Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
NCT number	NCT03987451
Sponsor trial ID:	NN9931-4492
Official title of study:	Investigation of Efficacy and Safety of Semaglutide s.c. Once-weekly Versus Placebo in Subjects With Non-alcoholic Steatohepatitis and Compensated Liver Cirrhosis
Document date:	21 February 2020

*Document date refers to the date on which the document was most recently updated.
Note: The date in the header of 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: Investigation of efficacy and safety of semaglutide s.c. once-weekly versus placebo in subjects with non-alcoholic steatohepatitis and compensated liver cirrhosis

Substance: Semaglutide

Universal Trial Number: U1111-1224-4062

EUdraCT Number: 2018-004484-31

Trial phase: 2a

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

Protocol amendment summary of changes table

DOCUMENT HISTORY		
Document	Date	Version
Protocol	21 February 2020	3.0
Original Protocol	11 January 2019	2.0

Protocol Version 3.0, 21 February 2020

The changes to Protocol Version 2.0 are 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 3.0 including a summary of changes table

Section # and name	***Description of change***	***Rationale***
Section 1 Synopsis, Section 4 Objectives and endpoints	The former secondary endpoint is changed to the primary endpoint: "At least one stage of liver fibrosis improvement with no worsening of NASH after 48 weeks (yes/no) (worsening defined as an increase of at least one stage of either lobular inflammation, hepatocyte ballooning or steatosis according to the NASH CRN criteria)." The former primary endpoint is changed to the secondary endpoint: "Relative change from baseline (week 0) to week 48 in liver stiffness measured by MRE."	The rationale for the protocol amendment is to align with requirements as per regulatory guidance regarding primary endpoint in NASH trials.
Section 2 Flowchart, Section 8.1 Discontinuation of trial product, Section 9.1.2 Liver biopsy, Appendix 7 Retention of human biosamples,	Liver biopsies needed at week 48 for subjects who discontinue treatment during the trial (V12A)	To ensure complete follow-up of primary endpoint assessment.
Section 1 Synopsis, Section 4 Objectives and endpoints, Section 10 Statistical considerations	Change to primary estimand	To reflect the change in primary endpoint

	Update of statistical considerations section	
Section 2 Flowchart, Section 6.3.1 Meals and dietary restrictions, Section 8.1 Discontinuation of trial treatment, Section 9.1.1 Magnetic Resonance Imaging, Section 9.1.3 Child-Pugh score	Delete calcitonin from fasting procedures. No MRI-PDFF and MR elastography needed at V12 for trial product treatment discontinued subjects. Delete visceral adipose tissue and abdominal subcutaneous adipose tissue from MRI assessments. All assessments included in the Child-Pugh score should be performed within the visit window. Encephalopathy was updated to hepatic encephalopathy	Clarification in the protocol

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1 Synopsis

Rationale:

Non-alcoholic fatty liver disease (NAFLD) represents a spectrum of liver damages ranging from simple steatosis (non-alcoholic fatty liver), non-alcoholic steatohepatitis (NASH) with or without fibrosis through to cirrhosis. Liver cirrhosis is defined by the NASH Clinical Research Network (CRN) as fibrosis stage 4 (F4)[2, 3]. NASH is reported in 3-5% of the Western population[4] and around 10% of patients with NASH develop cirrhosis[5]. NASH liver cirrhosis is today the third most common cause of liver transplantation in the USA and is expected to be the primary cause in 2020[6-8]. The pathophysiology of the progression to liver cirrhosis in NASH is not well understood, but overweight and obesity, insulin resistance, type 2 diabetes (T2D) and hypertension are recognised as key predisposing factors[9].

Patients with NASH and liver cirrhosis have the highest all cause and liver related mortality compared to patients with less severe liver fibrosis[10]. The increase in liver related mortality is associated with the transition from the compensated to decompensated stage, which occurs at a rate of approximately 5-7% per year[11]. Cirrhosis is not irreversible, as liver fibrosis in the cirrhotic range in other chronic liver diseases regresses with effective therapy, such as antiviral treatment for chronic hepatitis B or C[12, 13] and steroids for autoimmune hepatitis[14].

Currently, first-line treatment of NASH in patients with compensated liver cirrhosis and overweight is lifestyle interventions to provide weight loss[15] and to treat comorbidities (e.g. hyperlipidaemia, hypertension and diabetes) as no specific pharmaceutical therapies are approved. In the case of progression to end-stage liver disease, liver transplantation is the only treatment option[16].

Accordingly, there is a substantial unmet medical need for effective treatment in patients with NASH and compensated liver cirrhosis.

Objectives and endpoints:

Primary objective
To investigate the effect of semaglutide subcutaneous (s.c.) 2.4 mg once-weekly on liver fibrosis compared with placebo in subjects with NASH and compensated fibrosis stage 4[2, 3].

Primary estimand
In subjects with NASH and compensated fibrosis stage 4, the estimand addressing the primary objective is the proportion of subjects with liver fibrosis improvement with no worsening of NASH compared between semaglutide s.c. 2.4 mg once-weekly and placebo at 48 weeks if all randomised subjects had adhered to treatment. Generalisation of this estimand depends among other things on the extent to which treatment adherence in this trial reflects clinical practice.

Secondary efficacy objectives

To investigate the effect of semaglutide s.c. 2.4 mg once-weekly on NASH compared with placebo in subjects with NASH and compensated fibrosis stage 4.

Secondary safety objective

To evaluate the safety and tolerability of semaglutide s.c. 2.4 mg once-weekly compared with placebo in subjects with NASH and compensated fibrosis stage 4.

Primary and secondary endpoints

End point title	Time frame	Unit
Primary endpoint:		
At least one stage of liver fibrosis improvement with no worsening of NASH after 48 weeks (yes/no) (worsening defined as an increase of at least one stage of either lobular inflammation, hepatocyte ballooning or steatosis according to the NASH CRN criteria)[2, 3].	From baseline (week 0) to visit 12 (week 48)	Yes / no
Secondary endpoints:		
Relative change from baseline (week 0) to week 48 in liver fat content (%) measured by MRI-PDFF.	From baseline (week 0) to visit 12 (week 48)	Ratio to baseline
Relative change from baseline (week 0) to week 48 in liver stiffness measured by MRE.	From baseline (week 0) to visit 12 (week 48)	Ratio to baseline
NASH resolution after 48 weeks (yes/no) (defined by the NASH CRN as lobular inflammation 0 – 1 and ballooning 0)[2, 3].	From baseline (week 0) to visit 12 (week 48)	Yes / no

Change from baseline in Stage of fibrosis according to the NASH CRN fibrosis score.	From baseline (week 0) to visit 12 (week 48)	Scale (0-4)*
Change from baseline in NAFLD activity score (NAS) according to the NASH CRN criteria.	From baseline (week 0) to visit 12 (week 48)	Scale (0-8)*
Number of treatment-emergent adverse events.	From baseline (week 0) to visit 12 (week 48)	Count

*range of values on absolute scale at one time-point

Overall design:

This is a 48-week randomised, double-blind, placebo-controlled, parallel group, multi-centre trial with semaglutide s.c. 2.4 mg once-weekly versus semaglutide placebo once weekly in subjects with NASH and compensated fibrosis stage 4.

Key inclusion criteria:

- Male or female, aged 18-75 years (both inclusive) at the time of signing informed consent.
- Histologic evidence of NASH and fibrosis stage 4 according to the NASH CRN classification based on central pathologist evaluation of a liver biopsy obtained within 360 days prior to screening. In subjects who have never had a liver biopsy showing NASH and F4, liver stiffness >14 kPa by FibroScan® at screening must be documented before subjects can have a trial-related liver biopsy
- A histological NAFLD activity score (NAS) ≥3 with a score of 1 or more in lobular inflammation and hepatocyte ballooning based on central pathologist evaluation
- Body mass index ≥27 kg/m^2

Key exclusion criteria:

- Presence or history of hepatic decompensation (e.g. ascites, variceal bleeding, hepatic encephalopathy or spontaneous bacterial peritonitis) or liver transplantation
- Presence or history of gastroesophageal varices within the past 360 days prior to screening. For subjects with no known history of gastroesophageal varices and with a Fibroscan® ≥ 20 kPa and thrombocytes ≤ 150,000[17], a esophagogastroduodenoscopy must be performed to evaluate presence of gastroesophageal varices
- Presence or history of hepatocellular carcinoma
- Treatment with vitamin E (at doses ≥800 IU/day) or pioglitazone which has not been at a stable dose in the opinion of the investigator in the period from 90 days prior to screening

- Treatment with glucagon-like peptide-1 receptor agonists (GLP-1 RAs) in the period from 90 days prior to screening
- Treatment with other glucose lowering agent(s) (apart from what is listed in the exclusion criterion above) or weight loss medication not stable in the opinion of the investigator in the period from 28 days prior to screening

Number of subjects:

Approximately 240 subjects will be screened to achieve 69 subjects randomly assigned to trial product.

Treatment groups and duration:

The total trial duration for the individual subject is approximately 61 weeks. This includes a screening period of approximately 6 weeks followed by randomisation, a 48 weeks treatment period and a 7 weeks follow-up period after end of treatment.

Dose escalation of semaglutide/semaglutide placebo will take place every 4 weeks during the first 16 weeks after randomisation. All subjects must aim at reaching the recommended target dose of semaglutide s.c. 2.4 mg once-weekly or the corresponding volume of placebo.

Eligible subjects fulfilling all in- and exclusion criteria at visit 2 will be randomised in a 2:1 ratio to receive either:

- Semaglutide s.c. 2.4 mg once weekly
- Semaglutide placebo s.c. once weekly

Randomisation will be stratified based on T2D (with T2D or without T2D). During the trial all subjects will receive nutritional and physical activity counselling in accordance with site practice.

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

- Semaglutide B 3.0 mg/mL, solution for injection, PDS290 pre-filled pen-injector and semaglutide placebo, solution for injection, PDS290 pre-filled pen-injector

2 Flowchart

Trial Periods	Screening	Randomisation	Dose-escalation							Maintenance		EOT	FU	Treatment discontinuation during trial
Visit number	V1	V2	P3	V4	P5	V6	P7	V8	V9	V10	V11	V12	V13	V12A
Weeks in relation to visit 2	-6	0	2	4	6	8	10	12	16	24	36	48	55	48
Visit window, days	±7		±4	±4	±4	±4	±4	±4	±4	±7	±7	±7	+7	±7
SUBJECTS														
Informed consent (Appendix 3)	x													
In/exclusion criteria (6.1, 6.2)	x	x												
Discontinuation criteria (8.1)			x	x	x	x	x	x	x	x	x			
AUDIT questionnaire (9)	x													
Medical history/ Concomitant illness (9.4)	x													
Concomitant medication (7.7)	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Trial product compliance (7.1, 7.6)			x	x	x	x	x	x	x	x	x	x		
Demography[a]	x													
Tobacco use[b]	x													

Trial Periods	Screening	Randomisation	Dose-escalation							Maintenance		EOT	FU	Treatment discontinuation during trial
Visit number	V1	V2	P3	V4	P5	V6	P7	V8	V9	V10	V11	V12	V13	V12A
Weeks in relation to visit 2	-6	0	2	4	6	8	10	12	16	24	36	48	55	48
Visit window, days	±7		±4	±4	±4	±4	±4	±4	±4	±7	±7	±7	+7	±7
Childbearing potential (Appendix 5)	x[c]													
Eye examination (9.4.5)	x													
ECG (9.4.4)	x													
EGD[d]	x													
Calcitonin (Appendix 2)	x													
Hepatitis B and C (Appendix 2)	x													
HIV antigen/antibody screening test (Appendix 2)	x													
EFFICACY														
MRI[e] (9.1.1)		x								x		x[f]		x
Liver biopsy (9.1.2)	x[g]											x[f]		x
Child-Pugh Score[h] (9.1.3)	x							x		x		x		x
Height (9.1.4.1)	x													
Body weight (9.1.4.2)	x	x						x		x		x		x

