the first-trial-related activity after obtaining informed consent and until the follow up phone contact (7 weeks after the end of treatment).

If a pregnancy is reported in female subjects, the investigator should inform Novo Nordisk within 14 calendar days of learning of the pregnancy and should follow the procedures outlined in Figure 9-2 and Appendix 5.

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.

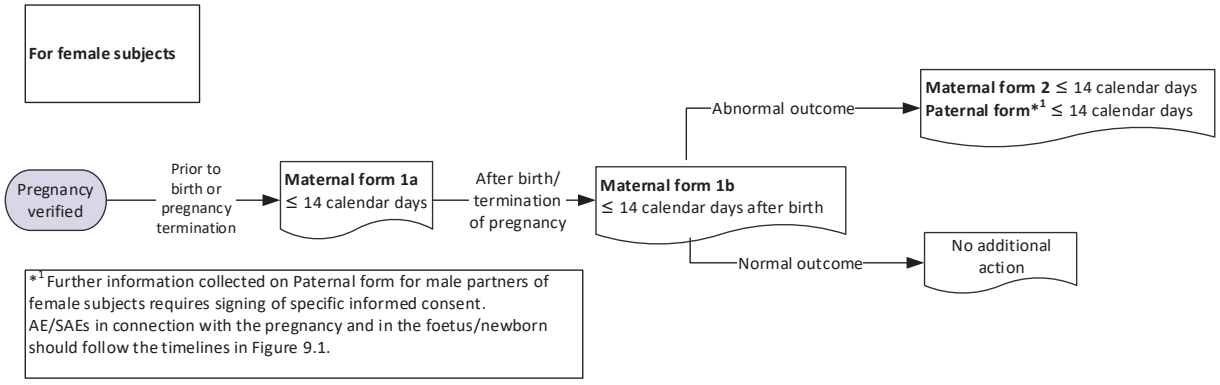

Figure 9-2 Decision tree for determining the forms to complete with associated timelines for pregnancy.

9.2.8 Medical device incidents (including malfunctions)

Section not applicable for this trial. Refer to technical complaints in Section 9.2.9.

9.2.9 Technical complaints

The investigator must assess whether a technical complaint is related to an AE.

The definitions and reporting process for technical complaints can be found in Appendix 6.

Timelines for reporting technical complaints are listed in Figure 9-3.

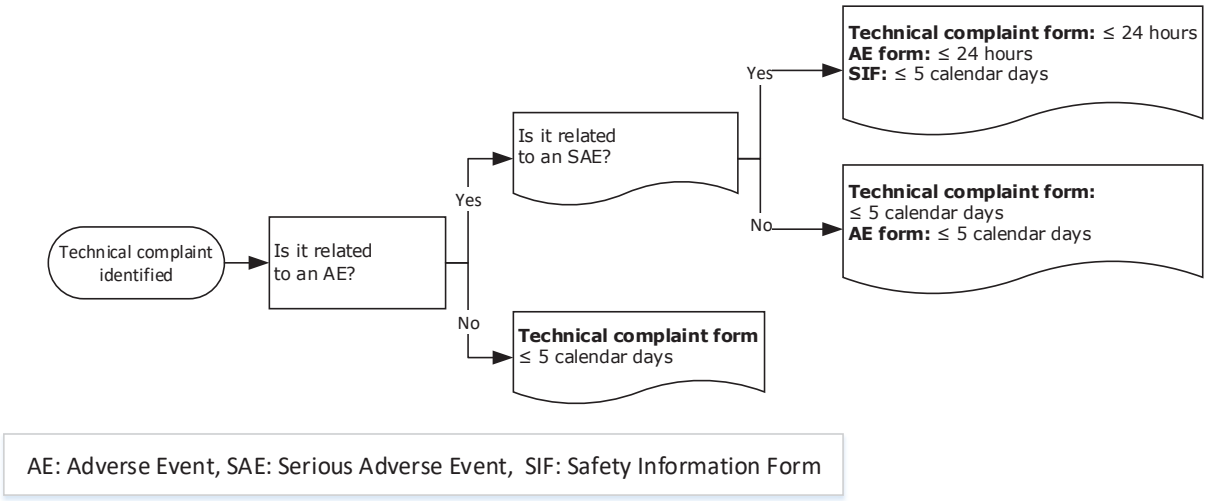

Figure 9-3 Decision tree for determining the forms to complete with associated timelines for technical complaints.

9.3 Treatment of overdose

Overdoses of up to 4.0 mg in a single dose and up to 4.0 mg in a week have been reported in clinical trials. The most commonly reported AE was nausea. All subjects recovered without complications.

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

Accidental overdose must be reported as a medication error. Refer to Section 9.2.1 for further details.

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

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

For more information on overdose, also consult the current version of the investigator's brochure and any updates hereof[15].

9.4 Safety assessments

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

A **concomitant illness** is any illness that is present at the start of the trial (i.e. at the first visit) 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 has experienced in the past. Only relevant and significant medical history as judged by the investigator should be recorded in the eCRF at the screening visit. Findings of specific medical history should de described in designated forms.

In case of an abnormal and clinically significant finding, the investigator must record the finding on the Medical History/Concomitant Illness form if it is present at screening. Any new finding fulfilling the AE definition (see Appendix4) during the trial and any clinically significant worsening from baseline must be reported as an AE (see Section 9.2).

9.4.1 Physical examinations

- A physical examination must be performed and include the following:
  General appearance, skin, thyroid gland, respiratory system, cardiovascular system, gastrointestinal system including mouth, central and peripheral nervous system, and lymph node palpation
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

9.4.2 Vital signs

- Pulse rate as well as diastolic and systolic blood pressure will be assessed.
- Blood pressure at randomisation will consist of 3 diastolic and systolic blood pressure measurements with intervals of at least 1 minute.
- Pulse rate at randomisation will also consist of 3 measurements.
- At randomisation, all blood pressure and pulse readings must be entered in the eCRF and the average of the 3 blood pressure and the average of the 3 pulse readings will be calculated in the eCRF. At the subsequent visits, the blood pressure and pulse should only be measured once.
- Blood pressure (diastolic and systolic) and pulse measurements should be preceded by at least 5 minutes of rest for the subject in a quiet setting without distractions (e.g. television, cell phones).
- Blood pressure and pulse measurements will be assessed in a sitting position with a completely automated device. Manual techniques will be used only if an automated device is not available.

9.4.3 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 healthcare provider 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 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 performed as per the flowchart in Section 2. Results must be available at V10 (end of treatment visit). An eye examination performed within 3 weeks prior to V10 is acceptable, provided no clinical symptoms suggestive of eye disease have occurred in the meantime.

The investigator should indicate the outcome of each eye examination. Relevant findings prior to randomisation must be recorded as concomitant illness/medical history, while relevant findings occurring after randomisation should be reported as an AE, if applicable according to Section 9.2.

9.4.4 Clinical safety laboratory assessments

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

9.5 Pharmacokinetics

- Single blood samples for measuring plasma concentration of semaglutide will be drawn on visits specified in the flowchart.
- Subject must be instructed to withhold their trial product dose in the morning of the clinic visit until blood sampling has been performed.
- The exact timing of obtaining the pharmacokinetic (PK) sample must be recorded on the laboratory form.
- 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.

9.6 Pharmacodynamics

Not applicable for this trial.

9.7 Genetics

Not applicable for this trial.

9.8 Biomarkers

Not applicable for this trial.

9.9 Severe hypersensitivity

In the event of a severe immediate hypersensitivity reaction to trial product, blood sampling for assessment of anti-semaglutide IgE and binding antibodies should be conducted after 1–2 weeks and 7 weeks of trial product wash-out (i.e. after the subject had the last dose of the trial product). In these cases, it is also recommended to test for tryptase (total and/or mature tryptase) within 3 hours of the hypersensitivity reaction. In case a tryptase sample was collected within 3 hours of the event of hypersensitivity reaction, a baseline tryptase sample should be taken at the same time points as the IgE sample is obtained (after 1-2 weeks of drug wash-out). Tryptase concentrations (if measured) as well as results of anti-semaglutide antibody and IgE isotype anti-semaglutide antibodies will be collected by Novo Nordisk and the results will be reported in the CTR.

10 Statistical considerations

10.1 Sample size determination

The primary endpoint is change from baseline (week 0) to week 40 in HbA_{1c} (%-point) and the confirmatory secondary endpoint is change from baseline (week 0) to week 40 in body weight (kg). Both endpoints will be tested for superiority. The type-I error rate will be controlled in the strong sense across the primary and the confirmatory secondary hypotheses, separately for each estimand, at an overall alpha level (two-sided) of 0.05. Multiplicity control and criteria for confirming the hypotheses is described in Section 10.3 below.

The sample size calculation is performed to ensure sufficient power for confirming superiority of semaglutide 2.0 mg vs. semaglutide 1.0 mg on change from baseline to week 40 in HbA_{1c} (%-point) based on each estimand separately.

Primary endpoint

An on-treatment HbA_{1c} treatment effect of −0.26%-point was predicted based on exposure-response modelling.

To accommodate the treatment policy estimand, the on-treatment effect is adjusted by 15% based on results from the SUSTAIN phase 3a programme, where a lower effect was observed for the treatment policy estimand as compared to the on-treatment effect. With the adjusted HbA_{1c} treatment effect of −0.22%-point and a standard deviation of 1.1%-point, 964 subjects will be randomised in order to obtain 87% power for confirming superiority for the primary endpoint based on the treatment policy estimand and at least 87% power for confirming superiority for the primary endpoint based on the hypothetical estimand. This is based on a 1:1 randomisation, a two-sided significance level of 0.05, and a t-test. The assumed standard deviation is based on the SUSTAIN programme.

Confirmatory secondary endpoint

With 964 subjects randomised to ensure sufficient power (87%) for confirming superiority for the primary endpoint based on the treatment policy estimand, a marginal power of 90% for confirming that semaglutide 2.0 mg is superior to semaglutide 1.0 mg on change from baseline to week 40 in body weight (based on each estimand) is obtained if the true treatment difference is as low as - 0.84 kg. This is based on a 1:1 randomisation, a two-sided significance level of 0.05, a t-test, and a standard deviation of 4.0 kg. The assumed standard deviation is based on the SUSTAIN programme.

Sensitivity analyses for the sample size calculation

The sensitivity of power for confirming superiority for the primary endpoint based on the treatment policy estimand for a fixed sample size of 964 subjects is presented in Table 10-1.

Table 10-1 Power for different scenarios

Scenario	On-treatment effect	Adjusted for the treatment policy estimand	Adjusted treatment effect	Randomised subjects	Power
Scenario 1	-0.25 %-point	15 %	-0.21	964	84 %
Scenario 2	-0.25 %-point	20 %	-0.20	964	81 %
Scenario 3	-0.27 %-point	15 %	-0.23	964	90 %
Scenario 4	-0.27 %-point	20 %	-0.22	964	87%
Scenario 5	-0.29 %-point	15 %	-0.25	964	94 %
Scenario 6	-0.29 %-point	20 %	-0.23	964	90 %

10.2 Definition of analysis sets

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

Full analysis set (FAS): All randomised subjects. Subjects will be analysed according to the treatment to which they were assigned at randomisation.

Safety analysis set (SAS): All subjects exposed to at least one dose of trial product. Subjects will be analysed according to the trial product received for the majority of the period they were on treatment.

'In-trial' observation period: This observation period is defined as the period from the date of randomisation to the first of the following dates, both inclusive:

- Date of the end-of-treatment visit (V10)
- Date of death
- Date when subject withdrew informed consent
- Date of last contact for subjects lost to follow-up

'On-treatment' observation period: This observation period is a sub-set of the 'in-trial' observation period and represents the time period where subjects are considered exposed to trial product. The observation period starts at the date of first dose of trial product and ends at an endpoint-specific end-date. For adverse events including hypoglycaemic events, the observation period ends at the first date of any of the following:

- The follow-up visit (P11)
- The treatment discontinuation follow-up visit (P11A)

- The date of last dose of trial product +49 days
- The end-date for the 'in-trial' observation period

The follow-up visit is scheduled to take place 7 weeks after the last date on trial product, i.e., 49 days.

For efficacy and other safety assessments (laboratory assessments, body measurements, and vital signs) the 'on-treatment' observation period ends at the last date on trial product with a visit window of +14 days. Hence, for these assessments, the 'on-treatment' observation period reflects the period in which subjects are treated.

'On-treatment without rescue medication' observation period: This observation period is a sub-set of the 'on-treatment' observation period and represents the time period where subjects are considered treated with trial product but have not initiated any rescue medications. The observation period starts at the date of first dose of trial product and ends at the first date of any of the following:

- Initiation of rescue medication
- The date of last dose of trial product +14 days

Data points collected outside an observation period will be treated as missing in the analysis. Baseline data will always be included in an observation period.

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

10.3 Statistical analyses

If necessary, a statistical analysis plan (SAP) may be written in addition to the protocol, including a more technical and detailed elaboration of the statistical analyses. The SAP will be finalised before the partial database lock.

General considerations

The comparison presented from a statistical analysis will be semaglutide 2.0 mg versus semaglutide 1.0 mg and results will be presented by the estimated treatment contrast with associated two-sided 95% confidence intervals and p-values corresponding to two-sided tests of no difference if not otherwise specified.

Data from all sites will be analysed and reported together.

If no statistical analysis is specified, data will be presented using relevant summary statistics. Accordingly, adverse events will be summarised descriptively. Data collected before randomisation (V2) will only be summarised descriptively.

Multiplicity control and criteria for confirming hypotheses

The statistical testing strategy will be performed for the primary analysis of each of the two estimands separately. In order to preserve the overall type-I error in the strong sense at a 5% significance level (two-sided), the conclusion of superiority of semaglutide 2.0 mg versus semaglutide 1.0 mg will be evaluated hierarchically according to the sequence below. The treatment difference is defined as μ = (semaglutide 2.0 mg minus semaglutide 1.0 mg).

1. Superiority of semaglutide 2.0 mg versus semaglutide 1.0 mg on change from baseline to week 40 in HbA_{1c}
   - H_0: $\mu \geq 0.0$ %-point against H_a: $\mu < 0.0$ %-point

2. Superiority of semaglutide 2.0 mg vs. semaglutide 1.0 mg on change from baseline to week 40 in body weight
   - H_0: $\mu \geq 0.0$ kg against H_a: $\mu < 0.0$ kg

10.3.1 Primary endpoint

The primary endpoint is change from baseline (week 0) to week 40 in HbA_{1c} (%-point).

Analyses addressing the hypothetical estimand

Primary analysis

The hypothetical estimand will be estimated based on FAS using post-baseline data collected up to and including week 40 from the 'on-treatment without rescue medication' observation period.