Trial Periods	Screening	Randomisation	Dose-escalation							Maintenance		EOT	FU	Treatment discontinuation during trial
Visit number	V1	V2	P3	V4	P5	V6	P7	V8	V9	V10	V11	V12	V13	V12A
Weeks in relation to visit 2	-6	0	2	4	6	8	10	12	16	24	36	48	55	48
Visit window, days	±7		±4	±4	±4	±4	±4	±4	±4	±7	±7	±7	+7	±7
Waist circumference (9.1.4.4)		x						x		x		x		x
Exploratory biomarkers (9.1.5, Appendix 2)		x								x		x		x
SAFETY														
Physical examination (9.4.1)	x													
Vital signs (9.4.2)	x	x						x		x		x		x
Haematology (Appendix 2)	x							x		x		x		x
Biochemistry (Appendix 2)	x	x						x		x		x		x
Lipids (Appendix 2)		x						x		x		x		x
INR (Appendix 2)	x	x						x		x		x		x
Glucose metabolism (Appendix 2)	x[i]	x						x		x		x		x
Pregnancy test[j] (Appendix 2, Appendix 5)	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	x

Trial Periods	Screening	Randomisation	Dose-escalation							Maintenance		EOT	FU	Treatment discontinuation during trial
Visit number	V1	V2	P3	V4	P5	V6	P7	V8	V9	V10	V11	V12	V13	V12A
Weeks in relation to visit 2	-6	0	2	4	6	8	10	12	16	24	36	48	55	48
Visit window, days	±7		±4	±4	±4	±4	±4	±4	±4	±7	±7	±7	+7	±7
Hypoglycaemic episodes (9.2.10, Appendix 8)			x	x	x	x	x	x	x	x	x	x	x	
Technical complaints (9.2.9, Appendix 6)			x	x	x	x	x	x	x	x	x	x		
OTHER ASSESSMENTS														
Semaglutide plasma concentration (9.5)								x		x		x		
Biosamples for future analysis (Appendix 7)	x									x[k]		x		x[k]
TRIAL MATERIAL														
Dispensing visit (7.1, 7.5)		x				x			x	x	x			
Hand out direction for use (7.1.1)		x												
Drug accountability (7.5)		x				x			x	x	x	x		
IWRS session	x	x				x			x	x	x	x		
REMINDERS														
Hand out ID card	x													
Fibroscan®	x[l]													

Trial Periods	Screening	Randomisation	Dose-escalation							Maintenance		EOT	FU	Treatment discontinuation during trial
Visit number	V1	V2	P3	V4	P5	V6	P7	V8	V9	V10	V11	V12	V13	V12A
Weeks in relation to visit 2	-6	0	2	4	6	8	10	12	16	24	36	48	55	48
Visit window, days	±7		±4	±4	±4	±4	±4	±4	±4	±7	±7	±7	+7	±7
Nutritional and physical activity counselling (5.1)		x		x		x		x	x	x	x	x	x	x
Hand out and instruct in BG-meter[m] (7.1)		x												
Training in trial product and pen handling (7.1.1)		x		x		x		x	x	x	x			
Handout and instruct in diary (9)		x		x		x		x	x	x	x			
Collect and review subject diary (9, Appendix 8)				x		x		x	x	x	x	x		
Attend visit fasting (6.3.1)		x						x		x		x		x

Abbreviations: P = Phone visit, V = Clinic visit, ECG = Electrocardiogram, EGD = Esophagogastroduodenoscopy; FU = follow-up, IWRS = interactive web response system, BG-meter = blood glucose meter, EOT = End of treatment

a) **Demography consists of date of birth (according to local regulation), sex, ethnicity (according to local regulation) and race (according to local regulation)**
b) **Smoking is defined as smoking at least one cigarette or equivalent daily**
c) **Only applicable for female subjects**
d) **Must be performed if no documentation of evaluation of gastroesophageal varices within the past 360 days prior to screening in subjects with a Fibroscan® ≥ 20 kPa and thrombocytes ≤ 150,000. An esophagogastroduodenoscopy (EGD) will be performed as per local guidelines. The result is not captured in the CRF**
e) **MRI consisting of MRI-PDFF and MR elastography. The MRI-PDFF and MR elastography assessments must be within -5 days to visit 2 and before first trial product intake. For V10 the MRI-PDFF and MR elastography should be within the +/- 7 days visit window. For V12 (V12A if discontinued trial product treatment during trial) the MRI-PDFF and MR elastography assessments should be within -7 days to V12/V12A**

f) For subjects discontinuing trial product treatment during the trial no liver biopsy sample, MRI-PDFF and MR elastography will be obtained at end of treatment visit (V12). A liver biopsy, MRI-PDFF and MR elastography will be obtained at V12A. If end of treatment is at the same time point as V10, then MRI-PDFF and MR elastography should be obtained

g) A recent liver biopsy obtained within 360 days prior to screening is acceptable. For subjects with no recent liver biopsy, this must be performed during the screening period after confirmation of liver stiffness > 14 kPA by Fibroscan®

h) All assessments included in the Child-Pugh score should be performed within the visit window

i) HbA1c only

j) Only applicable for female subjects. A urine pregnancy test will be performed at site visits without blood sampling (V4, V6, V9, V11 and V13). For women of childbearing potential: urine pregnancy test should be performed at any time during the trial if a menstrual period is missed

k) Only blood sampling, no liver tissue sampling

l) Only if needed to evaluate inclusion criteria 3 and/or exclusion criteria 3

m) Only applicable for subjects with type 2 diabetes

3 Introduction

3.1 Trial rationale

Non-alcoholic fatty liver disease (NAFLD) represents a spectrum of liver damages ranging from simple steatosis (non-alcoholic fatty liver), non-alcoholic steatohepatitis (NASH) with or without fibrosis through to cirrhosis. Liver cirrhosis is defined by the NASH Clinical Research Network (CRN) as fibrosis stage 4 (F4)[2, 3]. NASH is reported in 3-5% of the Western population[4] and around 10% of patients with NASH develop cirrhosis[5]. NASH liver cirrhosis is today the third most common cause of liver transplantation in the USA and is expected to be the primary cause in 2020.[6-8] The pathophysiology of the progression to liver cirrhosis in NASH is not well understood, but overweight and obesity, insulin resistance, type 2 diabetes (T2D) and hypertension are recognised as key predisposing factors[9].

Patients with NASH and liver cirrhosis have the highest all cause and liver related mortality compared to patients with less severe liver fibrosis[10]. The increase in liver related mortality is associated with the transition from the compensated to decompensated stage, which occurs at a rate of approximately 5-7% per year[11]. Cirrhosis is not irreversible, as liver fibrosis in the cirrhotic range in other chronic liver diseases regresses with effective therapy, such as antiviral treatment for chronic hepatitis B or C[12, 13] and steroids for autoimmune hepatitis[14].

Currently, first-line treatment of NASH in patients with compensated liver cirrhosis and overweight is lifestyle interventions to provide weight loss[15] and to treat comorbidities (e.g. hyperlipidaemia, hypertension and diabetes) as no specific pharmaceutical therapies are approved. In the case of progression to end-stage liver disease, liver transplantation is the only treatment option[16].

Accordingly, there is a substantial unmet medical need for effective treatment in patients with NASH and compensated liver cirrhosis.

3.2 Background

3.2.1 Semaglutide

Semaglutide is a potent human GLP-1 RA currently in development by Novo Nordisk A/S for weight management (NN9536) and for NASH (NN9931). Semaglutide s.c. is approved in several countries for treatment of adults with T2D under the tradename Ozempic®.

Semaglutide has been optimised from native GLP-1 resulting in a longer half-life of approximately 160 hours, making it suitable for once-weekly dosing[18]. GLP-1 is a physiological regulator of appetite and GLP-1 receptors are present in several areas of the brain involved in appetite regulation[19]. Both human and animal studies have shown a beneficial effect of GLP-1 RAs on liver lipid metabolism and reduction in progression of fatty liver to NASH[20-23]. The mechanism by which GLP-1 RAs affect NASH is not clear and neither murine nor human hepatocytes seem to have any

GLP-1 receptor expression[21, 24]. Semaglutide effectively lowers body weight and indirectly increase insulin sensitivity[23, 25, 26]. Additionally, semaglutide increases insulin and lowers glucagon levels, all of which may be beneficial in patients with NASH. Other mechanisms of actions based on the GLP-1 biology are anti-inflammatory and lipid lowering effects[21]. Marketed GLP-1 RAs are not known to be hepatotoxic[27-29]. In trial NN9535-3651, the exposure of semaglutide after a single s.c. dose of 0.5 mg was not affected by hepatic impairment and the PK properties of semaglutide were similar for subjects with mild, moderate or severe hepatic impairment compared to subjects with normal hepatic function[30].

The investigator sponsored study Liraglutide Efficacy and Action in NASH (LEAN), enrolled 52 overweight subjects with and without T2D, with biopsy-confirmed NASH and fibrosis stage 0-4 to receive 1.8 mg liraglutide s.c. or placebo once daily. After 48 weeks of treatment, 9 out of 23 (39%) subjects treated with liraglutide compared to 2 out of 22 (9%) subjects treated with placebo had resolution of NASH with no worsening of fibrosis (relative risk 4.3 [1.0–17.7] 95%CI). Furthermore, significantly fewer patients treated with liraglutide had worsening of fibrosis compared to placebo[26].

As semaglutide is structurally similar to liraglutide with similar mechanism of action and with a potential for more pronounced effect on glycaemic control and body weight, semaglutide has been selected as a development candidate for the treatment of NASH (NN9931).

3.3 Benefit-risk assessment

Subjects will be treated with a regimen anticipated to be better than or equal to the treatment they receive at the time of entry into the trial.

The LEAN study indicated a beneficial effect of liraglutide on NASH[26]. Furthermore, the phase 2 trial in weight management (NN9536-4153) showed that semaglutide as an adjunct to a reduced-calorie diet and increased physical activity was effective for weight loss in subjects with obesity while displaying a satisfactory tolerability profile. In NN9536-4153, a dose-dependent weight loss was observed across all tested doses of semaglutide (0.05 to 0.4 mg once-daily). The weight loss was 11.55% larger for the 0.4 mg group compared with placebo. Weight losses were accompanied by a consistent improvement in the weight-related comorbidities, indicated by cardiovascular risk factors, lipid profile and glycaemic factors, as well as improvements in clinical outcome assessments[31]. Finally, in a clinical trial investigating the effect of weight loss through lifestyle modification in histologic features of NASH, a 10% weight loss significantly reduced the fibrosis score by at least 1 point in 13 of 16 (81 %) patients with fibrosis at baseline[32].

Thus, in addition to these anticipated effects of semaglutide, it is expected that all subjects will benefit from participation in the trial through a close contact with the trial site including close follow-up of their NASH and general metabolic state, careful medical examination and also

nutritional and physical activity counselling. All of which will most likely result in intensified NASH management.

3.3.1 Risks and precautions

The sections below describe identified and potential risks associated with semaglutide treatment. 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.

- Gastrointestinal adverse events
    - Consistent with findings with other GLP-1 RAs, the most frequently reported adverse events (AE) in clinical trials with semaglutide were gastrointestinal AEs. A low starting dose and dose escalation steps will be implemented in the trial to mitigate the risk of gastrointestinal AEs.
- Cholelithiasis
    - Events of cholelithiasis were the most frequently reported gallbladder events in the phase 2 weight management trial (NN9536-4153) and were in a few instances co-reported with the event adjudication committee confirmed acute pancreatitis. As a precaution, if cholelithiasis is suspected, appropriate clinical follow-up is to be initiated at the investigator's discretion.
- Hypoglycaemia (in combination with SU and/or insulin) (identified for T2D patients)
    - There is a low risk of hypoglycaemic episodes when semaglutide is used as monotherapy. Subjects treated with semaglutide in combination with a SU or insulin have an increased risk of hypoglycaemia. The risk of hypoglycaemia can be lowered by reducing the dose of SU or insulin when initiating treatment with semaglutide.
- Diabetic retinopathy complication (identified for T2D patients)
    - The cardiovascular outcome trial in the semaglutide T2D development programme (NN9535-3744) 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. 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 and Section 9.4.5.
- Acute pancreatitis
    - Acute pancreatitis has been observed with the use of GLP-1 RA drug class. As a precaution, subjects with a history of chronic pancreatitis or recent acute pancreatitis will not be enrolled in the trial. In addition, trial product should be discontinued in case of suspicion of acute pancreatitis in accordance to Section 8.1.

- Medullary thyroid cancer (MTC) (based on non-clinical data)
    - 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 reports of MTC or 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, exclusion criteria related to medical history of multiple endocrine neoplasia type2 (MEN 2) or MTC and elevated plasma levels of calcitonin (biomarker for MTC) have been implemented in the trial.
- 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.
- 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.
- Pregnancy and fertility (based on non-clinical data)
    - 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. Exclusion and discontinuation criteria related to pregnancy have been implemented in the trial.

3.3.2 Conclusion on benefit-risk profile

Necessary precautions have been implemented in the design and planned conduct of the trial to minimise the risks and inconveniences of participation. The safety profile for semaglutide generated from the non-clinical and clinical development programme has not revealed any safety issues that would prohibit administration of semaglutide in patients with NASH and compensated F4. The results of the LEAN study[26] and the phase 2 trial with semaglutide in weight management (NN9536-4153) suggest that semaglutide may provide clinically meaningful treatment effects for patients with NASH and compensated F4.

Detailed information about the known and expected benefits and risks and reasonably expected adverse events of semaglutide s.c may be found in the current version of the investigator's brochure and any updates hereof [33].

4 Objectives and endpoints

4.1 Primary, secondary and exploratory objectives

4.1.1 Primary objective

To investigate the effect of semaglutide s.c. 2.4 mg once-weekly on liver fibrosis compared with placebo in subjects with NASH and compensated fibrosis stage 4[2, 3].

Primary estimand

In subjects with NASH and compensated fibrosis stage 4, the estimand addressing the primary objective is the proportion of subjects with liver fibrosis improvement with no worsening of NASH compared between semaglutide s.c. 2.4 mg once-weekly and placebo at 48 weeks if all randomised subjects had adhered to treatment. Generalisation of this estimand depends among other things on the extent to which treatment adherence in this trial reflects clinical practice.

4.1.2 Secondary efficacy objectives

To investigate the effect of semaglutide s.c. 2.4 mg once-weekly on NASH compared with placebo in subjects with NASH and compensated fibrosis stage 4.

4.1.3 Secondary safety objective

To evaluate the safety and tolerability of semaglutide s.c. 2.4 mg once-weekly compared with placebo in subjects with NASH and compensated fibrosis stage 4.

4.2 Primary and secondary endpoints

Primary and secondary endpoints are listed in Table 4-1.

Table 4-1 List of primary and secondary endpoints

End point title	Time frame	Unit
Primary endpoint:		
At least one stage of liver fibrosis improvement with no worsening of NASH after 48 weeks (yes/no) (worsening defined as an increase of at least one stage of either lobular inflammation, hepatocyte ballooning or	From baseline (week 0) to visit 12 (week 48)	Yes / no

steatosis according to the NASH CRN criteria)[2, 3].		
Secondary endpoints:		
Relative change from baseline (week 0) to week 48 in liver fat content (%) measured by MRI-PDFF.	From baseline (week 0) to visit 12 (week 48)	Ratio to baseline
Relative change from baseline (week 0) to week 48 in liver stiffness measured by MRE.	From baseline (week 0) to visit 12 (week 48)	Ratio to baseline
NASH resolution after 48 weeks (yes/no) (defined by the NASH CRN as lobular inflammation 0 – 1 and ballooning 0)[2, 3].	From baseline (week 0) to visit 12 (week 48)	Yes / no
Change from baseline in Stage of fibrosis according to the NASH CRN fibrosis score	From baseline (week 0) to visit 12 (week 48)	Scale (0-4)*
Change from baseline in NAFLD activity score (NAS) according to the NASH CRN criteria	From baseline (week 0) to visit 12 (week 48)	Scale (0-8)*
Number of treatment-emergent adverse events	From baseline (week 0) to visit 12 (week 48)	Count

*range of values on absolute scale at one time-point

5 Trial design

5.1 Overall design

- This is a 48-week randomised, double-blind, placebo-controlled, parallel group, multi-centre trial
- There is a 6 weeks screening period followed by a randomisation visit and a 48-week treatment period. The treatment period is divided into a dose escalation period of 16 weeks and a maintenance period of 32 weeks. The follow-up period is 7 weeks. Total trial duration is approximately 61 weeks
- Subjects will be randomised in a 2:1 ratio to receive either:
    - Semaglutide s.c. 2.4 mg once-weekly
    - Semaglutide placebo s.c. once-weekly
- During the trial all subjects will receive nutritional and physical activity counselling in accordance with site practice at the visits specified in the flowchart
- The trial population is subjects with NASH and compensated F4, with no previous events of decompensation, and no causes of chronic liver disease other than NAFLD. The population will suffer from overweight or obesity, and may have T2D

The trial design is outlined in Figure 5-1.

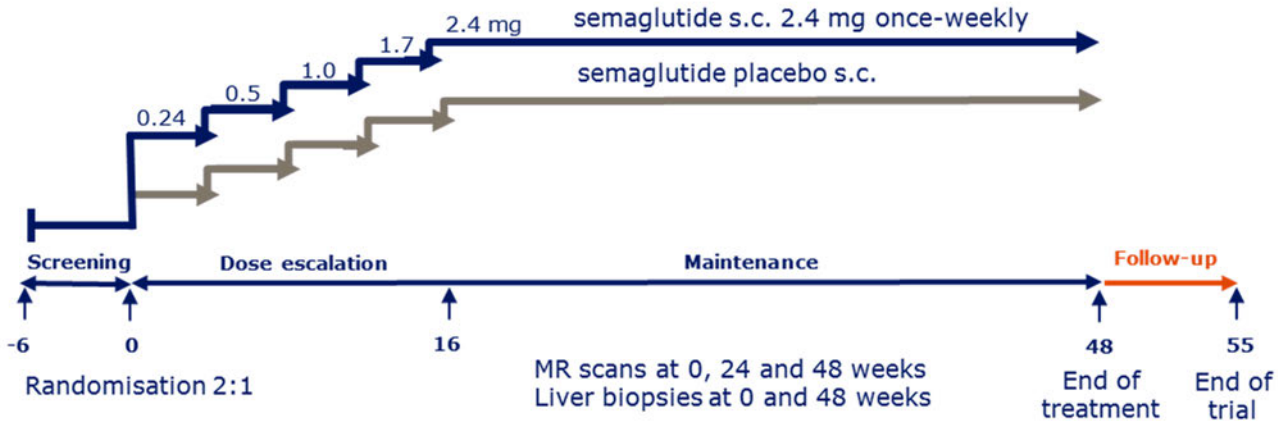


Figure 5-1 A schematic diagram of the trial design, with the duration of the trial periods including follow-up period.

5.2 Subject and trial completion

Approximately 240 subjects will be screened to achieve 69 subjects randomly assigned to trial product.

Trial period completion for a subject:

Trial period completion is defined as when the randomised subject has completed the final scheduled visit (FU visit (visit 12A for discontinued subjects during trial)) according to the flowchart).
'Date of trial completion' is the date the subject completed the final scheduled visit.

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 (visit 12) according to the flowchart.

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

A randomised, double-blind, placebo-controlled, parallel group, multi-centre trial is chosen to minimise bias in the assessment of the effect and safety of semaglutide s.c. 2.4 mg.

The trial includes 48-weeks of treatment which is in line with recent phase 2b and 3 trials in subjects with NASH and compensated cirrhosis (BMS' peg-FG21 clincaltrial.gov NCT03486912; Gilead's selonsertib clinicaltrial.gov NCT03053063). The 48 weeks are considered sufficient to establish if semaglutide has the effects on fibrosis and liver steatosis in subjects with compensated F4. The 7 weeks off treatment follow-up period is included to monitor safety until complete wash-out of semaglutide.

The trial includes a screening visit to assess the subject's eligibility followed by visits/phone contacts every second week during the first 12 weeks of the dose escalation period. From week 12 until end of treatment (week 48) there are 4 visits scheduled with increasing time interval from 4 to 12 weeks between the visits. The number and frequency of visits/phone contacts are balanced between adequate efficacy and safety evaluation and the time required by the subject to participate.

Due to the lack of pharmacological treatments for compensated F4, placebo is chosen as comparator. The trial has a 2:1 randomisation scheme which will increase the amount of semaglutide exposure data in the included population.

Subjects with T2D will be included in the trial population since the prevalence of T2D is high in patients with NASH and liver cirrhosis (approximately 65%)[34] and patients with T2D may benefit from treatment with semaglutide. Subjects will be stratified at randomisation based on T2D to ensure equal allocation to each treatment arm.

The primary and secondary endpoints are based on MR imaging and liver histology, which is in line with the current recommendations from Liver Forum[35].

5.5 Justification for dose

The recently completed phase 2 dose finding trial in weight management (NN9536-4153) and the 2 ongoing NASH trials (NN9931-4296 and NN9931-4381) have semaglutide s.c. 0.4 mg once-daily as maximum dose (range 0.05 to 0.4 mg once-daily).

The results from NN9536-4153 showed that the semaglutide s.c. 0.4 mg once-daily dose was most effective in terms of weight loss while displaying an acceptable tolerability profile. Using populated pharmacokinetic modelling, it was estimated that a once-weekly maintenance dose of s.c. 2.4 mg resulted in similar C_{max} at steady-state as that obtained by the 0.4 mg once-daily dose.

The target dose in the ongoing phase 3 programme in weight management (NN9536) was chosen to be semaglutide s.c. 2.4 mg once-weekly. A maintenance dose of semaglutide s.c. 2.4 mg once-weekly is also chosen as target dose in this trial, as it is anticipated to ease the burden of drug administration compared to once-daily injections in clinical practice.

It is well known that to mitigate GI side effects with GLP-1 RA treatment, dose escalation to the target dose is required. A fixed-dose escalation regimen similar to the regimen used in the phase 3 programme in weight management (NN9536) is applied. Subjects will be initiated at a once-weekly dose of 0.24 mg and follow a fixed-dose escalation regimen, with dose increase every 4 weeks (to doses of 0.5, 1.0, 1.7 and 2.4 mg/week), until the target dose is reached after 16 weeks.

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 of the following criteria apply:

1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial.

2. Male or female, aged 18-75 years (both inclusive) at the time of signing informed consent.

3. Histologic evidence of NASH and fibrosis stage 4 according to the NASH CRN classification based on central pathologist evaluation of a liver biopsy obtained within 360 days prior to screening. In subjects who have never had a liver biopsy showing NASH and F4, liver stiffness > 14 kPa by FibroScan® at screening must be documented before subjects can have a trial-related liver biopsy.