Imputation of missing data will be handled by multiple imputation (MI) assuming that missing data are missing at random (MAR). The imputation will be performed separately within each treatment group defined by randomised treatment. First, intermittent missing values are imputed using a Markov Chain Monte Carlo (MCMC) method, to obtain a monotone missing data pattern, generating 500 complete data sets. Secondly, a sequential conditional linear regression approach for imputing monotone missing values will be implemented starting with the first visit after baseline and sequentially continuing to the last planned visit at week 40. The model used for imputation will include the baseline and post-baseline HbA_{1c} values observed prior to the visit in question as covariates.

The 500 complete datasets will be analysed using an analysis of covariance (ANCOVA) with treatment and stratification as fixed factors and the baseline HbA_{1c} as covariate. Rubin's rule[19] will be applied to obtain inference.

Tipping point sensitivity analysis

For the tipping point sensitivity analysis, the primary analysis will be repeated, however, prior to analysis subjects from the semaglutide 2.0 mg group with missing observations at week 40 will be given a penalty, i.e., it is assumed that subjects with missing observations who are randomised to semaglutide 2.0 mg will receive a treatment that is less beneficial than subjects with observed values who are randomised to semaglutide 2.0 mg. The addition of the penalty values and subsequent analysis steps should be repeated with increasing penalty values until a significant result in the corresponding superiority analysis is no longer significant. This analysis will only be performed if superiority is confirmed based on the primary analysis.

Analyses addressing the treatment policy estimand

Primary analysis

The treatment policy estimand will be estimated based on the FAS using week 40 data from the 'in-trial' observation period.

Imputation of missing data will be handled by MI assuming that missing data are missing at random. The imputation will be performed by imputing missing week 40 data separately within groups defined by randomised treatment and treatment status at week 40 (retrieved drop-out), in total, four groups as follows; (i) semaglutide 1.0 mg and on-treatment at week 40, (ii) semaglutide 1.0 mg and off-treatment at week 40, (iii) semaglutide 2.0 mg and on-treatment at week 40, (iv) semaglutide 2.0 mg and off-treatment at week 40.

For each of the four groups an ANCOVA with baseline HbA1c as covariate will be fitted to observed values of the change from baseline in HbA1c at week 40. The estimated parameters for location and dispersion will then be used to impute 500 values for each subject with missing week 40 data based on only baseline HbA1c.

The 500 complete datasets will be analysed using an analysis of covariance (ANCOVA) with treatment and stratification as fixed factors and the baseline HbA1c as covariate. Rubin's rule[ref 19] will be applied to obtain inference.

Tipping point sensitivity analysis

The tipping point analysis will be performed in the same manner as for the tipping point sensitivity analysis addressing the hypothetical estimand, however, with the primary analysis addressing the

treatment policy estimand as foundation. This analysis will only be performed if superiority is confirmed based on the primary analysis.

10.3.2 Secondary endpoints

10.3.2.1 Confirmatory secondary endpoint

The confirmatory secondary endpoint is change from baseline (week 0) to week 40 in body weight (kg).

Analyses addressing the hypothetical estimand

Similar analyses as for the primary endpoint including body weight values instead of HbA_{1c} values will be performed.

Analyses addressing the treatment policy estimand

Similar analyses as for the primary endpoint including body weight values instead of HbA_{1c} values will be performed.

Overview of statistical analyses and intercurrent events

An overview of all analyses addressing the two estimands for the confirmatory endpoints is provided in Table 10-2.

Table 10-2 Statistical analyses of the confirmatory endpoints

Endpoint	Estimand	Analysis set	Observation period	Statistical model	Imputation approach	Sensitivity analysis
Primary endpoint						
Change in HbA_{1c} (%-point)	Hypothetical	FAS	On-treatment w/o rescue	ANCOVA	MAR within randomised treatment group	Tipping point analysis
	Treatment policy	FAS	In-trial	ANCOVA	MAR within group defined by randomised treatment and treatment status at week 40	Tipping point analysis
Confirmatory secondary endpoint						
Change in body weight (kg)	Hypothetical	FAS	On-treatment w/o rescue	ANCOVA	MAR within randomised treatment group	Tipping point analysis
	Treatment policy	FAS	In-trial	ANCOVA	MAR within group defined by randomised treatment and treatment status at week 40	Tipping point analysis

Abbreviations: ANCOVA; Analysis of Covariance; FAS: Full Analysis Set; MAR: Missing At Random.

The following Table 10-3 describes how anticipated intercurrent events during the trial are handled for confirmatory endpoints. The different intercurrent events will be handled in the same manner for both confirmatory endpoints.

Table 10-3 Statistical handling of intercurrent events for the primary analyses of the confirmatory endpoints

Intercurrent event	Handling			
	Hypothetical estimand		Treatment policy estimand	
	Strategy	Data	Strategy	Data
• Change in dose during and after the dose escalation period	Treatment policy	Assessments will be performed and collected at scheduled visits after the intercurrent event and used in the analysis	Treatment policy	Assessments will be performed and collected at scheduled visits after the intercurrent event and used in the analysis
• Treatment discontinuation due to AEs • Initiation of rescue (anti-diabetic) medication	Hypothetical	Assessments for scheduled visits after the time of the intercurrent event are considered missing and will be imputed assuming MAR as described in the analysis	Treatment policy	Assessments will be performed and collected at scheduled visits after the intercurrent event and used in the analysis

10.3.2.2 Supportive secondary endpoints

The supportive secondary endpoints are listed in Section 4.3.2.2. All analyses of these endpoints will be addressing a hypothetical estimand similar to the hypothetical estimand for the primary objective and based on the FAS using data from the 'on-treatment without rescue medication' observation period unless otherwise stated.

Continuous endpoints

The continuous endpoints will be analysed using a similar model approach as for the primary analysis of the primary endpoint with the associated baseline value as covariate instead of HbA_{1c} for their respective analyses. The analysis of change from baseline to week 40 in pulse rate will be based on SAS using data from the 'on-treatment' observation period.

Responder endpoints

To account for missing data, the binary endpoints will be derived from the 500 imputed datasets from the associated primary analysis addressing the hypothetical estimand. Each of the complete data sets will be analysed using a logistic regression (LR) model with treatment and stratification as fixed effects and associated baseline response as covariate. Estimated odds ratios will be log-transformed and inference will be drawn using Rubin's rule[19]. The results will be back-transformed and described by the odds ratio between treatments and the associated 95% CI and p-value for no treatment difference.

Other endpoints

Number of treatment emergent severe or blood glucose confirmed symptomatic hypoglycaemic episodes at week 40 will be analysed using a negative binomial regression (NBR) model with a log-link function and the logarithm of the time period covered by the subject's 'on-treatment' observation period as offset. The model will include treatment and stratification as fixed factors and baseline HbA_{1c} as a covariate. This analysis will be based on the SAS using the 'on-treatment' observation period. The results will be described by the rate ratio between treatments and the associated 95% CI and p-value for no treatment difference.

Overview of statistical analyses

An overview of all analyses of the supportive secondary endpoints is provided in Table 10-4.

Table 10-4 Statistical analyses of the supportive secondary endpoints

Endpoint	Estimand	Analysis set	Observation period	Statistical model	Imputation approach
Supportive secondary endpoints (effect related)					
Change in FPG (mmol/)	Hypothetical	FAS	On-treatment w/o rescue	ANCOVA	MAR within randomised treatment group
Change in BMI (kg/m^2)	Hypothetical	FAS	On-treatment w/o rescue	ANCOVA	MAR within randomised treatment group
Change in waist circumference (cm)	Hypothetical	FAS	On-treatment w/o rescue	ANCOVA	MAR within randomised treatment group
HbA_{1c} < 7% (yes/no)	Hypothetical	FAS	On-treatment w/o rescue	LR	MAR within randomised treatment group
$HbA_{1c} \leq 6.5\%$ (yes/no)	Hypothetical	FAS	On-treatment w/o rescue	LR	MAR within randomised treatment group
Weight loss ≥ 5% (yes/no)	Hypothetical	FAS	On-treatment w/o rescue	LR	MAR within randomised treatment group
Weight loss ≥ 10% (yes/no)	Hypothetical	FAS	On-treatment w/o rescue	LR	MAR within randomised treatment group
Supportive secondary endpoints (safety related)					
Change in pulse (bpm)	-	SAS	On-treatment	ANCOVA	MAR within randomised treatment group
Number of hypoglycaemic episodes	-	SAS	On-treatment	NBR	-

Abbreviations: ANCOVA; Analysis of Covariance; FAS: Full Analysis Set; LR: Logistic Regression; MAR: Missing At Random; NBR: Negative Binomial Regression; SAS: Safety Analysis Set

10.3.3 Other analyses

The binary assessment indicating whether a subject has had no treatment emergent severe or blood glucose confirmed symptomatic hypoglycaemic episodes at week 40 or at least one will be analysed

using a logistic regression model. The model will include treatment and stratification as fixed effects and baseline HbA_{1c} as covariate, and the analysis will be based on SAS using data from the 'on-treatment' observation period. The results will be described by the odds ratio between treatments and the associated 95% confidence interval and p-value for no treatment difference.

10.4 Pharmacokinetic and/or pharmacodynamic 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. The analysis will be further specified in a modelling analysis plan that is to be prepared before database lock.

The modelling analyses will be performed by Quantitative Clinical Pharmacology at Novo Nordisk A/S and will be reported separately from the CTR.

10.5 Partial database lock

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 patient last treatment (LPLT) visit. The database will be updated after the partial database lock to include remaining PK data and any additional safety information. The full database lock will be performed after the date of the last patient last visit (LPLV).

Novo Nordisk will become unblinded at the time of the partial database lock, whereas subjects and investigators will remain blinded until after last patient last visit (LPLV). The analysis of the primary endpoint and all other efficacy endpoints will be performed based on the data from the partial database lock. Analysis of safety and PK data will be performed after the full database lock. This approach is implemented to allow earlier availability of semaglutide 2 mg to the patient population expected to benefit from a higher dose and to support further development activities with semaglutide s.c. A detailed plan for data handling and operational aspects of the partial database lock and the database update will be finalised before the partial database lock.

11 References

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12 Appendices

Appendix 1 Abbreviations and Trademarks

AACE	American Association of Clinical Endocrinologists
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
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CRF	case report form
CTR	clinical trial report
CV	cardiovascular
DBP	diastolic blood pressure
DMC	data monitoring committee
DFU	directions for use
DPP-4i	dipeptidyl peptidase-4 inhibitor
DRE	disease related event
DUN	dispensing unit number
EAC	event adjudication committee
EASD	European Association for the Study of Diabetes

ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
ETD	estimated treatment differences
FAS	full analysis set
FDA	U.S. Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FPG	fasting plasma glucose
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
GIAE	gastrointestinal adverse event
GLP-1 RA	glucagon-like peptide-1 receptor agonist
HbA_{1c}	glycated haemoglobin
hCG	human chorionic gonadotropin
HRT	hormone replacement therapy
IB	investigator's brochure
ICH	International Council for Harmonisation
IEC	independent ethics committee
INR	international normalised ratio
IRB	institutional review board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IWRS	interactive web response system
KDIGO	Kidney disease improving global outcomes
LOCF	last available observation carried forward
LR	logistic regression
LSFT	last subject first treatment
MAR	missing at random
MCMC	Markov Chain Monte Carlo
MEdDRA	medical dictionary for regulatory activities

MEN2	multiple endocrine neoplasia type 2
MI	multiple imputation
MMRM	mixed model for repeated measurement
MTC	medullary thyroid cancer
NBR	negative binomial regression
NYHA	New York Heart Association
OD	once daily
PCD	primary completion date
PG	plasma glucose
PK	pharmacokinetic
PMM	pattern mixture model
PP	per protocol
PT	preferred terms
PYE	patient-years of exposure
SBP	systolic blood pressure
SAE	serious adverse event
SAP	statistical analysis plan
SMQ	standardised MedDRA queries
SMPG	self-measured plasma glucose
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
T2D	type 2 diabetes
TEAE	treatment-emergent adverse event
TMM	trial materials manual
ULN	upper limit of normal
WOCBP	woman of child bearing potential

Appendix 2 Clinical laboratory tests

- The tests detailed in Table 12-1 and Table 12-2 will be performed by the central laboratory.
- Additional tests may be performed at any time during the trial as determined necessary by the investigator or required by local regulations. Only laboratory samples specified in the protocol should be sent to the central laboratory for analysis; if additional laboratory sampling is needed, e.g. to follow up on AEs, this must be done at a local laboratory.
- The laboratory equipment may provide analyses not requested in the protocol but produced automatically in connection with the requested analyses according to specifications in the laboratory standard operating procedures.
- The investigator must review all laboratory results for concomitant illnesses and AEs.
- Laboratory samples will be destroyed no later than at finalisation of the clinical trial report.

Table 12-1 Protocol-required efficacy laboratory assessments

Laboratory assessments	Parameters
Glucose metabolism	• Fasting plasma glucose[1] • HbA_{1c}
NOTES: [1]A FPG result ≤3.9 mmol/L (70 mg/dL) in relation to planned fasting visits should not be reported as a hypoglycaemic episode.	

Table 12-2 Protocol-required safety laboratory assessments

Laboratory assessments	Parameters
Haematology	• Basophils • Eosinophils • Erythrocytes • Haematocrit • Haemoglobin • Leucocytes • Lymphocytes • Monocytes • Neutrophils • Thrombocytes
Biochemistry[1]	• Alanine Aminotransferase (ALT) • Alkaline phosphatase • Amylase • Aspartate Aminotransferase (AST) • Creatinine • Lipase • Potassium • Sodium • Total Bilirubin • Urea

Hormones	• Calcitonin (only for screening purposes)
Pregnancy Testing	• Urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[2]
Other tests	• eGFR calculated by the central laboratory based on the creatinine value using the CKD-EPI equation
Notes: [1]Details of required actions and follow-up assessments for increased liver parameters including any discontinuation criteria are given in Appendix 4 (Hy's Law) and Section 8.1. [2]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
- semaglutide plasma concentrations, which will be performed at a specialised laboratory and
- anti-semaglutide IgE and binding antibodies (in the event of a severe immediate hypersensitivity reaction to trial product), which will be performed at a specialised laboratory

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

Appendix 3 Trial governance considerations

1) Regulatory and ethical considerations

- This trial will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki[20] and applicable ICH Good Clinical Practice (GCP) Guideline[21]
  - Applicable laws and regulations
- The protocol, informed consent form, investigator's brochure (as applicable) and other relevant documents (e.g. advertisements), must be submitted to an IRB/IEC and reviewed and approved by the IRB/IEC before the trial is initiated.
- Regulatory authorities will receive the clinical trial application, protocol amendments, reports on SAEs, and the clinical trial report according to national requirements.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the trial design, except for changes necessary to eliminate an immediate safety hazard to trial subjects.
- Before a trial 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 clinical trial report (CTR) synopsis to the IRB/IEC.