4. A histological NAFLD activity score (NAS) ≥ 3 with a score of 1 or more in lobular inflammation and hepatocyte ballooning based on central pathologist evaluation

5. Body mass index ≥27 kg/m^2

6.2 Exclusion criteria

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

Liver-related:

1. Presence or history of chronic liver disease other than NAFLD

2. Presence or history of hepatic decompensation (e.g. ascites, variceal bleeding, hepatic encephalopathy or spontaneous bacterial peritonitis) or liver transplantation

3. Presence or history of gastroesophageal varices within the past 360 days prior to screening. For subjects with no known history of gastroesophageal varices and with a Fibroscan® ≥ 20 kPa and thrombocytes ≤ 150,000[17], a esophagogastroduodenoscopy must be performed to evaluate presence of gastroesophageal varices

4. Known or suspected abuse of alcohol (>12 g/day for women or >24 g/day for men) or alcohol dependence assessed by the Alcohol Use Disorders Identification Test (AUDIT questionnaire)

5. Presence or history of hepatocellular carcinoma

6. Treatment with vitamin E (at doses ≥800 IU/day) or pioglitazone which has not been at a stable dose in the opinion of the investigator in the period from 90 days prior to screening

7. Treatment with medications (for more than 14 consecutive days) with known effect on liver steatosis (e.g. treatment with Corticosteroids (topical and inhaled are allowed), Methotrexate, Tamoxifen, Valproic acid, Amiodarone or Tetracycline) which has not been stable in the opinion of the investigator in the period from 28 days prior to screening

8. Alanine aminotransferase (ALT) > 5 times upper normal limit (UNL)

9. Aspartate aminotransferase (AST) > 5 times UNL

10. Total bilirubin > 1.5 mg/dL. Total bilirubin level > 1.5 mg/dL is allowed if conjugated bilirubin is < 1.5 × UNL

11. International normalized ratio (INR) of prothrombin time > 1.4

12. Thrombocytes < 100,000 per µl

13. Model For End-Stage Liver Disease (MELD) score ≥ 12 points

14. Child-Pugh Score ≥ 7 points

15. Albumin < 3.4 g/dl

16. Positive result to test for hepatitis B surface antigen (HBsAg) or hepatitis C antibodies. In case screening test for hepatitis C is positive, the confirmative test is decisive

17. Diagnostic test results positive for HIV-1 or HIV-2 infection

Glycaemia-related:

18. Presence or history of type 1 diabetes

19. Glycosylated haemoglobin A1c (HbA1c) > 9.5%

20. Treatment with glucagon-like peptide-1 receptor agonists (GLP-1 RAs) in the period from 90 days prior to screening

21. Treatment with other glucose lowering agent(s) (apart from what is listed in exclusion criterion 20) or weight loss medication not stable in the opinion of the investigator in the period from 28 days prior to screening

Obesity-related:

22. Previous or planned (during the trial period) obesity treatment with surgery or a weight loss device. However, the following are allowed: (1) liposuction and/or abdominoplasty, if performed > 1 year before screening, (2) lap banding, if the band has been removed > 1 year before screening, (3) intragastric balloon, if the balloon has been removed > 1 year before screening or (4) duodenal-jejunal bypass sleeve, if the sleeve has been removed > 1 year before screening

General safety:

23. Presence or history within the past 5 years prior to the day of screening of malignant neoplasms other than described in exclusion criterion 5. Basal and squamous cell skin cancer and any carcinoma in-situ are allowed

24. Presence of acute pancreatitis within the past 180 days prior to the day of screening

25. History or presence of chronic pancreatitis

26. For subjects with type 2 diabetes only: 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

27. Personal or first degree relative(s) history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma

28. Any of the following: myocardial infarction, stroke, hospitalization for unstable angina pectoris or transient ischaemic attack within the past 90 days prior to the day of screening and between screening and randomisation

29. Presently classification of heart failure New York Heart Association (NYHA) Class IV

30. Presence or history of suffering from claustrophobia precluding magnetic resonance imaging

31. Presence of metallic implants, pacemaker, defibrillator, artificial valves in heart, internal electrical devices (e.g., cochlear implant, nerve stimulator, brain stimulator, gastric pacemaker, bladder stimulator etc.), aneurysm clips, permanent makeup or tattoos precluding magnetic resonance imaging

32. Unstable body weight defined as more than 5% self-reported change in body weight in the period from 28 days prior to screening

33. Any condition which, in the investigator's opinion might jeopardise subject's safety or compliance with the protocol

34. Mental incapacity, language barriers or unwillingness to comply with the requirements of the protocol, which may preclude adequate understanding or co-operation during the trial as judged by the investigator

35. Surgery scheduled for the trial duration period, except for minor surgical procedures, in the opinion of the investigator

36. Known or suspected hypersensitivity to trial product or related products

37. Previous participation in this trial. Participation is defined as randomisation

38. Participation in another interventional clinical trial within 60 days before screening

39. 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 (highly effective contraceptive measures as required by local regulation or practice)

40. Calcitonin ≥ 100 ng/L

41. Estimated Glomerular Filtration Rate (eGFR) < 30 mL/min/1.73 m^2 as defined by according to CKDEPI creatinine equation as defined by KDIGO 2012[36]

6.3 Lifestyle restrictions

6.3.1 Meals and dietary restrictions

- Subjects must attend some visits fasting according to the flowchart.
- Fasting is defined as at least eight hours 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 the fasting procedure i.e. MRI, fibroscan® and blood samples have been obtained.
- Fasting procedures include MR scans, body weight, Fibroscan® measurements and blood sampling (FPG, C-peptide, lipids (total cholesterol, free fatty acids, HDL cholesterol, LDL cholesterol, triglycerides, VLDL cholesterol) and semaglutide plasma concentration).
- Only four hours fasting is required prior to MR scanning and intake of water or liquid should be avoided or limited two hours before MR scanning.
- Only two hours fasting is required prior to Fibroscan® measurements.
- If the subject is not fasting as required, the subject must be called in for a new visit within the visit window to have the fasting procedures 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 demography, screen failure details, eligibility criteria, and any SAE. A screen failure session must be made in the IWRS.

Individuals who do not meet the criteria for participation in this trial may be re-screened once within the limits of the recruitment period. In the event of re-screening, a new informed consent must be obtained and a new subject number must be allocated.

Re-sampling of lab parameters is allowed once, within the screening visit window, provided the medical specialist responsible for the trial agrees to the individual case. In case of technical issues (e.g. haemolysed or lost), re-sampling is allowed for the affected parameters without asking for permission from the medical specialist at Novo Nordisk.

7 Treatments

7.1 Treatments administered

- All trial products listed in Table 7-1 are considered investigational medicinal products (IMP)
- Trial product must only be used, if it appears clear and colourless
- All baseline assessments must be done prior to administration of the first dose of trial product.

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

Trial product name:	Semaglutide B 3.0 mg/mL	Semaglutide placebo
Dosage form:	Solution for injection	Solution for injection
Route of administration:	Subcutaneous	Subcutaneous
Dosing instructions:	Once-weekly	Once-weekly
Delivery device:	3 mL PDS290 pre-filled pen-injector	3 mL PDS290 pre-filled pen-injector

- Dose escalation of semaglutide/semaglutide placebo should take place during the first 16 weeks after randomisation as described in Table 7-2. Semaglutide or semaglutide placebo will be initiated with a starting value of 8 (0.24 mg) for the first 4 weeks, and subsequently the value will be increased every 4 weeks as indicated in Table 7-2. All subjects must aim at reaching the recommended target dose of semaglutide s.c. 2.4 mg once-weekly or the corresponding volume of placebo.

Table 7-2 Dose escalation and maintenance dose of semaglutide s.c. 2.4 mg/semaglutide placebo once-weekly

IMP	Dose	Volume	Value shown in the dose counter	Duration
Semaglutide B 3.0 mg/mL PDS290 or semaglutide placebo	0.24 mg	80 µl	8	4 weeks
Semaglutide B 3.0 mg/mL PDS290 or semaglutide placebo	0.5 mg	170 µl	17	4 weeks
Semaglutide B 3.0 mg/mL PDS290 or semaglutide placebo	1.0 mg	340 µl	34	4 weeks
Semaglutide B 3.0 mg/mL PDS290 or semaglutide placebo	1.7 mg	570 µl	57	4 weeks
Semaglutide B 3.0 mg/mL PDS290 or semaglutide placebo	2.4 mg	800 µl	80	32 weeks (maintenance dose)

- If a subject does not tolerate the planned 4-week dose-escalation regimen due to GI AEs or for other reasons as judged by the investigator, the subject is allowed to stay longer at the individual dose steps. The Investigator must aim for maximum 1 extra week on each dose level. If the planned dose escalation regimen is not adhered to, the Investigator should evaluate weekly if the dose can be escalated to the next planned level.
- If a subject does not tolerate the recommended target dose of s.c. 2.4 mg once-weekly, the subject may stay at the lower dose level. This is only allowed if the subject would otherwise discontinue trial product completely and if considered safe to continue on trial product, as per the investigator's discretion. It is recommended that the subject makes at least one attempt to escalate to the recommended target dose of s.c. 2.4 mg once-weekly, as per the investigator's discretion.
- It is recommended that the investigator contact the monitor in case of persistent deviations from the planned escalation.
- Subjects should be instructed to inject semaglutide/semaglutide placebo once-weekly at the same day of the week throughout the trial.
- Injections may be administered in the thigh, abdomen or upper arm, at any time of day irrespective of meals. Subjects should be encouraged to inject in the same area throughout the trial, but changing between left and right side is allowed.
- If a single dose of trial product is missed, it should be administered as soon as noticed, provided the time to the next scheduled dose is at least 48 hours. If a dose is missed and the next scheduled dose is less than 48 hours away, the subject should not administer a dose until the next scheduled dose. A missed dose should not affect the scheduled dosing day of the week.
- If ≥ 2 consecutive doses of trial product are missed, the subject should be encouraged to recommence the treatment if considered safe as per the investigator's discretion and if the subject does not meet any of the discontinuation criteria (section 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.
- Auxiliary supplies will be provided in accordance with the trial materials manual (TMM).

Table 7-3 Auxiliary supplies provided by Novo Nordisk A/S

Auxiliary supply	Details
Needles	Needles for PDS290 pre-filled pen-injector. Details provided in the TMM. Only needles provided and approved by Novo Nordisk must be used for administration of trial product. Needles longer than 6 mm should not be used.
Direction for use (DFU)	DFU for 3 mL PDS290 pre-filled pen-injector
BG-meters (Abbott Precision Neo or Precision depending on country approval)	The BG-meters use test strips calibrated to plasma values. All measurements performed with capillary blood are automatically calibrated to plasma equivalent glucose values, which will be shown on the display.

At the randomisation visit (visit 2) subjects with T2D will be provided with a BG-meter including auxiliaries as well as instructions for use. In case a subject is diagnosed with T2D during trial participation the subject will be provided with a BG-meter. The subjects will be instructed in how to use the device. The BG-meter provided by Novo Nordisk should be used to measure the blood glucose in connection with symptoms of hypoglycaemia.

7.1.1 Medical devices

Information about the PDS290 pre-filled pen-injector are found in the IB and any updates hereof[33]. Information about the use of the PDS290 pre-filled pen-injector for semaglutide B 3.0 mg/mL and semaglutide placebo can be found in the DFU.

Training in the PDS290 pre-filled pen-injector
The investigator must document that DFU are given to the subject orally and in writing at the first dispensing visit (as specified in the flowchart). The subjects must be trained according to the direction for use in how to handle the medical device PDS290 pre-filled pen-injector when handed out the first time. Training must be repeated, during the trial in accordance with the flowchart in order to ensure correct use of the PDS290 pre-filled pen-injector. The DFU should be handed out at subsequent visits if needed. The PDS290 pre-filled pen-injector will display a value and not mg and subjects must be instructed to administer the value shown in the display. Training in PDS290 pre-filled pen-injector and injection technique are the responsibility of the investigator or a delegate.

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 eligible subjects will be centrally randomised using an IWRS and assigned to the next available treatment according to randomisation schedule. Trial product will be dispensed at the trial visits summarised in the flowchart.
- Randomisation will be stratified based on T2D (with T2D or without T2D).

7.4 Blinding

- The active drug and placebo are packed blinded and 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 subject's medical records.