Japan: For country specific requirements, refer to Apppendix 9

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

3) Informed consent process

- The investigator or his/her representative will explain the nature of the trial to the 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 will be required to sign and date a statement of informed consent that meets the requirements of local regulations, ICH guidelines[21], Declaration of Helsinki[20] and the IRB/IEC or trial site.
- The medical record must include a statement that written informed consent was obtained before any trial related activity and the date when the written consent was obtained. The authorised person obtaining the informed consent must also sign and date the informed consent form before any trial related activity.
- The responsibility of seeking informed consent must remain with the investigator, but the investigator may delegate the task of informing to a medically qualified person, in accordance with local requirements.
- Subjects must be re-consented to the most current version of the informed consent form(s) during their participation in the trial.
- A copy of the informed consent form(s) must be provided to the subject.

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.

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

- 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 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.

6) Committee structure

Novo Nordisk safety committee

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

7) Publication policy

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

No confidential information shall be disclosed to others without prior written consent from Novo Nordisk. Such information shall not be used except in the performance of this trial.
The information obtained during this trial may be made available to other investigators who are conducting other clinical trials with the trial product, if deemed necessary by Novo Nordisk. Provided that certain conditions are fulfilled, Novo Nordisk may grant access to information obtained during this trial to researchers who require access for research projects studying the same disease and/or trial product studied in this trial.

Novo Nordisk may publish on its clinical trials website a redacted clinical trial report for this trial. One (or two) investigator (s) will be appointed by Novo Nordisk to review and sign the clinical trial report (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.[22]

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

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

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

Authorship of publications should be in accordance with the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals by the International Committee of Medical Journal Editors[22].

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

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

Site-specific publication(s) by investigator(s)
For a multicentre clinical trial, analyses based on single-site data usually have significant statistical limitations and frequently do not provide meaningful information for healthcare professionals or 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.

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.

8) Dissemination of clinical trial data

Information of the trial will be disclosed at clinicaltrials.gov and novonordisk-trials.com. It will also be disclosed according to other applicable requirements such as those of the International Committee of Medical Journal Editors (ICMJE)[23], the Food and Drug Administration Amendments Act (FDAAA)[24], European Commission Requirements[1, 25] 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) + 40 weeks corresponding to V10 (end of treatment visit). If the last subject is withdrawn early, the PCD is considered the date when the last subject would have completed V10. The PCD determines the deadline for results disclosure at clinicaltrials.gov according to FDAAA.

9) Data quality assurance

Case Report Forms (CRFs)

- Novo Nordisk or designee is responsible for the data management of this trial including quality checking of the data.
- All 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 CRF is revoked or the CRF is temporarily unavailable:

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

- Corrections to the CRF data may be made by the investigator or the investigator's delegated staff. An audit trail will be maintained in the CRF application containing as a minimum: the old and the new data, identification of the person entering the data, date and time of the entry and reason for the correction. If corrections are made by the investigator's delegated staff after the date when the investigator signed the CRF, the CRF must be signed and dated again by the investigator.
- The investigator must ensure that data is recorded in the CRF as soon as possible, preferably within 5 working days after the visit. Once data has been entered, it will be available to Novo Nordisk for data verification and validation purposes.

Monitoring

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

- Trial monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorised site personnel are accurate, complete and verifiable from source documents; that the safety and rights of 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 trial sites.

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

Protocol compliance

Deviations from the protocol should be avoided. If deviations do occur, the investigator must inform the monitor and the implications of the deviation must be reviewed and discussed.

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

10) Source documents

- All data entered in the CRF must be verifiable in source documentation other than the CRF.
- 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 trial 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 trial site.
- Data reported on the paper CRF or entered in the electronic CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records. Also, current medical records must be available.
- It must be possible to verify 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 trial site. There will only be one source document defined at any time for any data element.

11) Retention of clinical trial documentation

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

provided electronic data (e.g. the CD-ROM) is not readable during the entire storage period, the investigator can request a new copy. A copy of all data will be stored by Novo Nordisk.

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

12) Trial and site closure

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

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

The investigator may initiate trial site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.
Reasons for the early closure of a trial site by Novo Nordisk or investigator may include but are not limited to:

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

13) Responsibilities

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

The investigator will take all necessary technical and organisational safety measures to prevent accidental or wrongful destruction, loss or deterioration of data. The investigator will prevent any unauthorised access to data or any other processing of data against applicable law. The investigator must be able to provide the necessary information or otherwise demonstrate to Novo Nordisk that such technical and organisational safety measures have been taken.

During any period of unavailability, the investigator must delegate responsibility for medical care of 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).

14) Indemnity statement

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

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

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

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

Events meeting the AE definition
• Any abnormal laboratory test results or safety assessments, including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. • A clinical abnormal laboratory finding which is clinically significant, i.e. an abnormality that suggests a disease and/or organ toxicity and is of a severity that requires active management. Active management includes active treatment or further investigations, for example change of medicine dose or more frequent follow-up due to the abnormality. • Abuse: Persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects (e.g. overdose with the intention to cause harm) • Misuse: Situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol or the terms of the marketing authorisation. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • Signs, symptoms or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms or the clinical sequelae of a suspected overdose of trial product regardless of intent. • • 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
• Pre-existing conditions, anticipated day-to-day fluctuations of pre-existing conditions, including those identified during screening or other trial procedures performed before exposure to trial product. Note: pre-existing conditions should be recorded as medical history/concomitant illness. • Pre-planned procedures, unless the condition for which the procedure was planned has worsened from the first trial related activity after the subject has signed the informed consent.

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

- **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 serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious.
  - Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

    Note:
    - Hospitalisations for administrative, trial related and social purposes do not constitute AEs and should therefore not be reported as AEs or SAEs.
    - Hospital admissions for surgical procedures, planned before trial inclusion, are not considered AEs or SAEs.
- **Results in persistent or significant disability/incapacity**
  - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
  - This definition is not intended to include experience of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g. sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- **Is a congenital anomaly/birth defect**
- **Important medical event:**
  - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations. This includes important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the 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 trial product.
    - risk of liver injury defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 x UNL and total bilirubin >2 x UNL, where no alternative aetiology exists (Hy's law).

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

AEs requiring additional data collection

AEs requiring additional data collection are AEs where the additional data will benefit the evaluation of the safety of the trial product (Table 9-1). 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.

Event type	Description
Medication error:	A medication error is an unintended failure in the trial drug treatment process that leads to, or has the potential to lead to, harm to the subject such as: • Administration of wrong drug or use of wrong device.

		Note: Use of wrong dispensing unit number (DUN) is not considered a medication error unless it results in an administration of wrong drug. • Wrong route of administration, such as intramuscular instead of subcutaneous. • Accidental administration of higher dose than intended during dose escalation or maintenance. However, 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.
	Acute pancreatitis	The diagnosis of acute pancreatitis requires two of the following three features: (1) abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back) (2) serum lipase activity (and/or amylase activity) at least three times greater than the upper limit of normal (3) characteristic findings of acute pancreatitis on imaging
	Acute gallbladder disease	Events of symptomatic acute gallbladder disease (including gallstones and cholecystitis)
	Malignant neoplasm	Confirmed malignant neoplasm by histopathology or other substantial clinical evidence
	Hepatic event	Hepatic event defined as: – Disorders of the liver including cholestatic conditions and liver related signs and symptoms – ALT or AST > 3x UNL and total bilirubin > 2x UNL* – ALT or AST > 3x UNL 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 a hepatic event defined as ALT or AST > 3x UNL and total bilirubin > 2x UNL, where no alternative aetiology exists (Hy's law), this must be reported as an SAE using the important medical event criterion if no other seriousness criteria are applicable.
	Acute renal failure	Events 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)
	Diabetic retinopathy	New onset or worsening of diabetic retinopathy

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 "SAE reporting via paper CRF" later in this section.
- Novo Nordisk products used as concomitant medication if an AE is considered to have a causal relationship with a Novo Nordisk marketed product used as concomitant medication in the trial, it is important that the suspected relationship is reported to Novo Nordisk, e.g. in the alternative aetiology section on the safety information form. Novo Nordisk may need to report this adverse event to relevant regulatory authorities.

Assessment of severity

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

- **Mild**: An event that is easily tolerated by the 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: Severe is a category used for rating the intensity of an event; and both an AE and SAE can be assessed as severe. An event is defined as 'serious' when it meets at least one of the outcomes described in the definition of an SAE and not when it is rated as severe.

Assessment of causality

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

Relationship between an AE/SAE and the relevant trial product*(s)* should be assessed as:

- Probable - Good reason and sufficient documentation to assume a causal relationship.
- Possible - A causal relationship is conceivable and cannot be dismissed.
- Unlikely - The event is most likely related to aetiology other than the trial product.

Alternative aetiology, such as underlying disease(s), concomitant medication, and other risk factors, as well as the temporal relationship of the event to trial product administration will be considered and investigated.

The investigator should use the investigator's brochure for the assessment. For each AE/SAE, the investigator must document in the medical records that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report. However, **it is important that the investigator always makes an assessment of causality for every event before the initial transmission of the SAE data**.

The investigator may change his/her opinion of causality in light of follow-up information and send a follow-up report with the updated causality assessment.

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 at the first trial-related activity after the subject signed the informed consent. • **Recovering/resolving:** The condition is improving, and the subject is expected to recover from the event. This term is only applicable if the subject has completed the trial or has died from another AE. • **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. • **Fatal:** This term is only applicable if the subject died from a condition related to the reported AE. Outcomes of other reported AEs in a subject before he/she died should be assessed as "recovered/resolved", "recovering/resolving", "recovered/resolved with sequelae" or "not recovered/not resolved". An AE with a fatal outcome must be reported as an SAE. • **Unknown:** This term is only applicable if the subject is lost to follow-up.

Follow-up of AE and SAE
The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Novo Nordisk to elucidate the nature and/or causality of the AE or SAE as fully as possible (e.g. severe hypersensitivity reactions). This may include additional laboratory tests (e.g. skin prick test) or investigations, histopathological examinations, or consultation with other health care professionals. If a subject dies during participation in the trial or during a recognised follow-up period, the investigator should provide Novo Nordisk with a copy of autopsy report including histopathology. New or updated information will be recorded in the CRF.

SAE reporting via electronic CRF
• Relevant forms (AE and safety information form) must be completed in the CRF. • For reporting and sign-off timelines, see box below. • If the CRF is unavailable for more than 24 hours, then the site will use the paper AE form and if the CRF is unavailable for more than 5 calendar days then the site will use the paper safety information form (see box below). • The site will enter the SAE data into the CRF as soon as it becomes available, see 9.2.1. • After the trial is completed at a given site, the CRF will be decommissioned to prevent the entry of new data or changes to existing data. If a site receives a report of a new SAE from a 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.

SAE reporting via paper CRF
• Relevant CRF forms (AE and safety information form) must be forwarded to Novo Nordisk either by fax, e-mail (in an encrypted manner) or courier. • Initial notification via telephone is acceptable, although it does not replace the need for the investigator to complete the AE and safety information forms within the designated reporting time frames (as illustrated in Figure 9-1):   • AE form within 24 hours.

- Safety information form within 5 calendar days.
- Both forms must be signed within 7 calendar days.

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

Appendix 5 Contraceptive guidance and collection of pregnancy information

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

Definitions

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

22. Premenarcheal
23. Premenopausal female with one of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

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

Contraception guidance

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

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

Table 12-3 Highly effective contraceptive methods

Highly effective contraceptive methods that are user dependent [a and b] Failure rate of <1% per year when used consistently and correctly.
Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation • oral • intravaginal • transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation • oral • injectable
Highly effective methods that are user independent [b]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation • Intrauterine Device (IUD) • Intrauterine hormone-releasing System (IUS) • Bilateral tubal occlusion
Vasectomised partner A vasectomised partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
Sexual abstinence[b] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial product. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject.
Notes: [a]Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical trials. [b]Contraception should be utilised during the treatment period and for at least 7 weeks after the last dose of trial product.

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

1) known intolerance to the highly effective methods mentioned in Table 12-3 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.

Pregnancy testing

- WOCBP should only be included after a negative highly sensitive urine pregnancy test.
- Additional urine pregnancy testing should be performed at every site visit (every 4-8 weeks) during the treatment period, at the end of treatment and after the 7 weeks follow-up period after the end of treatment, according to the flow chart.
- Pregnancy testing should be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.
- All subjects will be provided with a pregnancy test prior to the phone visits to perform them prior to the phone call, not only if pregnancy is suspected.

Collection of pregnancy information

Female subjects who become pregnant

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this trial.
- Information will be recorded on the appropriate form and submitted to Novo Nordisk within 14 calendar days of learning of a subject's pregnancy.
- 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. Generally, follow-up will not be required for longer than 1 month beyond the delivery date.
- Any termination of pregnancy will be reported, regardless of foetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-trial pregnancy which is considered possibly/probably related to the trial product by the investigator will be reported to Novo Nordisk as described in Appendix 4. While the investigator is not obligated to actively seek this information in former subjects, he or she may learn of an SAE through spontaneous reporting.

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

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

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

Examples of technical complaints:

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

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

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

Timelines for reporting of technical complaints to Novo Nordisk
The investigator must complete the technical complaint form in the CRF within the timelines specified in 9.2.9 If the CRF is unavailable or when reporting a technical complaint that is not subject related, the information must be provided on a paper form by fax, e-mail or courier to Customer Complaint Center, Novo Nordisk, within the same timelines as stated above. When the CRF becomes available again, the investigator must enter the information on the technical complaint form in the CRF.

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

Collection, storage and shipment of technical complaint samples

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

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 affiliate with a reference to trial ID.

Appendix 7 Hypoglycaemic episodes

Novo Nordisk classification of hypoglycaemia

In normal physiology, symptoms of hypoglycaemia occur below a PG level of 3.1 mmol/L (56 mg/dL)[26]. Therefore, Novo Nordisk has included hypoglycaemia with PG levels below this cut-off point in the definition of BG confirmed hypoglycaemia.

Novo Nordisk uses the following classification (Figure 12-1) in addition to the ADA classification[27]:

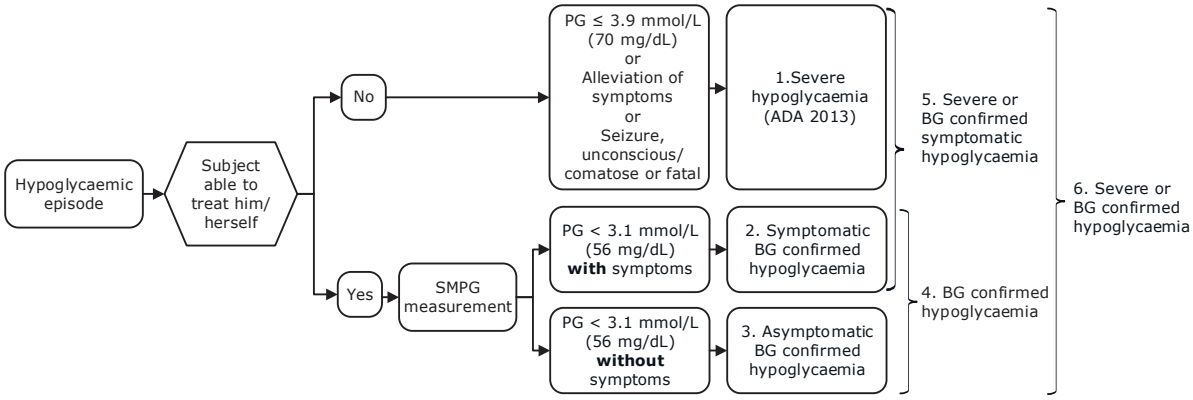
25. Severe hypoglycaemia according to the ADA classification[27].
26. Symptomatic BG confirmed hypoglycaemia: An episode that is BG confirmed by PG value <3.1 mmol/L (56 mg/dL) **with** symptoms consistent with hypoglycaemia.
27. Asymptomatic BG confirmed hypoglycaemia: An episode that is BG confirmed by PG value <3.1 mmol/L (56 mg/dL) **without** symptoms consistent with hypoglycaemia.
28. BG confirmed hypoglycaemia: The union of 2. and 3.
29. Severe or BG confirmed symptomatic hypoglycaemia: The union of 1. and 2.
30. Severe or BG confirmed hypoglycaemia: The union of 1., 2. and 3.

For hypoglycaemic episodes reported with missing information related to the classification, the following applies when classifying the episode according to the Novo Nordisk classification:

- A hypoglycaemic episode with missing information on symptoms will be classified as without symptoms.
- A hypoglycaemic episode with missing information on being able to self-treat will be regarded as an episode where the subject was able to self-treat and classified in accordance with the able to self-treat classifications.

Episodes that cannot be classified according to the above, are included in one of the following categories:

- 'Novo Nordisk unclassifiable' includes episodes where subjects were able to self-treat and with PG≥3.1 mmol/L (56 mg/dL) and hypoglycaemic episodes for a subject able to self-treat with missing PG as it is to be treated as an episode with PG>3.9 mmol/L (70 mg/dL).
- 'Not able to self-treat – unclassifiable' includes episodes where the subjects were not able to self-treat but neither of the following conditions were reported: PG≤3.9 mmol/L (70 mg/dL), alleviation of symptoms, seizure, unconscious/comatose or fatal.



Note: Glucose measurements are performed with capillary blood calibrated to plasma equivalent glucose values

BG: blood glucose PG: plasma glucose SMPG: Self-measured plasma glucose

Figure 12-1 Novo Nordisk classification of hypoglycaemia

ADA classification[27] of hypoglycaemia

- Severe hypoglycaemia: An episode requiring 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.
- Asymptomatic hypoglycaemia: An episode not accompanied by typical symptoms of hypoglycaemia, but with a measured PG concentration ≤3.9 mmol/L (70 mg/dL).
- Documented symptomatic hypoglycaemia: An episode during which typical symptoms of hypoglycaemia are accompanied by a measured PG concentration ≤ 3.9 mmol/L (70 mg/dL).
- Pseudo-hypoglycaemia: An episode during which the person with diabetes reports any of the typical symptoms of hypoglycaemia with a measured PG concentration > 3.9 mmol/L (70 mg/dL) but approaching that level.
- Probable symptomatic hypoglycaemia: An episode during which symptoms of hypoglycaemia are not accompanied by a PG determination but that was presumably caused by a PG concentration ≤ 3.9 mmol/L (70 mg/dL).

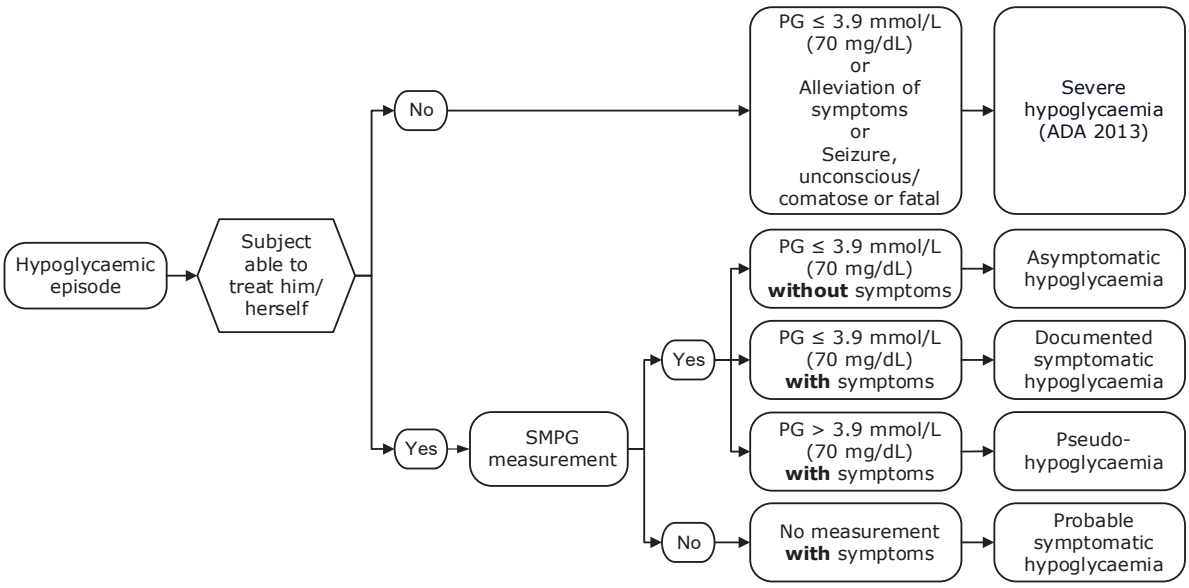
For hypoglycaemic episodes reported with missing information related to the classification, the following applies when classifying the episode according to the ADA classification:

- A hypoglycaemic episode with missing information on symptoms will be classified as without symptoms.

- A hypoglycaemic episode with missing information on being able to self-treat will be regarded as an episode where the subject was able to self-treat and classified in accordance with the able to self-treat classifications

Episodes that cannot be classified according to the above, are included in one of the following categories

- 'ADA unclassifiable' includes episodes where subjects were able to self-treat and with PG>3.9 mmol/L (70 mg/dL) or missing PG, and with no information on symptoms.
- 'Not able to self-treat – unclassifiable' includes episodes where the subjects were not able to self-treat but neither of the following conditions were reported: PG≤3.9 mmol/L (70 mg/dL), alleviation of symptoms, seizure, unconscious/comatose or fatal.



Note: Glucose measurements are performed with capillary blood calibrated to plasma equivalent glucose values

PG: plasma glucose SMPG: Self-measured plasma glucose

Figure 12-2 ADA classification of hypoglycaemia

Treatment-emergent: hypoglycaemic episodes will be defined as treatment-emergent, if the onset of the episode occurs in the on-treatment period (see definition in Section 10.2).

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

Hypoglycaemic episodes are classified according to the Novo Nordisk classification of hypoglycaemia and the ADA classification of hypoglycaemia.[27]

Reporting of hypoglycaemic episodes:
PG should always be measured and recorded when a hypoglycaemic episode is suspected.
All PG values:
≤3.9 mmol/L (70 mg/dL) or
>3.9 mmol/L (70 mg/dL) occurring in conjunction with hypoglycaemic symptoms should be reported as a hypoglycaemic episode according to the flowchart and instructions below. When subject experiences a hypoglycaemic episode, subject should record the general information in relation to the hypoglycaemia (timing, PG measurements, symptoms etc. as described in the diary). In case a subject is not able to fill in the diary (e.g. in case of hospitalisation or at the 'follow-up phone contact'), then investigator should report the hypoglycaemic episode in the CRF.

Upon onset of a hypoglycaemic episode the subject is recommended to measure PG every 15 minutes until the self-measured plasma glucose (SMPG) value is >3.9 mmol/L (70 mg/dL) and/or symptoms have been resolved in accordance with current guidelines[27].

Repeated SMPG measurements and/or symptoms will by default be considered as one hypoglycaemic episode until a succeeding SMPG value is >3.9 mmol/L (70 mg/dL) and/or symptoms have been resolved. One hypoglycaemic episode form is to cover these measurements and/or symptoms.

In case of several low SMPG values within the hypoglycaemic episode, the lowest value is the one that will be reported as the SMPG value for the hypoglycaemic episode, but the start time of the episode will remain as the time for the first low SMPG value and/or symptom.

The lowest value measured during the hypoglycaemic episode will be reported as the PG value for the episode. The remaining values will be kept as source data in the diary.

A hypoglycaemic episode starting without symptoms should be updated to symptomatic if the subject experiences symptoms later during the episode.
If the severity of a hypoglycaemic episode worsens, only one hypoglycaemic episode should be reported, reflecting the most severe degree of hypoglycaemia.

Investigator must instruct subjects that the answer to the question: "Was the subject able to treat him/herself?" must be answered "No" for an episode requiring 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[27].

Additional information (e.g. description of symptoms, alleviation of symptoms, seizure, coma, fatal) in relation to these severe hypoglycaemic episodes must be recorded.

Oral carbohydrates must not be given if the subject is unconscious.

For low SMPG values for hypoglycaemic episodes where the subject was able to self-treat: If a hypoglycaemic episode form is not completed within 7 calendar days of the SMPG measurement, the episode should be reported on a hypoglycaemic episode form with as much information as possible. Novo Nordisk will not query for additional data except for the start date, SMPG value and whether the subject was able to self-treat due to decreased validity of such data[28, 29]

The subject must be re-trained in how to report hypoglycaemic episodes if the investigator identifies low SMPG values not reported as hypoglycaemic episodes.

Appendix 8 NN9535-4191 Clinical Trial Report Synopsis

CTR synopsis

NAME OF SPONSOR
Novo Nordisk A/S, Novo Allé, DK-2880 Bagsvaerd, Denmark

NAME OF ACTIVE SUBSTANCE
Semaglutide

Trial registration ID-number
NCT02461589

UTN – U1111-1159-4923
IND number – 79,754
EudraCT number – 2014-003196-39

TITLE OF TRIAL
Dose-finding of semaglutide administered subcutaneously once daily versus placebo and liraglutide in subjects with type 2 diabetes

INVESTIGATORS
One principal investigator was appointed at each of the 139 trial sites in the trial. The following were designated signatory investigators for the trial, and were responsible for reviewing and approving the clinical trial report:

- [redacted]
- [redacted]

TRIAL SITES
The trial was conducted at 139 sites in 10 countries as follows:
Austria: 3 sites; Canada: 8 sites; Czech Republic 9 sites; Germany: 7 sites; Malaysia: 5 sites; Russian Federation: 7 sites; Serbia: 9 sites; South Africa: 7 sites; United Kingdom: 13 sites; United States: 71 sites.

PUBLICATIONS
No publications were available at the time of this clinical trial report synopsis.

TRIAL PERIOD
Initiation date: 21 September 2015
Completion date: 13 October 2016

DEVELOPMENT PHASE
Phase 2

DATA CUT-OFF DATE
The results presented reflect the data available in the clinical database as of 07 December 2016

DATE OF THE REPORT
16 May 2017

OBJECTIVES

Primary objective:

- To compare the efficacy of 4 dose-levels of semaglutide administered subcutaneously (s.c.) once daily (OD) versus placebo on glycaemic control after 26 weeks of treatment.

Secondary objectives:

- To compare the efficacy of semaglutide administered s.c. OD versus liraglutide on glycaemic control after 26 weeks of treatment.

- To compare semaglutide administered s.c. OD versus placebo and liraglutide on other parameters of efficacy, patient reported outcomes, safety and tolerability after 26 weeks of treatment.

METHODOLOGY
This was a 26-week multicentre, randomised, 13-arm, dose-finding trial investigating the efficacy and safety of semaglutide administered s.c. OD versus placebo and liraglutide in subjects diagnosed with type 2 diabetes (T2D) treated with diet and exercise with or without metformin. Subjects randomised to the 12-arm groups (double-blinded within dose level) followed a fixed-dosing regimen and a flexible dose-escalation regimen based on tolerability was explored for semaglutide in an open-label setting for subjects in the 13th treatment arm. For all treatment arms, semaglutide, liraglutide, or placebo was added on to their previous, stable therapy consisting of diet and exercise with or without metformin.

The trial consisted of a 2-week screening period, up to 16 weeks of a dose-escalation period in the fixed-dose arms followed by a minimum of 10 weeks of maintenance therapy, and a 7-week follow-up period. The total trial duration for individual subjects participating in the trial was 35 weeks. For the fixed-dose groups, the dose was not to be changed in the remaining treatment period after the maintenance dose was reached. For the open-label semaglutide treatment arm, a flexible dose-escalation regimen based on gastrointestinal (GI) tolerability was followed.

After the screening visit, eligible subjects were randomised in a 2:2:1 manner to either the semaglutide, liraglutide, or placebo arm in one out of four volume-matched dose levels (50 µL, 100 µL, 200 µL, and 300 µL). Subjects were to initiate treatment with either 0.05 mg of semaglutide (50 µL), 0.30 mg of liraglutide (50 µL), or 50 µL of placebo. Subjects in the lowest dose-volume (50 µL) did not follow a dose-esclation regimen.The doses in the fixed-dose groups were escalated from an initial dose of 0.05 mg and maintained for 4 weeks prior to escalating to the next dose, and continued up to 12 weeks. The highest dose for any trial subject would be 0.30 mg semaglutide administered OD (300 µL), or 1.80 mg liraglutide administered OD (300 µL). All subjects used NovoPen® 4 durable device for trial product administration. Metformin was considered a non-investigational medicinal product and was not supplied by Novo Nordisk.