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

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

7.5 Preparation/Handling/Storage/Accountability

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

- Storage conditions, in-use conditions and in-use times can be found in the TMM.
- Each trial site will be supplied with sufficient trial products for the trial on an on-going basis controlled by the IWRS. Trial product will be distributed to the trial sites according to screening and randomisation.
- The investigator must confirm that appropriate temperature conditions have been maintained during transit for all trial products received and any discrepancies are reported and resolved before use of the trial products.
- All trial products must be stored in a secure, controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.
- The investigator must inform Novo Nordisk immediately if any trial product has been stored outside specified conditions. Additional details regarding handling of temperature deviations can be found in the TMM.
- Trial product that has been stored improperly must not be dispensed to any subject before it has been evaluated and approved for further use by Novo Nordisk.
- The investigator is responsible for drug accountability and record maintenance (i.e. receipt, accountability and final disposition records).
- The trial products will be dispensed to each subject as required according to treatment group. Each dispensing unit is uniquely numbered with a Dispensing Unit Number (DUN). The correct DUN(s) must be dispensed to the subject.
- Drug accountability is performed using the IWRS drug accountability module. The trial products must be accounted for at pen level and either recorded as used/partly used, unused or lost. Returned pens must be sent for destruction, thus may not be re-allocated to new subjects.
- The subject must return all used, partly used and unused trial product including empty packaging material during the trial as instructed by the investigator.
- Destruction of trial products can be performed on an ongoing basis and will be done according to local procedures after accountability is finalised by the site and reconciled by the monitor.
- Destruction of trial products must be documented in the IWRS.
- All returned, expired or damaged trial products (for technical complaint samples see Appendix 6) must be stored separately from non-allocated trial products. No temperature monitoring is required.

- Non-allocated trial products including expired or damaged products must be accounted as unused, at the latest at closure of the trial site.

7.6 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 will be assessed by asking subject about missed doses and monitoring the diary. Information about compliance and missed doses should be described in the subject's medical records.

7.7 Concomitant medication

The following medications must be stable as described in exclusion criteria 6, 7, 21:

- Vitamin E and pioglitzone
- Medications with known effect on liver steatosis
- Glucose-lowering and weight-loss medications

Throughout the trial subjects cannot initiate treatment with:

- GLP-1 RAs (other than trial product) or SGLT-2 inhibitors
- Vitamin E or pioglitazone
- Drugs with potential effect on steatosis (corticosteroids (topical, inhaled and short term systemic use (≤ 14 days) are allowed), methotrexate, tamoxifen, valproic acid, amiodarone or tetracycline)
- Drugs that could promote weight loss (orlistat, zonisamide, topiramate, phentermine, lorcaserin, bupropion and naltrexone alone or in combination with any other medication that could promote weight loss)

Neither can the subjects participate in any organised weight reduction programme throughout the trial.

For subjects treated with vitamin E or pioglitazone according to exclusion criterion 6, these medications must be kept at a stable dose throughout the trial.

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) other than the trial product that the subject is receiving at the time of visit 1 or receives during the trial must be recorded along with:

- Trade name or generic name
- Dates of administration including start and stop dates
- For vitamin E and pioglitazone the daily dose must be recorded as well

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

7.7.1 Subjects treated with insulin

Throughout the trial, insulin dose should be titrated at the discretion of the investigator. For the individual subject, increasing the insulin dose before two weeks after the end of the final dose escalation should be avoided, unless required to control acute hyperglycaemia and acute diabetic complications.

Subjects treated with insulin and HbA1c ≤ 8.0 % at screening
Subjects treated with semaglutide in combination with insulin may have an increased risk of hypoglycaemia. The risk of hypoglycaemia can be lowered by reducing the dose of insulin, and a dose reduction at randomisation and throughout the trial should be considered at the discretion of the investigator.

7.7.2 Subjects treated with SU

Subjects treated with semaglutide in combination with a sulfonylurea may have an increased risk of hypoglycaemia. The risk of hypoglycaemia can be lowered by reducing the dose of sulfonylurea, and a dose reduction at randomisation and throughout the trial should be considered at the discretion of the investigator.

7.7.3 Subjects developing type 2 diabetes

Subjects who are diagnosed with T2D as a result of a screening procedure or are diagnosed with T2D during the trial should receive diabetes treatment within the restriction of the protocol and at the discretion of the investigator. GLP -1 RAs (other than trial product) and SGLT-2 inhibitors must not be used. The antidiabetic medication prescribed by the investigator will not be provided nor reimbursed by Novo Nordisk.

7.8 Treatment after the end of the trial

After the end of trial the subject should be treated at the discretion of the investigator. Novo Nordisk will not provide trial products following the end of the trial.

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.

8.1 Discontinuation of trial treatment

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

Subjects who discontinue trial product should continue with the scheduled visits and assessments and subjects must be educated about the continued scientific importance of their data, even if they discontinue trial product.

- If a subject discontinues trial product treatment, the investigator must undertake procedures similar to those for visit 12 (end of treatment) as soon as possible and the follow-up visit (visit 13) must be performed 7 weeks later. No liver biopsies, MRI-PDFF and MR elastography will be taken at V12 for trial product treatment discontinued subjects. If the subject discontinues trial product treatment at the same timepoint as visit 10 (24 weeks after randomisation), then a MRI-PDFF and MR elastography must be included in visit 12 (end of treatment) as per original visit schedule. See the flowchart for data to be collected.
- Following visit 13, subjects should continue with the originally scheduled site visits/contacts up to and including visit 12A. Visit 12A must take place 48 weeks (± 7 days) after the randomisation date. A liver biopsy, MRI-PDFF and MR elastography will be obtained at V12A (see flowchart for additional data to be collected). However the following should not be done after visit 13 for subjects discontinuing trial product: Semaglutide plasma concentration, hypo reporting and handing out subject diaries.
- Subjects who discontinue trial product treatment will continue to receive nutritional and physical exercise counselling throughout their trial participation.
- Efforts must be made to have subjects attend and complete all scheduled visit procedures. If the subject does not wish to attend the scheduled clinic visits efforts should be made to have the visits converted to phone contacts and all efforts should be made to have the subject to attend at least visit 12A (48 weeks post-randomisation), to collect the required data for the analysis of the primary endpoint.

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

1. Pregnancy
2. Intention of becoming pregnant
3. Simultaneous participation in another clinical trial of an approved or non-approved investigational medicinal product
4. Diagnosis of acute pancreatitis
5. Diagnosis of medullary thyroid carcinoma
6. Surgical treatment for obesity

7. Treatment with other GLP-1 receptor agonists or SGLT-2 inhibitors
8. Abnormal liver blood parameters indicating drug induced liver injury (DILI)
9. Events of hepatic decompensation (e.g. ascites, variceal bleeding, hepatic encephalopathy or spontaneous bacterial peritonitis)
10. Safety concerns as judged by the investigator

Subjects meeting discontinuation of trial treatment criterion no. 3, 4, 5, 6, and 9 are not allowed to resume trial product if the criteria is met.

Subjects meeting discontinuation of trial treatment criterion no. 1, 2, 7, 8, and 10 are allowed to resume trial product, if the criteria are no longer met.

For discontinuation of trial treatment criterion no. 8: If an alternative etiology is not definitively defined and/or liver blood parameters have not returned to pre-event levels, DILI cannot be excluded and trial product must be permanently discontinued. See Appendix 2 for more details.

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

8.1.1 Temporary discontinuation of trial treatment

If a subject has discontinued trial product and is allowed to resume, the subject should follow the instruction for missed doses in section 7.1. Similarly, a subject who discontinues trial product on their own initiative should be encouraged to resume the trial product.

Missed doses should be recorded in the CRF. If a 'treatment status' session previously has been made in IWRS to indicate discontinuation of trial product, a new 'treatment status' session must be made to resume trial product.

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 12 (no liver biopsy and MR scan if the subject withdraws consent before visit 12 according to original schedule). See the flowchart 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 status' session to register discontinuation of treatment 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 or not 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.
- Frequency of alcohol consumption and screen for alcohol-related problems and dependence symptoms should be evaluated by interviewing subjects using the AUDIT questionnaire
- The esophagogastroduodenoscopy should be performed before obtaining a liver biopsy, if needed according to exclusion criteria 3.
- Subjects who have never had a liver biopsy showing NASH and F4 must have a FibroScan® not older than 12 weeks showing liver stiffness >14 kPa before the subjects proceed to have a liver biopsy at screening.
- Source data of clinical assessments performed and recorded in the CRF must be available and will usually be the subject's medical records. Additional recording to be considered source data includes, but is not limited to laboratory reports, ECG and diary recordings.
- Subjects will be instructed in how to complete the diary
- Only the subject can make entries about trial product dose (date, time, dose, injection site) and hypoglycaemic episodes in the diary.
- The investigator must review the subject diary at each clinic visit after randomisation.
- Review of completed diaries, ECG, laboratory reports must be documented either on the documents or in the subject's source documents. If clarification of entries or discrepancies in the diary is needed, the subject must be questioned and a conclusion made in the subject's source documents. Care must be taken not to bias the subject.

9.1 Efficacy assessments

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

9.1.1 Magnetic Resonance Imaging

MRI must be done according to the imaging manual provided by the central imaging supplier.

Images will be analysed by a central imaging supplier. For standardisation purposes the central imaging lab supplier will train the trial specific MRI clinics, as applicable, and the central imaging supplier will do centralised blinded (blinded to treatment allocation) image analysis/interpretation.

Magnetic resonance elastography

Liver stiffness is measured by MRI using a MRE technique. A result measured in kPa will be obtained and data will be transferred electronically from the central imaging lab supplier to Novo Nordisk. Data will be provided to the investigator after the subject has completed the trial.

Magnetic resonance imaging-estimated proton density fat fraction

Liver steatosis will be assessed via MRI-PDFF technique. A result measured in % will be obtained and data will be transferred electronically from the central imaging lab supplier to Novo Nordisk.

Liver fat volume will be calculated based on assessment of liver steatosis via MRI-PDFF and liver volume assessed via MRI. A result measured in L will be obtained and data will be transferred electronically from central imaging lab supplier to Novo Nordisk.

Liver volume will be assessed via MRI. Results measured in L will be obtained and data will be transferred electronically from the central imaging lab supplier to Novo Nordisk.

Data assessed by MRI-PDFF will be provided to the investigator after the subject has completed the trial.

9.1.2 Liver biopsy

Liver biopsy must be performed according to site standard procedures.

In case the liver biopsy obtained during the screening period or up to 360 days prior to screening cannot be used to evaluate eligibility of the subject due to technical issues with the biopsy sample, the subject should be asked to have another liver biopsy performed. If the subject does not agree to that, the subject is a screen failure.

All randomised subjects completing 48 weeks of trial product treatment or discontinuing trial product treatment during the trial, should have a liver biopsy performed 48 weeks after the randomisation (visit 12/12A). In case conclusive evaluation of this biopsy is not possible due to technical issues with the biopsy sample, the subject should be asked to have another liver biopsy performed.

Handling of histology samples will be done by a central laboratory. Descriptions of laboratory supplies, procedures for preparation of tissue samples, handling, storage, shipments and return of tissue samples, will be given in the trial-specific laboratory manual provided by the central laboratory.

Histology results will be made available to the investigator.

Only tissue samples requested in the protocol must be sent to the central laboratory.

9.1.2.1 Central pathology evaluation

The histologic evidence of NASH and histology based scores will be centrally assessed by an independent pathologist with expertise and experience in NASH. The central pathology evaluation will include the following:

- Presence or absence of NASH
- Stage of fibrosis (according to NASH CRN criteria)
- Lobular inflammation, hepatocyte ballooning and steatosis (NASH CRN criteria)
- NAFLD Activity Score (NAS) (according to NASH CRN criteria)
- Ishak Fibrosis score (reported to Novo Nordisk only)
- Hepatic collagen content assessed via morphometry (collagen proportionate area) (reported to Novo Nordisk only)

The NAFDL activity score is the sum of the scoring of lobular inflammation, hepatocyte ballooning and steatosis. The pathologist will be blinded to the subject and treatment.