Similar to the fixed dose-escalation arms, subjects in the open-label arm would start treatment at 0.05 mg semaglutide OD (50 µL) and 4-week dose-escalation steps would be used by default. However, based on the investigator's assessment, the dose level would be temporarily reduced in subjects with poor GI tolerability. Subjects experiencing moderate/severe nausea or vomiting for at least 3 days in the week preceding the planned visit/phone contact would be required to reduce the dose to the previous dose level. Dose reductions were to be only decided at planned visits/phone contacts. Subjects who experienced moderate/severe nausea or vomiting already at the lowest dose level were required to stay at least 4 additional weeks at the lowest dose from the decision point before reconsidering dose-escalation. An additional, mandatory safety visit was only applicable for subjects in the flexible dose-escalation arm who had been dose-escalated at week 20. No dose-escalations were allowed after week 22.

If necessary, for safety reasons suspected to be due to trial product, unacceptable intolerability or at request of subject, the trial product could be discontinued (without withdrawing the subject from the trial) at the investigator's discretion. For premature treatment discontinuations, treatment was not to be re-initiated, except in cases where suspicion of acute pancreatitis was ruled out. Subjects discontinuing trial product prematurely were to be called in for an 'end of treatment - premature discontinuation visit' as soon as possible and for a 'follow-up - premature discontinuation visit' 7 weeks after last dose of trial product. Furthermore, subjects with unacceptable hyperglycaemia were to be offered rescue medication and trial product was to be prematurely discontinued.

An external data monitoring committee (DMC) was not constituted for this trial. An independent external event adjudication committee (EAC) was constituted to perform ongoing adjudication, standardisation, and assessment of selected events. The purpose of the adjudication was to consistently confirm events by independent external medical experts according to standardised criteria.

NUMBER OF SUBJECTS PLANNED AND ANALYSED

A total of 1280 subjects were planned for screening and 704 planned for randomisation. In total, 1096 and 706 subjects were actually screened and randomised, respectively.

	Sema 0.05 mg **N (%)**	Sema 0.10 mg **N (%)**	Sema 0.20 mg **N (%)**	Sema 0.30 mg **N (%)**	Lira 0.30 mg **N (%)**	Lira 0.60 mg **N (%)**	Lira 1.20 mg **N (%)**	Lira 1.80 mg **N (%)**	Placebo **N (%)**	Sema flex **N (%)**	Total **N (%)**
Screened											1096
Randomised	64	63	65	63	64	64	64	65	129	65	706

Exposed FAS/SAS	64 (100.0)	63 (100.0)	65 (100.0)	63 (100.0)	64 (100.0)	64 (100.0)	64 (100.0)	65 (100.0)	129 (100.0)	64 (98.5)	705 (99.9)
Treatment completers	53 (82.8)	56 (88.9)	52 (80.0)	53 (84.1)	52 (81.3)	56 (87.5)	51 (79.7)	56 (86.2)	95 (73.6)	58 (90.6)	582 (82.6)
Premature treatment discontinuation	11 (17.2)	7 (11.1)	13 (20.0)	10 (15.9)	12 (18.8)	8 (12.5)	13 (20.3)	9 (13.8)	34 (26.4)	6 (9.4)	123 (17.4)
Trial completers	58 (90.6)	61 (96.8)	60 (92.3)	58 (92.1)	62 (96.9)	61 (95.3)	58 (90.6)	60 (92.3)	123 (95.3)	60 (93.8)	661 (93.8)
Premature withdrawal at or after premature treatment discontinuation	6 (9.4)	2 (3.2)	4 (6.2)	5 (7.9)	2 (3.1)	2 (3.1)	6 (9.4)	5 (7.7)	5 (3.9)	2 (3.1)	39 (5.5)
Premature withdrawal after treatment completion			1 (1.5)			1 (1.6)			1 (0.8)	2 (3.1)	5 (0.7)

Abbreviations: N: Number of subjects, %: Percentages of subjects, FAS: Full Analysis Set, SAS: Safety Analysis Set; Sema: semaglutide, Lira: liraglutide; flex: flexible dose

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION

Main inclusion criteria: Male or female, age ≥18 years at the time of signing informed consent; subjects diagnosed with T2D at least ≥90 days prior to screening; subjects should be on stable diabetes treatment consisting of diet and exercise with or without metformin (≥1500 mg daily or maximum tolerated dose documented in the patient medical record) for at least 90 days prior to screening. Glycated haemoglobin (HbA_{1c}): 53-86 mmol/mol (7.0-10.0%) (both inclusive). Body mass index (BMI): 25.0 – 40.0 kg/m^2 (both inclusive).

Main exclusion criteria: Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using adequate contraceptive methods throughout the trial including the 7-week follow-up period (adequate contraceptive measures as required by local regulation or practice). Any condition which, in the opinion of the investigator, might jeopardise subject safety or compliance with the protocol; treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria in a period of 90 days before screening (an exception is short-term insulin treatment for acute illnesses for a total of ≤14 days). Anticipated initiation or change in concomitant medications (for more than 14 consecutive days or on an frequent basis) known to affect weight or glucose metabolism (e.g. orlistat, thyroid hormones, corticosteroids). History of pancreatitis (acute or chronic). Screening calcitonin ≥50 ng/L. Family or personal history of Multiple Endocrine Neoplasia Type 2 (MEN2) or Medullary Thyroid Carcinoma (MTC). Uncontrolled hypertension (defined as systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥100 mmHg) at screening. If white-coat hypertension is suspected at the screening visit, repeated measurement at the screening visit is allowed. Severe to moderate renal impairment defined as GFR, estimated <60 ml/min/1.73 m^2 per Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI). Within the past 180 days before screening any of the following: myocardial infarction, stroke or hospitalisation for unstable angina or transient ischemic attack. Currently planned coronary, carotid or peripheral artery revascularisation. Patients presently classified as being in New York Heart Association (NYHA) Class III or IV.

Main treatment discontinuation criteria: Safety concerns suspected to be related to the trial products or unacceptable intolerance to the treatment.

Withdrawal criterion: Subjects could electively withdraw from the trial at any time by withdrawal of informed consent.

TRIAL PRODUCTS, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER

Trial Product	Dose	Administration Route	Batch Number	Expiry Date
Semaglutide 1.0 mg/mL, 3 mL	0.05, 0.10, 0.20, or 0.30 mg daily	Subcutaneous injection	EW5G922	27 April 2017
Liraglutide, 6.0 mg/mL, 3 mL	0.30, 0.60, 1.20 or 1.80 mg daily	Subcutaneous injection	EW5F506	14 July 2017
Placebo, 0 mg/mL, 3 mL	0 mg daily	Subcutaneous injection	DW5D550	29 March 2017

DURATION OF TREATMENT

26 weeks

CRITERIA FOR EVALUATION – EFFICACY

HbA_{1c}, body weight, fasting plasma glucose, and systolic and diastolic blood pressure.

CRITERIA FOR EVALUATION – SAFETY

Treatment-emergent adverse events (TEAEs, including pre-defined medical events of special interest adjudicated by an independent external adjudication committee), hypoglycaemic episodes, pulse rate, and laboratory safety variables.

STATISTICAL METHODS

Power calculation

The sample size calculation was based on a comparison of change from baseline to end-of-treatment at week 26 in HbA_{1c} between the highest dose of semaglutide OD and the four pooled placebo arms. The assumed treatment effect of the highest dose of semaglutide relative to placebo at week 26 was an average of 0.65% improvement in HbA_{1c}. Due to premature treatment discontinuations, however, this effect could not be expected to manifest itself as the statistical model's estimated treatment effect. A 50% smaller effect was assumed in the 30% of subjects assumed to discontinue treatment prematurely leading to a placebo-adjusted treatment effect of 0.55%, which was the value used in the sample size calculation. With the above assumptions, 64 subjects would be allocated to each of the semaglutide and liraglutide arms and twice that number of subjects to the pooled placebo (32 subjects in each arm) to yield a 90% power in order to detect a difference between the highest semaglutide dose and the pooled placebo arms at a Type I error rate of 5%
(2-sided). Thus, the total sample size would be (9×64) + (4×32) = 704 subjects.

Definition of analysis sets

The full analysis set (FAS) included all randomised subjects exposed to at least one dose of trial product. Subjects in the FAS would contribute to the evaluation 'as randomised'. The safety analysis set (SAS) included all randomised subjects exposed to at least one dose of trial product. Subjects in the SAS would contribute to the evaluation 'as treated'.

Observation periods

In-trial: The time period in which a subject was considered a trial participant and where data were collected systematically. The 'in-trial' observation period included observations recorded at or after randomisation and not after the last subject-investigator contact, which was scheduled to take place 7 weeks after planned last dose of trial product at a follow-up visit. This period was used for supportive analyses of both efficacy and safety.

On-treatment: The observation period where the subject was expected to be treated and exposed to randomised treatment. This was the primary observation period for examination of safety endpoints including adjudicated events, electrocardiograms (ECGs), and adverse events (AEs) including hypoglycaemic episodes.

On-treatment until rescue medication: This observation period was a subset of the 'on-treatment' observation period. To avoid potential confounding of initiation of anti-diabetic rescue therapies on efficacy endpoints, observations that were collected until initiation of permanent anti-diabetic rescue therapies were excluded from this observation period. 'On-treatment until rescue' observation period would be used when examining efficacy endpoints and was the observation period used for the primary analysis. Specifically, it included observations recorded at or after date of first dose of trial product and not after the first occurrence of the last dose of trial product plus the 7-days visit window or date of initiation of rescue therapy. This period was the primary observation period for examination of efficacy endpoints.

Statistical analysis

Primary endpoint: change from baseline in HbA_{1c} after 26 weeks of treatment

This analysis was based on FAS and observations within the 'on-treatment until rescue medication' period. All post-baseline measurements obtained at scheduled visits were analysed by a standard mixed model for repeated measurement (MMRM). In the primary analysis, all continuous data were evaluated using a standard MMRM analysis model with treatment, stratification factor (metformin use at baseline) and region as fixed factors, and the corresponding baseline value as covariate. The four placebo groups were pooled into one placebo arm. Missing data were assumed to be missing-at-random (MAR).

Supportive secondary efficacy endpoints

Change from baseline to week 26 in:

- Body weight
- Fasting plasma glucose (FPG)
- Systolic and diastolic blood pressure (SBP and DBP, respectively)

for the following pre-specified treatment comparisons:

- Semaglutide 0.05 mg/day vs. Placebo
- Semaglutide 0.10 mg/day vs. Placebo
- Semaglutide 0.20 mg/day vs. Placebo
- Semaglutide 0.30 mg/day vs. Placebo
- Liraglutide 0.30 mg/day vs. Placebo
- Liraglutide 0.60 mg/day vs. Placebo
- Liraglutide 1.20 mg/day vs. Placebo
- Liraglutide 1.80 mg/day vs. Placebo
- Semaglutide 0.05 mg/day vs. Liraglutide 0.30 mg/day

- Semaglutide 0.10 mg/day vs. Liraglutide 0.60 mg/day
- Semaglutide 0.20 mg/day vs. Liraglutide 1.20 mg/day
- Semaglutide 0.30 mg/day vs. Liraglutide 1.80 mg/day

Continuous endpoints were analysed separately using the standard MMRM model as for the primary endpoint but with the associated baseline value as a covariate. The same estimated treatment differences (ratios) as presented for the primary endpoint were presented with two sided p-values and 95% confidence intervals

Sensitivity analyses

To evaluate the robustness of the conclusions of the primary analysis, pre-specified sensitivity analyses were performed for change in HbA_{1c} and change in body weight at 26 weeks. These pre-specified sensitivity analyses investigated the sensitivity of the results due to the impact of missing values. For the primary analysis, the 'on-treatment until rescue medication' observation period was used for three of the sensitivity analyses (analysis of covariance [ANCOVA] based on last available observation carried forward [LOCF] analysis, complete case [MMRM-based] analysis, and the placebo and comparator-based imputation models based on the pattern mixture model [PMM]).

Subjects who after 26 weeks treatment achieved (yes/no):

- HbA_{1c} <7.0% (<53 mmol/mol) American Diabetes Association (ADA) target
- HbA_{1c} ≤6.5% (48 mmol/mol) American Association of Clinical Endocrinologists (AACE) target

These endpoints were analysed separately using a logistic regression model presenting odds ratio and 95% CI for the odds ratio and associated p-value. The model included treatment, region, and stratification variable (diet and exercise with or without metformin) as fixed effects and baseline value as covariate. Missing response data at 26 weeks were imputed from the MMRM used to analyse the two original continuous endpoints.

Supportive secondary safety endpoints

- Treatment-emergent AEs (TEAEs) were summarised descriptively. TEAEs, along with all other safety endpoints, were analysed using SAS. A TEAE was defined as an event that had an onset date (or increase in severity) during the on-treatment observation period. TEAEs were summarised descriptively in terms of the number of subjects with at least one event (N), the percentage of subjects with at least one event (%), the number of events (E) and the event rate (R) per 100 patient-years of exposure (PYE).
- Episodes of hypoglycaemia were classified according to the Novo Nordisk A/S and the ADA classification of hypoglycaemia. Treatment-emergent episodes of hypoglycaemia were summarised descriptively and presented as the episode rate per 100 PYE.
- Pre-defined groups of AEs of special interest were evaluated based on Medical Dictionary for Regulatory Activities (MedDRA) searches (version 19.0). These groups were defined by Novo Nordisk A/S Global Safety and consisted of pre-specified preferred terms.
- Pulse rate was analysed with the standard MMRM.

- Laboratory assessments were summarised and evaluated by descriptive statistics using the SAS.

Importantly, for data presentation of all endpoints, the word 'significant' is only used if supported by a statistical analysis and a p-value < 0.05.

DEMOGRAPHY OF TRIAL POPULATION

	Sema 0.05mg	Sema 0.10 mg	Sema 0.20 mg	Sema 0.30 mg	Lira 0.30 mg	Lira 0.60 mg	Lira 1.20 mg	Lira 1.80 mg	Placebo	Sema flex	Total
N	**64**	**63**	**65**	**63**	**64**	**64**	**64**	**65**	**129**	**65**	**706**
Female, N (%)	31 (48.44)	28 (44.44)	22 (33.85)	31 (49.21)	35 (54.69)	32 (50.00)	30 (46.88)	32 (49.23)	57 (44.19)	28 (43.75)	326 (46.24)
Age (years) [min-max]	57.5 [28-74]	57.5 [36-76]	58.4 [34-74]	54.8 [31-76]	57.2 [35-77]	59.5 [32-76]	53.7 [25-77]	55.8 [32-74]	57.1 [29-79]	54.8 [33-79]	56.7 [25-79]
HbA_{1c} (%), mean [min-max]	7.87 [6.7-9.8]	7.91 [6.3-10.0]	7.96 [6.7-9.9]	8.23 [6.9-10.3]	8.06 [6.8-10.4]	8.12 [6.80-9.9]	8.14 [6.5-10.3]	8.07 [6.6-10.0]	8.12 [6.6-10.8]	8.10 [6.7-10.1]	8.06 [6.3-10.8]
FPG (mmol/L), mean [min-max]	9.26 [5.9-16.3]	8.97 [3.3-17.4]	9.20 [5.6-16.4]	9.67 [4.3-15.6]	9.32 [5.2-17.5]	9.34 [5.5-16.9]	9.91 [5.2-16.6]	9.18 [5.5-16.4]	9.67 [4.5-23.1]	9.82 [6.3-20.6]	9.45 [3.25-23.12]
Diabetes duration (years) [min-max]	6.55 [0.3-17.5]	8.12 [0.4-36.1]	7.16 [0.3-25.9]	6.49 [0.38-21.0]	8.10 [0.3-44.9]	6.77 [0.6-24.1]	6.93 [0.5-23.1]	6.63 [0.3-22.8]	7.12 [0.4-20.8]	8.00 [0.4-35.9]	7.18 [0.3-44.9]
Body weight (kg) [min-max]	93.44 [55.3-132.9]	92.40 [63.9-133.0]	98.07 [63.9-140.6]	94.82 [54.8-136.1]	92.25 [66.4-137.5]	92.68 [63.0-127.6]	96.67 [53.6-155.6]	93.40 [59.6-151.5]	93.98 [58.8-148.5]	95.29 [52.6-129.5]	94.28 [52.6-155.6]
BMI (kg/m^2) [min-max]	32.32 [25.2-39.9]	32.40 [24.6-39.7]	32.83 [24.8-40.0]	33.10 [24.4-40.8]	32.94 [24.9-40.1]	33.02 [25.4-39.9]	33.29 [25.1-39.7]	32.06 [24.7-40.3]	32.76 [24.8-40.2]	33.22 [25.1-39.8]	32.79 [24.4-40.8]
	Sema 0.05mg	**Sema 0.10 mg**	**Sema 0.20 mg**	**Sema 0.30 mg**	**Lira 0.30 mg**	**Lira 0.60 mg**	**Lira 1.20 mg**	**Lira 1.80 mg**	**Placebo**	**Sema flex**	**Total**
Ethnicity; N (%)											
Not Hispanic or Latino	55 (85.94)	56 (88.89)	59 (90.77)	59 (93.65)	57 (89.06)	58 (90.63)	58 (90.63)	57 (87.69)	113 (87.60)	57 (89.06)	629 (89.22)
Race; N (%)											
American Indian or Alaska native			1 (1.54)		1 (1.56)						2 (0.28)
Asian	6 (9.38)	9 (14.29)	5 (7.69)	7 (11.11)	4 (6.25)	2 (3.13)	4 (6.25)	11 (16.92)	14 (10.85)	4 (6.25)	66 (9.36)
Black or African American	9 (14.06)	4 (6.35)	6 (9.23)	11 (17.46)	4 (6.25)	4 (6.25)	6 (9.38)	4 (6.15)	11 (8.53)	4 (6.25)	63 (8.94)
White	49 (76.56)	50 (79.37)	51 (78.46)	44 (69.84)	53 (82.81)	56 (87.50)	54 (84.38)	48 (73.85)	103 (79.84)	52 (81.25)	560 (79.43)
Other			2 (3.08)	1 (1.59)	2 (3.13)	2 (3.13)		2 (3.08)	1 (0.78)	4 (6.25)	14 (1.99)
Renal function; N (%)											
Normal	36 (56.25)	34 (53.97)	34 (52.31)	43 (68.25)	39 (60.94)	33 (51.56)	44 (68.75)	45 (69.23)	78 (60.47)	46 (71.88)	432 (61.28)
Mild	28 (43.75)	28 (44.44)	31 (47.69)	20 (31.75)	24 (37.50)	31 (48.44)	19 (29.69)	20 (30.77)	51 (39.53)	18 (28.13)	270 (38.30)

Moderate	1 (1.59)	1 (1.56)	1 (1.56)	3 (0.43)

Abbreviations: N: Number of subjects, %: Percentage of subjects, BMI: Body mass index, HbA_{1c}: glycosylated haemoglobin, FPG: fasting plasma glucose; Sema: semaglutide; Lira: liraglutide; Flex: flexible dose

EFFICACY RESULTS

Primary endpoint: change from baseline in HbA_{1c} after 26 weeks of treatment

Treatment with semaglutide significantly improved glycaemic control after a 26-week treatment period as compared with placebo or liraglutide.

- A dose-dependent significant reduction in HbA_{1c} was obtained with semaglutide as compared with placebo, with estimated treatment differences (ETDs) ranging from
  -1.04%-points $[-1.30; -0.77]_{95\%CI}$ for semaglutide 0.05 mg vs. placebo to
  -1.86%-points $[-2.12; -1.60]_{95\%CI}$ for semaglutide 0.30 mg vs. placebo.

- A significant reduction in HbA_{1c} was obtained with semaglutide as compared with each volume-matched liraglutide dose with ETDs of -0.55%-points $[-0.85; -0.25]_{95\%CI}$ for semaglutide 0.05 mg vs. liraglutide 0.30 mg; to -0.57%-points $[-0.87; -0.27]_{95\%CI}$ for semaglutide 0.30 mg vs. liraglutide 1.80 mg. Overall, semaglutide led to reductions in HbA_{1c} between -1.05%-points and -1.88%-points from a mean baseline of 8.06% compared to (-0.50 to -1.31)%-points for liraglutide and -0.02%-points for placebo.

- At week 26, a -1.67%-points reduction in HbA_{1c} was obtained with the open-label semaglutide flexible dose group, with an ETD of -1.64%-points $[-1.89; -1.39]_{95\%CI}$ as compared to placebo.

- The robustness of the primary analysis was supported by three sensitivity analyses that showed significantly better glycaemic control with similar, dose-dependent, and significant ETDs, ranging -0.86%-points $[-1.12; -0.60]_{95\%CI}$ to -1.02%-points $[-1.31; -0.73]_{95\%CI}$ for semaglutide 0.05 mg vs. placebo and -1.54%-points $[-1.80; -1.28]_{95\%CI}$ to
  -1.80%-points $[-2.09; -1.50]_{95\%CI}$ for semaglutide 0.30 mg vs. placebo.

- The dose response modelling potency of semaglutide was 28-fold higher than liraglutide with an estimated treatment ratio (ETR) of 27.59 $[18.52; 41.11]_{95\%CI}$ for $HbA_{1c,}$ as liraglutide 1.80 mg was equipotent to semaglutide 0.062 mg.

Supportive secondary efficacy endpoint: change from baseline in body weight after 26 weeks of treatment

Treatment with semaglutide led to significantly greater weight loss after a 26-week treatment period as compared with placebo or liraglutide.

- A dose-dependent significant reduction in body weight was obtained with semaglutide as compared with placebo, with ETDs ranging from
  -1.53 kg $[-2.76; -0.31]_{95\%CI}$ for semaglutide 0.05 mg vs. placebo to
  -7.00 kg$[-8.23; -5.77]_{95\%CI}$ for semaglutide 0.30 mg vs. placebo.

- A significant reduction in body weight was obtained with semaglutide as compared with each volume-matched liraglutide dose with ETDs of -1.26 kg $[-2.67; -0.14]_{95\%CI}$ for semaglutide 0.05 mg vs. liraglutide 0.30 mg to -4.48 kg $[-5.89; -3.08]_{95\%CI}$ for semaglutide 0.30 mg vs. liraglutide 1.80 mg. Overall, semaglutide led to weight

loss between -2.76 kg and -8.23 kg from a mean baseline weight of 94.18 kg compared to -1.50 to -3.75 kg for liraglutide and -1.23 kg for placebo.

- At week 26, a -6.42 kg reduction in body weight was observed with the open-label semaglutide flexible dose group, with an ETD of -5.15 kg [-6.47; -3.84]$_{95\%CI}$ as compared to placebo.

- The robustness of the primary analysis was supported by three sensitivity analyses that showed significantly better weight loss with similar, dose-dependent, and significant ETDs, ranging from
  -1.33 kg [-2.52; -0.14]$_{95\%CI}$ to -1.48 kg [-2.72; -0.24]$_{95\%CI}$ for semaglutide 0.05 mg vs. placebo and
  -6.45 kg [-7.65; -5.24]$_{95\%CI}$ to -6.66 kg [-7.93; -5.39]$_{95\%CI}$ for semaglutide 0.30 mg vs. placebo.

- The dose response modelling showed that the potency of semaglutide was 30-fold higher than liraglutide with an ETR of 29.81 [17.65; 50.35]$_{95\%CI}$ for body weight, as liraglutide 1.80 mg was equipotent to semaglutide 0.06 mg.

Other supportive secondary efficacy endpoints

- HbA_{1c} treatment targets were achieved by larger proportions of subjects in the semaglutide groups compared with placebo or liraglutide groups, and the odds for reaching both targets were significantly higher with semaglutide when compared with placebo or liraglutide:

  - HbA_{1c} ≤6.5% (AACE target) was achieved by a greater proportion of subjects with semaglutide (43-73%) when compared with liraglutide (14-42%) or placebo (6%). Approximately 67% of subjects in the open-label semaglutide flexible group achieved this target. The estimated odds ratios ranged from
    10.95 [4.55; 26.36]$_{95\%CI}$ for semaglutide 0.05 mg vs. placebo to
    59.58 [23.22; 152.88]$_{95\%CI}$ for semaglutide 0.30 mg vs. placebo; and from
    4.31 [1.79; 10.39]$_{95\%CI}$ for semaglutide 0.05 mg vs. liraglutide 0.30 mg to
    5.16 [2.33; 11.44]$_{95\%CI}$ for semaglutide 0.30 mg vs. liraglutide 1.80 mg.

  - HbA_{1c} <7.0% (ADA target) was achieved by a greater proportion of subjects with semaglutide (58-89%) when compared with liraglutide (33-62%) or placebo (13%). Approximately 84% of subjects in the open-label semaglutide flexible group achieved this target. The estimated odds ratios ranged from
    10.34 [4.77; 22.43]$_{95\%CI}$ for semaglutide 0.05 mg vs. placebo to
    101.61 [36.05; 286.39]$_{95\%CI}$ for semaglutide 0.20 mg vs. placebo; and from
    2.64 [1.21; 5.76]$_{95\%CI}$ for semaglutide 0.05 mg vs. liraglutide 0.30 mg to
    9.01 [3.31; 24.56]$_{95\%CI}$ for semaglutide 0.20 mg vs. liraglutide 1.20 mg.

- A greater reduction in FPG levels from baseline to week 26 was observed with semaglutide compared with either placebo or liraglutide with ETDs ranging from
  -1.80 mmol/L [-2.32; -1.27]$_{95\%CI}$ for semaglutide 0.05 mg vs. placebo to
  -2.97 mmol/L [-3.50; -2.44]$_{95\%CI}$ for semaglutide 0.30 mg vs. placebo; and from
  -0.79 mmol/L [-1.39; -0.19]$_{95\%CI}$ for semaglutide 0.05 mg vs. liraglutide 0.30 mg to
  -1.58 mmol/L [-2.19; -0.98]$_{95\%CI}$ for semaglutide 0.20 mg vs. liraglutide 1.20 mg.
  The ETDs in mg/dL ranged from
  -32.37 mg/dL [-41.85; -22.89]$_{95\%CI}$ for semaglutide 0.05 mg vs. placebo to
  -53.50 mg/dL [-63.05; -43.95]$_{95\%CI}$ for semaglutide 0.30 mg vs. placebo; and from
  -14.25 mg/dL [-25.07; -3.44]$_{95\%CI}$ for semaglutide 0.05 mg vs. liraglutide 0.30 mg to
  -28.56 mg/dL [-39.50; -17.62]$_{95\%CI}$ for semaglutide 0.20 mg vs. liraglutide 1.20 mg

- At week 26, a -3.40 mmol/L reduction in FPG was obtained with the open-label semaglutide flexible dose group, which was greater than fixed-dose semaglutide 0.20 mg (-2.64 mmol/L) but lower than the fixed-dose semaglutide 0.30 mg group (-3.53 mmol/L).

- The dose-response modelling showed that the potency of semaglutide was 38-fold higher than liraglutide with an ETR of 37.67 $[21.49; 66.03]_{95\%CI}$) for FPG, as liraglutide 1.80 mg was equipotent to semaglutide 0.05 mg.

- Systolic blood pressure levels at week 26 were significantly improved with semaglutide 0.30 mg (-10.02 mmHg) as compared with placebo (-2.42 mmHg) and liraglutide 1.80 mg (-3.58 mmHg) with ETDs of
  -7.60 mmHg $[-11.35; -3.8]_{95\%CI}$ between semaglutide 0.30 mg and placebo, and
  -6.44 mmHg $[-10.66; -2.22]_{95\%CI}$ between semaglutide 0.30 mg and liraglutide 1.80 mg.

  - At week 26, a -6.62 mmHg decrease in SBP was obtained for the open-label semaglutide flexible dose group, which was less than the fixed-dose semaglutide 0.30 mg group (-9.85 mmHg).

- Diastolic blood pressure levels at week 26 were significantly improved with semaglutide 0.30 mg (-3.88 mmHg) as compared with placebo (-0.64 mmHg) and liraglutide 1.80 mg (0.36 mmHg) with ETDs of
  -3.24 mmHg $[-5.82; -0.66]_{95\%CI}$ between semaglutide 0.30 mg and placebo, and
  -4.23 mmHg $[-7.13; -1.33]_{95\%CI}$ between semaglutide 0.30 mg and liraglutide 1.80 mg

  - At week 26, a -1.58 mmHg decrease in DBP was obtained for the open-label semaglutide flexible dose group, which was less than the fixed-dose semaglutide 0.30 mg group (-4.02 mmHg).

SAFETY RESULTS

During the 26 weeks of treatment, semaglutide, liraglutide, and placebo were generally safe and well tolerated.

Overall AE safety profile

- One (1) fatal event was reported with liraglutide 1.80 mg (due to 'acute myocardial infarction') that was assessed as unlikely related to treatment.

- Overall, low proportions of subjects across all treatment groups reported serious adverse events (SAEs) (3.1% to 9.4% in semaglutide, 1.6% to 10.8% in liraglutide, 3.1% in placebo, and 6.3% in the open-label semaglutide flexible group.There was no consistent pattern in reported SAEs across treatment groups or preferred terms (PTs). Incidences of SAEs were mainly driven by events within the system organ class (SOC) 'cardiovascular disorders', infections and infestations', and 'neoplasms' in descending order, with highest frequency reported in semaglutide 0.05 mg and liraglutide 1.80 mg.