9.1.3 Child-Pugh score

Child-Pugh Score is calculated based on central laboratory total bilirubin, albumin and INR, combined with clinical scoring by site staff of ascites (assessed by ultrasound) and hepatic encephalopathy (assessed by questionnaire). Figure 9-1 shows the Child-Pugh classification and how calculation of Child-Pugh will be done in this trial[37]. The score of ascites and hepatic encephalopathy together with the total score should be recorded in the CRF.

Table 9-1 Child-Pugh classification

	Calculation of Child-Pugh Score	
Encephalopathy	None	1 point
	Grade 1/2	2 points
	Grade 3/4	3 points
Ascites	Absent	1 point
	Slight	2 points
	Moderate/large	3 points
Bilirubin level	<2 mg/dL	1 point
	2-3 mg/dL	2 points
	>3 mg/dL	3 points
Albumin level	>3.5 g/dL	1 point
	2.8-3.5 g/dL	2 points
	<2.8 g/dL	3 points
International Normalized Ratio	<1.7	1 point
	1.7-2.3	2 points
	>2.3	3 points
Assignment of Child-Pugh Classification From Child-Pugh Score		
5-6 points		Child class A
7-9 points		Child class B

10-15 points	Child class C

9.1.4 Body measurements

9.1.4.1 Height

Height is measured without shoes in centimetres or inches.

9.1.4.2 Body weight

The body weight should be measured with an empty bladder, without shoes and only wearing light clothing. It should be measured on a digital scale and recorded in kilograms or pounds (one decimal) using the same scale throughout the trial. The scale must be calibrated according to the directions for use.

9.1.4.3 Body mass index (BMI)

BMI will be calculated by the CRF from screening data.

9.1.4.4 Waist circumference

Waist circumference is defined as the abdominal circumference located midway between the lower rib margin and the iliac crest.

Measures must be obtained in standing position with a non-stretchable measuring tape and to the nearest cm or inch. The tape should touch the skin but not compress soft tissue and twists in the tape should be avoided. The subject should be asked to breathe normally. The same measuring tape should preferably be used throughout the trial. The measuring tape will be provided by Novo Nordisk to ensure standardisation.

9.1.5 Exploratory biomarkers

Collection of samples for biomarker research is part of this trial to support the efficacy objectives. The following blood samples are required and will be collected from all subjects in this trial as specified in the flowchart (See also Appendix 2):

- Pro-C3 (collagen marker)
- ELF
- Adiponectin
- High sensitivity C reactive protein (hsCRP)

9.1.6 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.

9.2 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 visit (visit 12A for subjects discontinuing trial product during trial), at the time points specified in the flowchart.

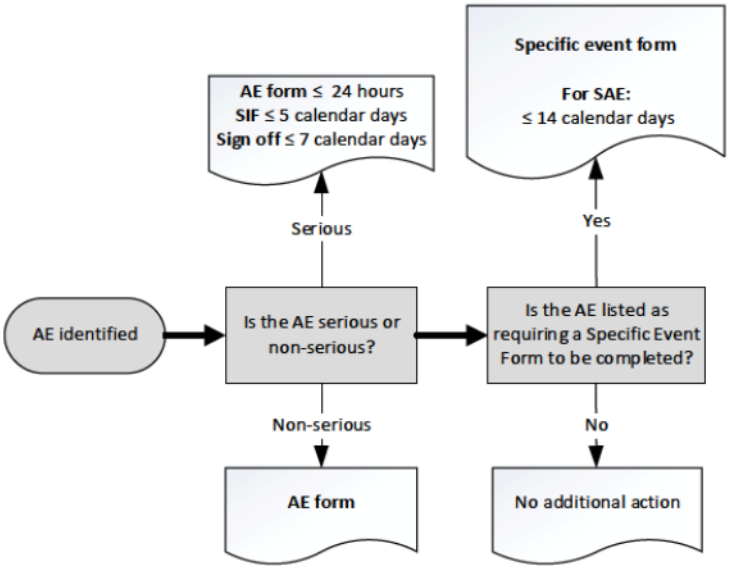
All SAEs will be recorded and reported to Novo Nordisk or designee within 24 hours, as indicated in Appendix 4. The investigator must submit any updated SAE data to Novo Nordisk within 24 hours of it being available.

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 9-2 and the reporting timelines in Figure 9-1.



Timelines are from the awareness of an AE.
Queries and follow-up requests to be resolved ≤ 14 calendar days.

AE: Adverse Events, SAE: Serious Adverse Events, SIF: Safety Information Form

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

Table 9-2 AEs requiring additional data collection (via specific event form)

Event type	AE requiring additional event form
Acute gallbladder disease	X
Hepatic event	X
Medication error	X
Malignant neoplasm	X
Acute pancreatitis	X
Diabetic retinopathy	X

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, stabilization, 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

Not applicable for this trial.

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 visit (visit 12A for subjects who discontinue trial product during trial).

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.

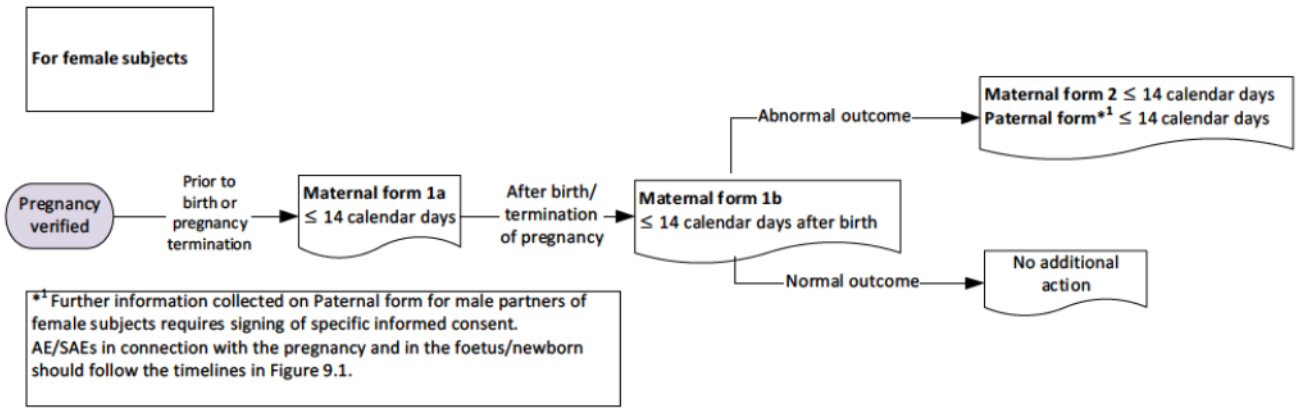


Figure 9-2 Decision tree for determining the forms to complete with associated timelines for pregnancy.

9.2.8 Medical device incidents (including malfunctions)

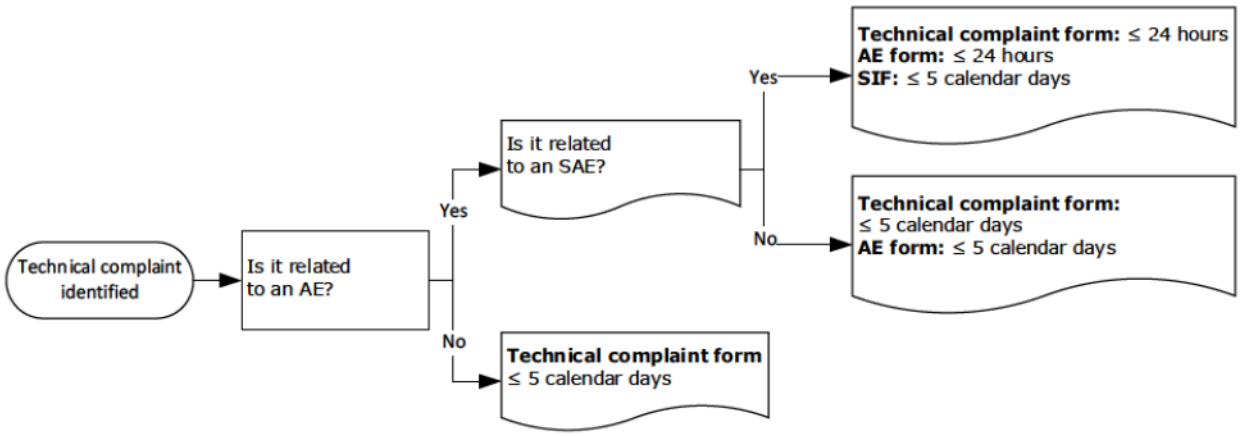
Section not applicable for this trial. Refer to technical complaints in Section 9.2.9 and Appendix 6.

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.



AE: Adverse Event, SAE: Serious Adverse Event, SIF: Safety Information Form

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

9.2.10 Hypoglycaemic episodes

For subjects without T2D:

- Hypoglycaemic episodes must be reported as an AE in accordance with Appendix 4.

For subjects with T2D:

Subjects must be instructed to measure their blood glucose in connection with symptoms of hypoglycaemia. Investigator should ensure throughout the trial that the subject is able to correctly measure blood glucose at any time.

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

If the hypoglycaemic episode fulfils the criteria for an SAE then in addition to the above, an AE form and a safety information form (SIF) 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. Definitions, classification and reporting requirements are described in Appendix 8.

9.3 Treatment of overdose

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

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 (Appendix 4). Refer to Section 9.2.1 for further details. Intentional overdose should be reported as AE.

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[33].

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 (visit 1) 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. Specific medical history of gallbladder disease should only be entered on the specific form. The information collected for concomitant illness and medical history should include diagnosis, date of onset and date of resolution or continuation, as applicable.

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 Appendix 4) 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 will include assessments of the general appearance, skin, thyroid gland, lymph node palpation, head, ears, eyes, nose, throat and neck as well as the cardiovascular, respiratory, gastrointestinal including mouth, musculoskeletal, central and peripheral systems. The outcome will be reported in the CRF.
- 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 and pulse measurements assessment 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 at screening will consist of 3 diastolic and systolic blood pressure measurements with intervals of at least 1 minute in between. All three readings must be entered in the CRF and the average of the 3 blood pressure readings will be calculated in the CRF. At subsequent visits, the blood pressure should only be measured once.
- Blood pressure and pulse measurements should be assessed in a sitting position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- The same arm and an appropriate cuff size should be used for blood pressure measurement at all visits.

9.4.3 Tobacco use

The investigator must document the smoking status and entered in the CRF as:
- Never smoked
- Previous smoker
- Current smoker

9.4.4 Electrocardiograms

A 12-lead ECG will be performed on local machines as per local guidelines and recorded in the CRF as:
- normal
- abnormal

9.4.5 Eye examination

Only applicable for subjects with T2D:
Subjects with uncontrolled and potentially unstable diabetic retinopathy or maculopathy are not eligible as this indicates retinopathy that has recently progressed to a level that requires intervention or is approaching intervention, but has yet to be brought under control.

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

If the subject had such an eye examination performed within 90 days prior to screening, the investigator may base his/her evaluation upon the results of that examination. The examination must be repeated before randomisation if the subject has experienced worsening of visual function since the last examination. If the applicable eye examination was performed before the subject signed the

informed consent form, it must be documented that the reason for performing the examination was not related to this trial. Germany: For country specific requirements see Appendix 9.

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 and Appendix 4.

9.4.6 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 Section 2.

9.5 Pharmacokinetics

- A single blood sample for measurement of plasma semaglutide concentration will be drawn for both semaglutide and semaglutide placebo subjects at the visits specified in the flowchart.
- Subjects must be instructed to withhold their trial product dose in the morning until blood sampling is performed at the visit. In addition subjects must be instructed to complete their diary and bring it to the visits.
- The PK dosing information in the diary should be transcribed into the CRF for the last two doses of trial product prior to the visits with PK assessment.
- The exact timing of obtaining the PK sample must be recorded on the laboratory form.
- The purpose of measuring plasma semaglutide levels is to perform population PK analyses (Pop-PK). Having Pop-PK in this trial will further support bridging of Pop-PK from trials conducted in other populations.