- Adverse events were reported by comparable proportions of subjects among the fixed-dose groups, but at a higher rate in all doses of semaglutide than either liraglutide or placebo during the on-treatment period, with the highest proportion and rates in the open-label semaglutide flexible dose group:

  - semaglutide 0.05 mg: 62.5%; 538 events per 100 PYE

  - semaglutide 0.10 mg: 69.8%; 590 events per 100 PYE

  - semaglutide 0.20 mg: 73.8%; 590 events per 100 PYE

- semaglutide 0.30 mg: 73.0%; 642 events per 100 PYE
- liraglutide 0.30 mg: 76.6%; 402 events per 100 PYE
- liraglutide 0.60 mg: 67.2%; 515 events per 100 PYE
- liraglutide 1.20 mg: 70.3%; 420 events per 100 PYE
- liraglutide 1.80 mg: 76.9%; 521 events per 100 PYE
- placebo: 72.9%; 375 events per 100 PYE
- open-label semaglutide flexible group: 82.8%; 719 events per 100 PYE

- The differences in AEs were mostly related to gastrointestinal AEs (GIAEs), infections and infestations, nervous system disorders, musculoskeletal and connective tissue disorders, and metabolism and nutrition disorders.
- Overall in all treatment groups, the majority of AEs reported were of mild or moderate severity (in total, 96.4% or 2092 events of 2171). Overall, few severe events were reported across all groups (total 31 events of 2171). Majority of subjects reporting AEs had recovered or were recovering, with or without sequalae, from the majority of the reported AEs at the end of the trial, with only 315 of 2171 events not having been resolved by the end of the trial, with highest incidence in liraglutide 0.60 mg within the 'musculoskeletal and connective tissue disorders' SOC and lowest in the semaglutide 0.30 mg group 'gastrointestinal disorders' SOC.
- The most frequently reported AEs with semaglutide and liraglutide were within the SOC 'gastrointestinal disorders', whereas the most frequently reported AEs in subjects treated with placebo were within the SOC 'infections and infestations'.
- The proportion of subjects with AEs leading to premature treatment discontinuation was generally higher with placebo (10.9%) than semaglutide (6.3% to 9.2%), liraglutide (3.1% to 7.8%), or the open-label semaglutide flexible group (4.7%). The number of AEs leading to premature treatment discontinuation in the semaglutide and liraglutide groups was predominantly due to a higher frequency of subjects experiencing gastrointestinal AEs. For the placebo group, premature discontinuations were mainly due to hyperglycaemia. In some cases, subjects had hyperglycaemic episodes requiring rescue medication, thus these events were included in the 'lack of efficacy' category as the primary reason of premature treatment withdrawal and not under 'adverse event' in the end-of-trial form. This discrepancy was more apparent in the subject disposition reporting for the liraglutide and placebo groups, since a greater proportion of subjects in those groups reported 'lack of efficacy' as compared to semaglutide groups. It should be noted that subject disposition was based on end-of-trial form while AEs leading to withdrawal information was based on AE summary form.
- The proportion of subjects discontinuing treatment due to AEs in the open-label semaglutide flexible group was similar to the fixed-dose semaglutide groups.
- The dose response modelling showed that the potency of semaglutide was 7.5 (ETR: 7.43 $[2.36; 23.33]_{95\%CI}$) for treatment discontinuation due to AEs as liraglutide 1.80 mg was equipotent to semaglutide 0.24 mg.

Hypoglycaemia

- No 'severe' hypoglycaemic episodes (as defined by the ADA classification) were reported.

- 'Severe or blood glucose (BG)-confirmed symptomatic' hypoglycemic episodes (as defined by Novo Nordisk classification) were reported by 2 subjects (3.1%) with semaglutide 0.05 mg, 2 subjects (3.2%) with semaglutide 0.10 mg, 3 subjects (4.6%) with semaglutide 0.20 mg, 2 subjects (3.2%) with semaglutide 0.30 mg; 2 subjects (3.1%) with liraglutide 0.60 mg, 1 subject (1.6%) with liraglutide 1.20 mg, 3 subjects (4.6%) with liraglutide 1.8 mg; 4 subjects (3.1%) with placebo; and 2 subjects (3.1%) with the open-label semaglutide flexible group.

- No significant differences were observed in the proportion of subjects experiencing 'severe or BG-confirmed symptomatic' hypoglycaemia between semaglutide and liraglutide or placebo groups.

Safety areas of interest

- *Gastrointestinal disorders*

  - Gastrointestinal disorders were the most frequently reported AEs with semaglutide and liraglutide, with higher reporting in semaglutide with a dose effect observed. Similar proportions of subjects reported GIAEs in the fixed-dose semaglutide 0.30 mg (54.0%) and the open-label semaglutide flexible dose groups (56.3%).The most frequently (≥5%) reported GIAEs were 'nausea', 'diarrhoea', 'vomiting', 'constipation' and 'dyspepsia' in descending order, with 'nausea' and 'diarrhoea' reported at a higher rate and by a higher proportion of subjects with semaglutide doses than with the liraglutide or placebo.

  - The proportions of subjects reporting the most frequent PTs (respectively for fixed-dose semaglutide; liraglutide; placebo; and the open-label semaglutide flexible dose group) were as follows:
    nausea (17.2% to 25.4%; 9.4% to 20.0%; 4.7%; and 39.1%)
    diarrhoea (10.9% to 25.4%; 7.8% to 10.8%; 10.9%; and 17.2%)
    vomiting (6.3% to 9.5%; 1.6% to 10.9%, 2.3%; and 9.4%)

  - The majority of the events occurred within the initial 12 weeks of treatment and the median duration of the GIAEs were slightly higher with semaglutide than liraglutide or placebo, and varied across types of events.

  - The majority of GIAEs were largely mild or moderate in severity and 2 subjects (1 on semaglutide 0.10 mg ['anal fistula'] and 1 on placebo ['epiploic appendagitis']) reported gastrointestinal SAEs.

  - All reported GIAEs in the semaglutide 0.30 mg OD group, a dose level for which Novo Nordisk has had no previous experience in humans, were non-serious, mild-to-moderate in severity, and only one AE ('dyspepsia') led to drug withdrawal. None of the GIAEs reported in the open-label semaglutide flexible dose group were serious, majority were mild-to-moderate in severity, and only 2 AEs ('impaired gastric emptying' and 'abdominal pain') led to drug withdrawal.

  - The dose response modelling showed that the potency of semaglutide was 13 (ETR: 12.81 $[6.22; 26.36]_{95\%CI}$) for proportion of subjects reporting at least 1 GIAE as liraglutide 1.80 mg was equipotent to semaglutide 0.14 mg.

- *Cardiovascular disorders*

  - There were 18 EAC-confirmed events in 9 subjects in the trial. Twelve (12) CV events in 7 subjects were confirmed during the on-treatment observation period (4 events in 2 subjects in semaglutide 0.05mg, 6 events in 3 subjects in liraglutide 1.80 mg, 1 event in 1 subject in placebo, and 1 event in the open-label semaglutide flexible dose group). Two (2) additional events in semaglutide 0.05 mg and 2 events in liraglutide 1.20 mg were EAC-confirmed in the in-trial observation period and 2 events in liraglutide 1.20

mg occurred after end of trial. Six (6) EAC-confirmed events in 5 subjects were MACEs (4 acute myocardial infarction events in 3 subjects, 1 cardiovascular death, and 1 stroke).

- A total of 68 cardiovascular disorder events were captured by the MedDRA search and reported in 48 subjects, with varied frequencies across all groups (4.8% to 9.4% in semaglutide; 4.7% to 12.3% in liraglutide; 7.0% in placebo; and 4.7% in the open-label semaglutide flexible dose group).).

- There were a total of 17 cardiovascular SAEs in 11 subjects (4 events in 2 subjects in semaglutide 0.05 mg; 1 event in semaglutide 0.20 mg; 1 event in semaglutide 0.30 mg; 2 events in 1 subject in liraglutide 1.20 mg; 6 events in 3 subjects in liraglutide 1.80 mg; 2 events in 2 subjects in placebo; and 1 event in the open-label semaglutide flexible dose group). Majority of these CV SAEs were severe, none were assessed as likely related to treatment. With the exception of the fatal event in liraglutide 1.80 mg (due to 'acute myocardial infarction') and ischaemic stroke event in the open-label semaglutide flexible dose group, all subjects recovered from these SAEs, all subjects recovered from these SAEs. No differences were apparent in type and frequency of events among the treatment groups.

- After 26 weeks of treatment, the estimated mean pulse rate increased with all treatment groups, except placebo and semaglutide 0.05 mg, albeit to a greater level with liraglutide 1.20 mg (5 bpm) and liraglutide 1.80 mg (4 bpm). Increases in semaglutide were 1-3 bpm, compared to 1 bpm for placebo. The increase in pulse rate from baseline to end of treatment were only significant for higher doses of liraglutide versus placebo, with ETDs in bpm of 4.52 $[1.68; 7.36]_{95\%CI}$ and 2.85 $[0.07; 5.36]_{95\%CI}$ with liraglutide 1.20 mg and 1.80 mg, respectively.

- Overall, the proportion of subjects with ECG abnormalities was similar among the treatment groups for the majority of the abnormality categories and the majority of the measurements were 'normal' at baseline and persisted at week 26 (77.1-90.0%) and week 33 (77.1%-86.7%) with no apparent differences between treatment groups. Three (3) ECG-related AEs and 1 'blood pressure increased' event were reported; all of which were non-serious, mild, and unlikely related to trial product

- *Pancreatitis*

  - One (1) event of 'pancreatitis chronic' and 1 'pancreatic enzymes increased' event were sent for adjudication, both of which were non-confirmed by the EAC; no other events were identified by the Novo Nordisk pre-defined preferred term query (NN PTQ) search, nor considered adjudicable.

  - One (1) non-serious, mild, 'pancreatitis chronic' event was identified by the MedDRA search, from which the subject [redacted]

  - Mean lipase and amylase activities from baseline to end of treatment (week 26) were significantly increased for semaglutide and liraglutide groups as compared to placebo. The vast majority of the subjects had enzyme activities <2xULN throughout the trial, and most of the subjects with lipase activity >5xULN (upper limit of normal) and amylase activity >2xULN, only had single incidences of outliers. Only 1 subject, treated with liraglutide 0.60 mg, had elevated amylase (>2xULN) and lipase (>5xULN) activities during treatment, and did not report any concurrent gastrointestinal AEs, hepatobiliary or pancreatitis-related AEs.

- *Hepatobiliary disorders*

- Gallbladder disorder adverse events were reported in 3 subjects (single events in liraglutide 0.30 mg, liraglutide 1.80 mg, and placebo). All 3 events were identified via MedDRA search and were reported within the SOC 'hepatobiliary disorders' as 'cholelithiasis' or 'hydrocholecystis' (PT). All 3 events were non-serious, mild in severity, resulted in no change in treatment dosage, were assessed as unlikely related to trial product, two of the subjects had [redacted] from these events by the end of the trial, and none of these events led to premature treatment discontinuation.

- Sixteen (16) hepatic disorders were identified via MedDRA search and reported mostly as single events, distributed across groups, all of which were non-serious, mild-to-moderate in severity, and only 1 event in a placebo-treated subject led to premature treatment discontinuation.

- In general, there was a fluctuating pattern in the levels of liver tests, but no mean increases were observed. There were 11 cases of outliers in liver function tests: 2 subjects with outliers of alanine aminotransferase >5xULN (both treated with placebo); 4 subjects with outlier of aspartate aminotransferase >5xULN (1 with semaglutide 0.30 mg, 1 with liraglutide 0.60 mg, and 2 with placebo); and 1 subject with outlier of total bilirubin >3xULN (semaglutide 0.30 mg). No outliers of alkaline phosphatase >5xULN (>675 U/L) were detected. The mean changes for all 4 liver function parameters from baseline were comparable among treatment groups and were not considered clinically relevant.

- One (1) subject (semaglutide 0.30 mg) had concurrent elevation of AST >3xULN and total bilirubin >2xULN. Alternative aetiology was present [redacted], thus did not qualify as a Hy's law case.

- *Neoplasms*

  - Overall, the proportions of subjects as well as the number of EAC-confirmed neoplasms were low (5 events in 5 subjects; 1.19 events per 100 PYE [0.7%]) and primarily occurred as single events in single subjects and were generally equally distributed with regards to type (tissue or organ of origin) across the treatment groups: (1 subject each with semaglutide 0.05 mg ['pancreatic carcinoma']; semaglutide 0.30 mg ['spinal meningioma']; liraglutide 0.60 mg ['basal cell skin carcinoma]; liraglutide 1.80 mg ['prostate adenocarcinoma]; and with open-label semaglutide flexible dose ['clear cell renal cell carcinoma']). Four (4) events were malignant neoplasms and 1 was benign ('spinal meningioma'); no pre-malignant/carcinoma *in situ*/ borderline or unclassified neoplasm events were confirmed by the EAC.

  - With respect to the MedDRA search of subjects experiencing at least one event, 21 neoplasm-related events were identified in 18 subjects distributed across most groups: 2 events in 2 subjects with semaglutide 0.05 mg (3.1%), 3 events in 2 subjects in semaglutide 0.20 mg (3.1%), 3 events in 3 subjects in semaglutide 0.30 mg (4.8%), 1 event in liraglutide 0.30 mg (1.6%), 4 events in 4 subjects in liraglutide 0.60 mg (6.3%), 3 events in 3 subjects with liraglutide 1.80 mg (4.6%), 1 event in placebo (0.8%), and 4 events in 2 subjects in the open-label semaglutide flexible dose group (3.1%). Of the 21 events, 7 were serious, 3 were severe, 18 were mild-to-moderate in severity, 1 was assessed as possibly related to treatment, 20 were unlikely treatment-related, dose was not changed for 19 events, and none led to premature discontinuation of trial product.

  - No thyroid neoplasms were EAC-confirmed in this trial.

- *Thyroid disorders*

- There was 1 EAC-confirmed event of thyroid disease requiring thyroidectomy ('post-procedural hypothyroidism') in a subject treated with placebo. This event was non-serious, moderate in severity, unlikely related to treatment, did not result in dose change, did not lead to premature treatment discontinuation, and from which the subject had [redacted] by the end of the trial.

- Ten (10) thyroid disease AEs were captured by the pre-defined MedDRA search, 8 of which were in the on-treatment period, 1 additional event in the in-trial observation period, and 1 event 13 days prior to randomisation. These events were distributed across treatment groups. One clinical laboratory AE (CLAE; 'blood calcitonin increased') was reported by one subject treated with liraglutide 1.80 mg, from which the subject [redacted].

- A total of 7 subjects (4 with semaglutide and 3 with placebo) had at least 1 calcitonin value >20 ng/L during the trial; 6 of which occurred at the screening visit. There were no other clinically relevant changes in mean and individual calcitonin levels throughout the treatment period within or between treatment groups.

- *Renal disorders*

  - Few AEs captured by the broad standardised MedDRA queries (SMQ) search 'acute renal failure' were reported during the trial (7 events in 6 subjects: 5 events in 4 subjects treated with semaglutide and 3 events in liraglutide). All events were non-serious, all but 1 were mild-or-moderate in severity, 6 were unlikely related to treatment, none led to premature treatment discontinuation, 2 subjects reported concurrent dehydration, and subjects [redacted] from 6 of the 7 events.

  - There were no clinically relevant changes in any renal laboratory parameters or urinalyses over time, within, and across treatment groups, with comparable changes in eGFR observed in all groups.

- *Immunogenicity-related AEs and injection site reactions*

  - In total, 25 allergic reaction events were reported by 25 subjects (6 events per 100 PYE [3.5%]). Nineteen (19) events related to skin disorders distributed across all groups except semaglutide 0.05 mg and liraglutide 1.20 mg; 3 events related to immune system disorders; 2 respiratory, thoracic, and mediastinal disorder; and 1 event related to gastrointestinal disorders. All events were non-serious, majority were mild-to-moderate in severity, unlikely related to trial product and resulted in no change in drug dosage, and the majority of the subjects [redacted] from these events by the end of the trial.

  - One (1) subject in the open-label semaglutide flexible group tested positive for anti-semaglutide antibodies at all visits; all samples were negative for antibodies cross-reacting with endogenous glucagon-like peptide-1 (GLP-1). This subject with anti-semaglutide-positive antibodies at follow-up did not show neutralising effects to semaglutide and there was no indication of a treatment-induced anti-semaglutide antibody response.

  - Four (4) events of immune complex disease were reported by 4 subjects (1 event per 100 PYE [0.6%]): 'nephritis' (semaglutide 0.10 mg), 'proteinuria' (liraglutide 1.20 mg), 'protein urine present' (semaglutide 0.10 mg), and 'seizure' (liraglutide 0.60 mg). Three (3) of the 4 events were non-serious, mild-to-moderate in severity, one event was an SAE, none led to premature treatment discontinuation, and all subjects [redacted] from these 4 events.

  - Thirty five (35) events of injection site reactions were reported by 20 subjects (8 events per 100 PYE [2.8%]) distributed across all groups except semaglutide 0.05 mg, with highest rate reported in liraglutide

0.60 mg (29 events per 100 PYE). The most commonly reported PTs were 'injection site bruising' (14 events in 7 subjects), 'injection site pain' (7 events in 6 subjects), and 'injection site haemorrhage' (4 events in 4 subjects); with 11 AEs reported in 2 subjects treated with liraglutide 0.60 mg. All 35 events were non-serious, mild-to-moderate in severity, majority were possibly or probably related to trial product, did not result in dose change, subjects recovered from all but 1 event, and none led to premature treatment discontinuation.

- *Medication errors*
  - There were a total of 5 medication error AEs reported in 5 subjects (3 events in 3 subjects treated with semaglutide 0.05 mg ('incorrect dose administered' and 'overdose' and 'injury associated with device'); 1 event in liraglutide 0.30 mg ('accidental overdose'); and 1 event in liraglutide 0.60 mg; ('accidental overdose'). All the events were non-serious, mild-or-moderate in severity, 4 of the 5 events were unlikely related to treatment, and subjects recovered from all AEs.
- *Overdose*
  - There were 3 overdose AEs in 3 subjects in the trial, single events in semaglutide 0.05 mg ('overdose'), liraglutide 0.30 mg ('accidental overdose'), and liraglutide 0.60 mg; ('accidental overdose'). All the events were non-serious, mild-or-moderate in severity, 2 of the 3 events were unlikely related to treatment, and subjects recovered from all AEs.
- *Suspected transmission of infectious agent*
  - No events of suspected transmission of infectious agent via trial product were reported for this trial.
- *Rare events*
  - There was 1 rare event [redacted] identified in a subject treated with liraglutide 1.80 mg. The AE was non-serious, mild, unlikely related to treatment, and from which the subject [redacted]
- *Diabetic retinopathy*
  - There were a total of 11 diabetic retinopathy events reported in 6 subjects (single subjects in semaglutide 0.10 mg and 0.30 mg; liraglutide 0.30 mg, 0.60 mg, 1.20 mg, and open-label semaglutide flexible group) in the trial in the following PTs: 'diabetic retinopathy' (6 events in 4 subjects), 'macular oedema' (2 events in 2 subjects), 'maculopathy' (1 event), 'retinal detachment' (2 events in 1 subject). Two (2) of the AEs reported were serious events ('retinal detachment' in a subject in the liraglutide 1.20 mg group). None of the diabetic retinopathy events were assessed as related to respective treatment.

Other clinical laboratory evaluations, physical examination and pregnancies

- For biochemistry or haematology laboratory parameters not presented in the safety areas of interest, no clinically relevant changes were observed.
- No clinically relevant treatment differences were observed in physical examination findings or fundoscopy.
- Two (2) pregnancy cases were reported in this trial. One subject treated with semaglutide 0.05 mg, with a history of an uncomplicated pregnancy, was treated for [redacted] days and was discontinued from treatment on trial day [redacted]

upon positive pregnancy test. This subject had a spontaneous abortion at trial day [redacted]. The subject reported mild nausea on trial day [redacted], possibly related to treatment, [redacted]. The second subject treated with liraglutide 1.80 mg had a positive pregnancy test at the end-of-treatment visit, and no AEs were reported in connection to the pregnancy. The subject delivered a healthy [redacted] child on [redacted] at gestational week [redacted] and [redacted] days; no health problems, congentinal abnormalities, or receipt of replacement medications have been reported for the infant at 1 month of age.

CONCLUSIONS

In this 26-week multicentre, randomised, double-blinded (within dose level), dose-finding trial, the following is concluded:

- Semaglutide administered once-daily effectively lowered HbA_{1c} and body weight significantly more than placebo and dose-matched liraglutide at week 26.
- Significantly greater reduction in HbA_{1c} from baseline to week 26 was seen with semaglutide 0.30 mg (-1.88%-points) than liraglutide 1.80 mg (-1.31%-points) and placebo (-0.02%-points).
- Significantly greater reductions in body weight was seen with semaglutide 0.30 mg (-8.23 kg) than liraglutide 1.80 mg (-3.75 kg) and placebo (-1.23 kg).
- Semaglutide administered once-daily at doses up to 0.30 mg was well tolerated and no unanticipated safety concerns were identified.
- Dose-response modelling indicated greater efficacy with semaglutide versus liraglutide, whereas the overall tolerability was similar between the two treatments.

The trial was conducted in accordance with the Declaration of Helsinki, ICH Good Clinical Practice and EN ISO 14155 Part 1 and 2, and 21 CFR 312.120.

Appendix 9 Country-specific requirements

Section 6.1 Inclusion criteria

For Japan:

Age ≥ 20 years at the time of signing informed consent.

Section 7.5 Preparation/Handling/Storage/Accountability

For Japan: According to Japanese GCP, storage and drug accountability of the trial products at the study site is not in charge of Investigator, but in charge of the head of study site.

The head of study site should assign some or all the responsibilities for accountability of the trial products at the sites to a trial product storage manager (a pharmacist in principle). The trial product storage manager should control and take accountability of the trial products in accordance with procedures specified by the sponsor. The head of study site or the trial product storage manager must ensure the availability of proper storage conditions, and record and evaluate the temperature.

Section 9 Trial assessments and procedures

For US and Canada only: This trial will include an option for subjects to complete an anonymised questionnaire, 'Study Participant Feedback Questionnaire' for subjects to provide feedback on their clinical trial experience at the beginning (V1), the middle (V7) and the end (V10) of the trial. Individual subject level responses will not be reviewed by investigators. Responses would be used by the sponsor to understand where improvements can be made in the clinical trial process. This questionnaire does not collect data about the subject's disease, symptoms, treatment effect or adverse events and therefore would not be considered trial data or entered into the trial database.

Appendix 3 Trial governance considerations

For Japan: A seal is accepted as a signature.

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, including version 1: 05 July 2019, 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[1].

Overall rationale for preparing protocol version 2:

Section # and name	Description of change	Brief rationale
7.7 Concomitant medication	Update on the concomitant medication section to reflect stable background treatment throughout the trial.	To clarify the requirements for stable background medication during the trial, further to established eligibility criterion and protocol recommended initial dose reduction of sulphonylurea.
9.4.3 Eye examination	Text added to specify that at the end of treatment visit the eye examination result should be available and that the examination can be performed within 3 weeks prior to the end of treatment visit.	To clarify the timing of the availability of the eye examination result at the end of treatment visit. The extended window of availability will also facilitate data collection.

Global and country key Novo Nordisk staff

Attachments I and II (if applicable) to the protocol are located in the Trial Master File.

Content: Global key staff and Country key staff

Protocol Amendment No.1 to Protocol, version 1.0 dated 21 March 2019

Trial ID: NN9535-4506

Efficacy and safety of semaglutide 2.0 mg s.c. once-weekly compared to semaglutide 1.0 mg s.c. once-weekly in subjects with type 2 diabetes

Trial phase: 3b

Applicable to Czech Republic

Table of Contents

1 Introduction including rationale for the protocol amendment

This Protocol Amendment 1 was created based on the requirements of Czech Regulatory Authority (SUKL) and is applicable for the Czech Republic only. Since reproductive toxicity has been demonstrated during preclinical studies, Czech Regulatory Authority requires women with childbearing potential to use only a highly reliable methods of contraception (Pearls index <1), which does not include a two-barrier method. This requirement is in line with the recommendation of „Recommendations related to contraception and pregnancy testing in clinical trials“, which can be located at:
http://www.hma.eu/fileadmin/dateien/Human_Medicines/01About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf.
Therefore, adequate modification of recommended contraceptive methods in the Protocol – Appendix 5 has been done.

In this protocol amendment:

- Any new text is written *in italics.*
- Any text deleted from the protocol is written using ~~strike through.~~

2 Changes

Appendix 5 Contraceptive guidance and collection of pregnancy information

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

Definitions
Woman of Childbearing Potential (WOCBP)
A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile.

Women in the following categories are not considered WOCBP

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

    Note: Documentation can come from the site personnel's review of subject's medical records, medical examination or medical history interview.
3. Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high Follicle Stimulating Hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not

using hormonal contraception or Hormonal Replacement Therapy (HRT). However, in the absence of 12 months of amenorrhea, a single Follicle-Stimulating Hormone (FSH measurement is insufficient.

- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the trial. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before trial enrolment.

Contraception guidance

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

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

Table 12-3 Highly effective contraceptive methods

Highly effective contraceptive methods that are user dependent [a and b] Failure rate of <1% per year when used consistently and correctly.
Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation • oral • intravaginal • transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation • oral • injectable
Highly effective methods that are user independent [b]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation • Intrauterine Device (IUD) • Intrauterine hormone-releasing System (IUS) • Bilateral tubal occlusion
Vasectomised partner A vasectomised partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
Sexual abstinence [b] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial product. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject.
Notes: [a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical trials. [b] Contraception should be utilised during the treatment period and for at least 7 weeks after the last dose of trial product.

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

1. ~~known intolerance to the highly effective methods mentioned in Table 12-3 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.~~

Pregnancy testing

- WOCBP should only be included after a negative highly sensitive urine pregnancy test.
- Additional urine pregnancy testing should be performed at every site visit (every 4-8 weeks) during the treatment period, at the end of treatment and after the 7 weeks follow-up period after the end of treatment, according to the flow chart.
- Pregnancy testing should be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.
- All subjects will be provided with a pregnancy test prior to the phone visits to perform them prior to the phone call, not only if pregnancy is suspected.

Collection of pregnancy information

Female subjects who become pregnant

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this trial.
- Information will be recorded on the appropriate form and submitted to Novo Nordisk within 14 calendar days of learning of a subject's pregnancy.
- 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. Generally, follow-up will not be required for longer than 1 month beyond the delivery date.
- Any termination of pregnancy will be reported, regardless of foetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.

- Any SAE occurring as a result of a post-trial pregnancy which is considered possibly/probably related to the trial product by the investigator will be reported to Novo Nordisk as described in Appendix 4. While the investigator is not obligated to actively seek this information in former subjects, he or she may learn of an SAE through spontaneous reporting.

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

Protocol Amendment

no 2

to Protocol, version 1 dated 21 March 2019

Trial ID: NN9535-4506

Efficacy and safety of semaglutide 2.0 mg s.c. once-weekly compared to semaglutide 1.0 mg s.c. once-weekly in subjects with type 2 diabetes

Trial phase: 3b
Applicable to all countries

Table of Contents

1 Introduction including rationale for the protocol amendment

This protocol is amended for the following reasons:

- To clarify requirements for stable background medication during the trial, further to established eligibility criterion and protocol recommended initial dose reduction of sulphonylurea
- To clarify the timing of the availability of the eye examination result at the end of treatment visit. The extended window of availability will also facilitate data collection.

In this protocol amendment:

- Any new text is written *in italics.*
- Any text deleted from the protocol is written using ~~strike through.~~

2 Changes

2.1 Section 7.7 Concomitant medication

Any medication (including over-the-counter or prescription medicines) other than the trial product 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)

~~Treatment with metformin and SU is considered non-investigational medicinal products and should be used according to their respective labels and will be used open-label throughout the trial.~~

~~To mitigate SU induced hypoglycaemia, subjects treated with SU will be asked to reduce the SU dose by approximately 50% at the discretion of the investigator, from randomisation. In case of persistent hyperglycaemia, glycaemic rescue treatment could be initiated as described in Section~~

After signing the informed consent, subjects must continue their anti-diabetic background medication (metformin with or without SU) throughout the entire trial.

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 8.1.2) or safety concern related to the use of background medications arises.

In addition, all background medication:

- *is considered to be non-investigational medicinal product.*
- *will not be provided by Novo Nordisk A/S, except if required by local regulations and not in contradiction to local regulations.*
- *should be used in accordance with standard of care and current approved label in the individual country.*
- *should not exceed the maximum approved dose in the individual country.*

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

Any change 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 9.2

2.2 Section 9.4.3 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 healthcare provider 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 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 performed as per the flowchart in Section 2. *Results must be available at V10 (end of treatment visit). An eye examination performed within 3 weeks prior to V10 is acceptable, provided no clinical symptoms suggestive of eye disease have occurred in the meantime.*

The investigator should indicate the outcome of each eye examination. Relevant findings prior to randomisation must be recorded as concomitant illness/medical history, while relevant findings occurring after randomisation should be reported as an AE, if applicable according to Section 9.2