See also Appendix 2.

The sampling must be conducted in accordance with the laboratory manual.

9.6 Pharmacodynamics

Not applicable for this trial.

9.7 Genetics

Not applicable for this trial.

9.8 Biomarkers

See section 9.1.5 for exploratory biomarkers and Appendix 7 for biosamples for future analysis.

10 Statistical considerations

10.1 Sample size determination

The sample size calculation was originally based on an aim to detect a difference in the treatment ratio for MRE between semaglutide and placebo at a 5% significance level using the assumption of a t-test for 2 independent groups and a log-normal distributed outcome with a 2:1 randomisation. The power was set to 90%.

In Protocol Version 3.0, the primary endpoint was changed from relative change from baseline (week 0) to week 48 in liver stiffness measured by MRE to the binary endpoint of at least one stage of liver fibrosis improvement with no worsening of NASH after 48 weeks. This section of the protocol is therefore supplemented with power calculation for this endpoint which has been inserted after the original sample size calculation for MRE.

Statistics in relation to effect of semaglutide on MRE are not present. Hence the below assumptions are based on statistics collected from scientific publications with other treatment effects on MRE[9,38,39].

Table 10-1 Number of randomised subjects needed assuming all subjects completing the trial on treatment and a power of 90% for rejecting the null hypothesis (treatment ratio=1) at the 5% significance level in a 2:1 randomisation scheme.

Treatmentratio	Coefficient of variation			
	0.16	**0.17**	**0.18**	**0.19**
0.87	66	72	81	90
0.86	57	63	69	78
0.85	48	**54**	60	66
0.84	42	48	54	60
0.83	39	42	48	51

Assuming a 2:1 randomisation scheme, a treatment ratio of 0.85 and a coefficient of variation of 0.17, 54 subjects need to complete the 48 weeks of treatment. Hence, assuming 20% withdrawal/prematurely trial product discontinuation in both arms, a total sample size of 68 subjects is needed. To have a number that is divisible with 3, a total number of 69 subjects is needed (46 subjects randomised to semaglutide and 23 randomised to placebo).

It is anticipated that the responder rate for liver fibrosis improvement with no worsening of NASH will be up to 10% for subjects randomised to placebo. The number of placebo responders was 15 (10.4%) of 144 subjects in CENTAUR[40] and 37 (11.9%) of 311 subjects in REGENERATE[41].

There is currently no guidance on minimum treatment effect on histological endpoints that would be considered clinically relevant. [redacted] shows the sensitivity in power f or different responder proportions, assuming 69 subjects complete the 48 weeks of treatment.

Table -10-2 Power for rejecting the null hypothesis of no difference in the proportion between semaglutide s.c. 2.4 mg once-weekly and placebo at 5% significance level in a 2:1 randomisation scheme with total number of subjects equal to 69.

Semaglutide responder proportion	Placebo responder proportion		
	7.5%	**10.0%**	**12.5%**
25.0%	39.7%	28.7%	20.3%
35.0%	73.5%	62.0%	50.6%
45.0%	93.7%	88.2%	80.8%

For example, assuming a semaglutide responder proportion of 35% and a placebo responder proportion of 10% results in a power of 62% for the binary histology endpoint.

10.2 Definition of analysis sets

The full analysis set (FAS) will be used in the analysis of the efficacy endpoints whereas the safety analysis set (SAS) will be used for the safety endpoints.

The FAS includes all randomised subjects. Subjects in the FAS will contribute to the evaluation "as randomised". The SAS includes all subjects receiving at least one dose of randomised treatment. Subjects in the SAS will contribute to the evaluation "as treated".

Observation periods

- In-trial: This period starts on the date of the randomisation visit and ends on the date of the last trial-related procedure/assessment
- On-treatment: For evaluation of AEs and hypoglycaemic episodes, this period starts on the date of first administration of trial product and ends on the date of whatever comes first of: a) last dose of trial product + 49 days (7 half-lives of semaglutide), b) follow-up visit (visit 13), or c) end of the in-trial period.

The statistical analyses of the efficacy endpoints will primarily be based on the in-trial period. The on-treatment period will be used for analyses of safety endpoints.

Missing data

With respect to the primary analysis of the primary endpoint, missing week 48 data will be imputed as no improvement in liver fibrosis.

10.3 Statistical analyses

A statistical analysis plan (SAP) will be written in addition to the protocol, including a more technical and detailed elaboration of the statistical analyses. The SAP will be finalised before first subject, first visit (FSFV). In case, that an interim reporting (see section 10.3.4) is decided then a designated SAP will be produced and finalised before the database lock in relation to the interim.

The estimand addressing the primary objective is the proportion of subjects with liver fibrosis improvement with no worsening of NASH compared between treatment groups at 48 weeks in subjects with NASH and compensated fibrosis stage 4 regardless of adherence to treatment.

Generalisation of this estimand depends among other things on the extent to which treatment adherence in this trial reflects clinical practice.

The statistical analyses will in general consist of the following treatment comparison:

- semaglutide s.c. 2.4 mg once-weekly versus placebo

The results of the comparisons will be presented as estimated treatment contrasts together with two-sided 95% confidence intervals and p-values corresponding to two-sided tests of no difference.

10.3.1 Primary endpoint

The primary endpoint is the binary outcome of at least one stage of liver fibrosis improvement with no worsening of NASH at 48 weeks (yes/no). The analysis will be based on the Cochran-Mantel-Haenszel (CMH) test. The test will adjust for baseline diabetes status (with T2D or without T2D).

The response data will consist of the outcomes of the week 48 biopsy including assessments taken after premature discontinuation of trial product. Missing response data will be imputed as non-responders. This approach does not rely on an assumption of missing at random and should be considered conservative for estimating the treatment effect.

Sensitivity analysis

Analysis using imputation based on unconditional reference: An analysis based on the same type of non-parametric method as for the primary analysis but with missing data handled by an MI method which assumes that the unobserved outcomes are well described by the observed outcomes from subjects in the placebo arm and with similar baseline characteristics. The imputation will be done by random sampling of observed outcomes from subjects with the same baseline diabetes status and

baseline fibrosis stage. 500 replicates of a complete data set will be generated that will then be analysed and the results combined using Rubin's rule to draw inference.

More details will be specified in the SAP.

10.3.2 Secondary endpoints

10.3.2.1 Supportive secondary endpoints

The change in MRE from baseline to 48 week's measurements will be analysed using a MMRM with the log transformed value of MRE (kPa) as the endpoint and with treatment (semaglutide versus placebo), T2D (with T2D or without T2D), body weight (kg) and the log transformed baseline MRE (kPa) as covariates, all nested within weeks (visits) as a factor. T2D (with T2D or without T2D) is included as this is the stratification variable in the randomisation scheme. An unstructured covariance matrix will be used to describe the variability for the repeated measurements for a subject. From this MMRM model the treatment ratio at week 48 will be estimated for semaglutide versus placebo and the corresponding 95% confidence interval and the 2-sided p-value will be calculated together with the estimated geometric means. All measurements from the scheduled visits (from baseline to week 48) will be included in the MMRM.

Subjects without any post-randomisation data for the endpoint will not be included in the analysis.

10.3.3 Exploratory endpoints

Will be described in SAP.

10.3.4 Interim reporting

An interim analysis of the MR scans may be performed at week 24 in order to support internal business decisions in relation to e.g. initiation of a phase 3 programme.

This interim analysis will not affect the continuation of the trial and hence no alpha-spending is considered.

In case the interim analysis is performed, sponsor is unblinded after the interim, whereas investigator and subjects remain blinded for the rest of the trial. Novo Nordisk personnel who will have access to data after the interim will be described in an interim data access plan which, will be finalised before FSFV. No public disclosure of the interim results will be made.

The same MMRM model as used in the primary analysis will be used for analysis of the change in MR-MRE from baseline to 24 weeks. This model is equivalent to an ANOVA model with change in MR-MRE from baseline for the completers after 24 weeks.

10.4 Pharmacokinetic and/or pharmacodynamic modelling

Not applicable for this trial.

11 References

1. The European Parliament and the Council of the European Council. Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the member states relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. 2001.
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12 Appendices

Appendix 1 Abbreviations and Trademarks

ADA	American Diabetes Association
AE	adverse event
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
AUDIT	Alcohol Use Disorders Identification Test
BG	blood glucose
BMI	body mass index
BMS	Bristol-Myers Squibb
BUN	blood urea nitrogen
CKDEPI	Chronic Kidney Disease Epidemiology Collaboration
CI	confidence interval
Cmax	maximum concentration
CRF	case report form
CRN	Clinical Research Network
CTR	clinical trial report
DFU	direction for use
DILI	drug induced liver injury
DNA	deoxyribonucleic acid
DUN	dispensing unit number
ECG	electrocardiogram
eCRF	electronic case report form
EGD	esophagogastroduodenoscopy
eGFR	estimated glomerular filtration rate
ELF	enhanced liver fibrosis
EOT	end of treatment
F4	fibrosis stage 4
FAS	full analysis set

FDA	U.S. Food and Drug Administration
FDAAA	FDA Amendments Act
FPG	fasting plasma glucose
FSFV	first subject first visit
FSH	follicle-stimulating hormone
FU	follow-up
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GLP-1	glucagon-like-peptide-1
GLP-1 RA	glucagon-like-peptide-1-receptor agonist
HbA1c	glycated haemoglobin
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HDL	high density lipoprotein
HIV	human immunodeficiency virus
HOMA-IR	homeostatic model assessment – insulin resistance
HRT	hormone replacement therapy
hsCRP	high-sensitivity C-reactive protein
IB	investigator's brochure
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	independent ethics committee
IMP	investigational medicinal product
INR	international normalized ratio
IRB	institutional review board
IU	International Unit
IWRS	interactive web response system
KDIGO	Kidney Disease Improving Global Outcomes (organisation)
LDL	low-density lipoprotein
MELD	model for end-stage liver disease

MMRM	mixed model for repeated measures
MR	magnetic resonance
MRE	magnetic resonance elastography
MR-MRE	magnetic resonance – magnetic resonance elastography
MRI	magnetic resonance imaging
MRI-PDFF	magnetic resonance imaging - Proton density fat fraction
MTC	medullary thyroid cancer
Na	sodium
NAFLD	non-alcoholic fatty liver disease
NAS	NAFLD activity score
NASH	non-alcoholic steatohepatitis
P	phone visit
PCD	primary completion date
PG	plasma glucose
PK	pharmacokinetic
PP	per protocol
Pro-C3	type III collagen formation
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
s.c.	subcutaneous
SGLT-2	sodium-glucose co transporter 2
SIF	safety information form
SMPG	self-measured plasma glucose
SU	sulphonylurea
SUSAR	suspected unexpected serious adverse reaction
T2D	type 2 diabetes
TMM	trial materials manual
V	visit
UNL	upper normal limit

UTN	universal trial number
VLDL	very low density lipoprotein
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 or laboratory sub-contracted by central laboratory.
- Urine pregnancy tests will be supplied by the central laboratory. The test will be performed at the site.
- Laboratory samples specified in the protocol must be sent to the central laboratory for analysis. Semaglutide plasma concentration and some explorative biomarkers will be analysed at a specialised 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 and measurement of amylase and lipase in suspicion of acute pancreatitis, this must be done at a local laboratory.
- The laboratory equipment may provide analyses not requested in the protocol but produced automatically in connection with the requested analyses according to specifications in the laboratory standard operating procedures. Such data will not be transferred to the trial database, but abnormal values will be reported to the investigator.
- 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.
- Human biosamples for future analysis will be stored as described in Appendix 7.

Table 12-1 Protocol-required efficacy laboratory assessments

Laboratory assessments	Parameters
Exploratoy biomarkers	• Pro-C3 (collagen marker) • ELF • Adiponectin • hsCRP
Other tests	• Biosamples for future analysis • Semaglutide plasma concentration

Table 12-2 Protocol-required safety laboratory assessments

Laboratory assessments	Parameters
Haematology	• Erythrocytes • Haematocrit • Haemoglobin • Leucocytes • Thrombocytes
Biochemistry[1]	• Alanine Aminotransferase (ALT) • Albumin • Alkaline phosphatase

	• Amylase • Aspartate Aminotransferase (AST) • Calcium • Creatinine • Creatinine kinase • Gamma-Glutamyl Transferase (GGT) • HOMA-IR • Lipase • MELD-Na-score • MELD-score • Potassium • Sodium • Total bilirubin (+ direct bilirubin) • Urea/BUN
Coagulation parameter	• INR
Lipids	• Cholesterol • High density lipoprotein (HDL) cholesterol • Low density lipoprotein (LDL) cholesterol • Very-low density lipoprotein (VLDL) cholesterol • Triglycerides • Free fatty acid
Hormones	• Calcitonin at screening only
Serology	• HIV 1 antibody at screening only • HIV 2 antibody at screening only • HIV antigen at screening only • Hepatitis B surface antigen (HBsAg) at screening only • Hepatitis C virus antibody at screening only
Pregnancy Testing for women of childbearing potential	• Serum human chorionic gonadotropin (hCG) pregnancy test at V1, V2, V8, V10, V12. Urine hCG pregnancy test at V4, V6, V9, V11 and V13 for women of childbearing potential
Other tests	• eGFR calculated by the central laboratory based on the creatinine value using the CKD-EPI equation
Glucose metabolism	• HbA1c • Fasting Plasma Glucose (FPG)[2] • C-peptide
Notes : [1]Details of required actions and follow-up assessments for increased liver parameters including any discontinuation criteria are given below, in Appendix 4 (potential Hy's Law) and Section 8.1. [2]A FPG result ≤ 3.9 mmol/L (70 mg/dL) in relation to planned fasting visits should not be reported as a hypoglycaemic episode but as an AE at the discretion of the investigator (Appendix 4). A FPG result >16.7 mmol/L (300 mg/dL) should be reported as an AE at the discretion of the investigator (Appendix 4).	

The results of plasma concentrations of semaglutide will not be provided to the investigator, as these results will not be used for any clinical evaluation during the trial and would potentially unblind the treatment.

Exploratory biomarker results and HOMA-IR will not be provided to the investigator, as these results will not be used for any clinical evaluation during the trial.

Assessments in case of increased levels of liver blood parameters

Temporary discontinuation of trial drug should be considered in case any of the below criteria is met:

- ALT or AST > 8 x UNL
- Total bilirubin > 2.0 mg/dl
- INR > 1.6

Trial product must be temporarily discontinued in case any of the below criteria is met:

- ALT or AST > 3x UNL and total bilirubin > 2x UNL, where no alternative aetiology exists (Potential Hy's Law) (see Appendix 4).
- ALT or AST increase to > 5x baseline value in subjects where the baseline ALT or AST were < 2x UNL.
- ALT or AST increase to > 3x baseline value or > 300 U/L, whichever occurs first, in subjects where the baseline values were ≥ 2x UNL but < 5x UNL.
- Bilirubin increase accompanied by signs and symptom(s) compatible with drug induced liver injury (DILI) such as rash, eosinophilia, nausea, vomiting, or right upper quadrant pain, regardless of the transaminase concentrations.

Event must be reported according to Appendix 4.

For all such events repeat testing must occur within 48 to 72 hours and work up for competing etiologies must be performed[42] including:

- Complete liver profile including ALT, AST, alkaline phosphatase, total bilirubin and INR. Hereafter, repeat testing should be done 2 to 3 times weekly. If close monitoring is not possible the trial drug should be discontinued. The frequency of retesting can decrease to once a week or less if abnormalities stabilise and the subject is asymptomatic.
- A detailed history of symptoms and prior or concurrent diseases.
- History of concomitant drug use (including non-prescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- Ruling out acute viral hepatitis; autoimmune or alcoholic hepatitis; hypoxic/ischemic hepatopathy; and biliary tract disease.
- Obtaining a history of exposure to environmental chemical agents.

Trial drug can be restarted if an alternative etiology is definitively identified and liver blood parameters have returned to pre-event levels.

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[43] and applicable ICH Good Clinical Practice (GCP) Guideline[44]
  - 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.

2) Financial disclosure

Investigators and subinvestigators will provide Novo Nordisk with sufficient, accurate financial information as requested to allow Novo Nordisk to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the trial and one year after completion of the trial.
For US trial sites: verification under disclosures per Code of Federal Regulations (CFR) of Financial Conflict of Interest.

3) Informed consent process

- The investigator or his/her representative will explain the nature of the trial to the 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.
- The subject will be presented with two informed consent forms – a main mandatory inform consent form to consent to the trial and an optional inform consent form for biosamples for future analysis.
- Subjects will be required to sign and date a statement of informed consent that meets the requirements of local regulations, ICH guidelines[44], Declaration of Helsinki[43] 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

Sites 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.

Initiatives for subject retention will be instituted for this trial. These may include retention activities, materials and items, if locally acceptable. The retention items will be relevant for the subjects' participation in the trial and /or their disease.

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.

United Kingdom: For country specific requirements see Appendix 9.

6) Committee structure

Novo Nordisk safety committee

Novo Nordisk will constitute an internal semaglutide safety committee to perform ongoing safety surveillance. The semaglutide 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(s)) 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[45].

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[45].

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)[46], the Food and Drug Administration Amendment Act (FDAAA)[47], European Commission Requirements[48, 49] 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) + 48 weeks corresponding to visit 12. If the last subject is withdrawn early, the PCD is considered the date when the last subject would have completed visit 12. 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.
- For some data both electronic and paper CRFs are used.

- 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 e.g. the diaries 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.
- 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 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

Spain: For country specific requirements see Appendix 9.

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 subinvestigator for the trial, must be responsible for all trial-related medical decisions.

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

The investigator will take all necessary technical and organisational safety measures to prevent accidental or wrongful destruction, loss or deterioration of data. The investigator will prevent any unauthorised access to data or any other processing of data against applicable law. 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.

Novo Nordisk may pay additional costs incurred in relation to assessments relevant for following the safety of the subject. Investigator must contact Novo Nordisk on a case by case basis for whether the costs will be covered.

Novo Nordisk accepts liability in accordance with:

France: For country specific indemnity statements see Appendix 9.

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. • Abuse: Persistent or sporadic, intentional excessive use of medical product, which is accompanied by harmful physical or psychological effects (e.g. overdose with the intention to cause harm). • Misuse: Situation where the medicinal product is intentionally and appropriately used not in accordance with the protocol or the terms of the marketing authorization. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • Signs, symptoms or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms or the clinical sequelae of a suspected overdose of trial product regardless of intent.
Events NOT meeting the AE definition
• Pre-existing conditions, anticipated day-to-day fluctuations of pre-existing conditions, including those identified during screening or other trial procedures performed before exposure to trial product. Note: pre-existing conditions should be recorded as medical history/concomitant illness. • Pre-planned procedures, unless the condition for which the procedure was planned has worsened from 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 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 (potential Hy's law).

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

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-RA drug class as well as regulatory requirements.

Event type	Description
Acute gallbladder disease	Events of symptomatic acute gallbladder disease (including gallstones and, cholecystitis)
Hepatic event	• ALT or AST >8xUNL • Total bilirubin > 2.0 mg/dl • INR > 1.6 • ALT or AST > 3x UNL and total bilirubin > 2x UNL, where no alternative aetiology exists (potential Hy's Law) • ALT or AST increase to > 5x baseline value in subjects were the baseline ALT or AST were < 2x UNL • ALT or AST increase to > 3x baseline value or > 300 U/L, whichever occurs first, in subjects were the baseline values were ≥ 2x UNL but < 5x UNL. • Bilirubin increase accompanied by signs and symptom(s) compatible with drug induced liver injury (DILI) such as rash, eosinophilia, nausea, vomiting, or right upper quadrant pain, regardless of the transaminase concentrations.

	• Model For End-Stage Liver Disease (MELD) score ≥ 15 or MELD-Na ≥ 12 • Liver transplant • Ascites requiring medical intervention • Gastroesophageal variceal bleeding • Hepatic encephalopathy • Spontaneous bacterial peritonitis • Hepatic events leading to trial product discontinuation
Malignant neoplasms	Malignant neoplasm, including hepatocellular carcinoma, by histopathology or other substantial clinical evidence
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.
Diabetic retinopathy	New onset or worsening of diabetic retinopathy
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. Note: Use of wrong dispensing unit number (DUN) is not considered a medication error unless it results in confirmed administration of wrong drug. • Wrong route of administration, such as intramuscular instead of subcutaneous. • Accidental administration of higher dose than intended. 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. Drug pauses will not to be reported as a medication error.

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.

- 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, if 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 sequelae 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, if available.

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 in an encrypted manner by e-mail or fax/courier.
- Initial notification via telephone is acceptable, although it does not replace the need for the investigator to complete the AE and safety information form within the designated reporting time frames (as illustrated in Figure 9-1):
  - AE form within 24 hours.
  - Safety information form within 5 calendar days.
  - Both forms must be signed within 7 calendar days.

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

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 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 [b] • 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 [b] • 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 Failure rates may differ from 1% per year, if not 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 49 days after the last dose of trial product.

Pregnancy testing

- WOCBP should only be included after a negative highly sensitive serum pregnancy test.
- Pregnancy testing should be performed at every site visit during the treatment period according to the flowchart and Appendix 2.
- Additional urine pregnancy testing should be performed at monthly intervals during the treatment period, if required locally (Appendix 9).
- Pregnancy testing should be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.
- WOCBP needs the last urine pregnancy test at FU visit. If the FU visit is a phone contact, the subjects can take the urine test at home and inform the investigator of the result.

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 Figure 9-3. 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 Retention of human biosamples

Biosamples for future analysis

- The trial will involve collection of human biosamples to be stored in a central archive. Subjects who do not wish to contribute with biosamples for storage may still participate in the trial.
- Subjects must sign and date a separate informed consent form before biosamples are collected to be stored for future analysis.
- The material to be collected is blood and liver tissue.
- Blood will be collected at screening (visit 1), week 24 (visit 10), and week 48 (visit 12/12A). Liver tissue will be collected at screening (visit 1) and week 48 (visit 12/12A). The liver tissue will be taken from the liver biopsy obtained for the main trial, no additional liver biopsy will be obtained.
- Biosamples will be used to improve the understanding of NASH, mechanism of action and disease aetiology. Biosamples may also be used to identify disease sub-populations such as high-responders or subjects prone to adverse events. The analysis of biosamples may include DNA and RNA sequencing, epigenetic analysis and other methods in 'omics' used to characterise the disease. As new knowledge may arise related to NASH and semaglutide during the conduct of the trial, the analyses of the stored biosamples may include biomarkers presently not known, which have not been included up-front in the scientific hypotheses of this trial.
- The biosamples will be stored at a central laboratory for up to 15 years after end of trial. Only Novo Nordisk staff and personnel from the central laboratory will have access to the stored specimens. The biosamples may be transferred to other countries for analysis and will be destroyed at the latest 15 years after end of trial.
- Subject's identity will remain confidential and the samples will be identified only by subject number, visit number and trial identification number. No direct identification of the subject will be stored together with the samples.
- The subject may request the stored biosamples to be destroyed by withdrawing the designated informed consent. The results obtained from any already performed analyses of the samples will still be used.
- In the event that the collected biosamples (serum, plasma, liver biopsy samples) will be used in the future, the investigator will become directly informed by Novo Nordisk about the results, if the findings are deemed clinically relevant and analytically valid and quantifiable. In such case, a written summary of the findings, including listings of subject specific values, will be provided once a firm conclusion from the results has been drawn by Novo Nordisk. Potentially, observations of neoplastic diseases, serious hereditary diseases, other un-treatable diseases or any other abnormal findings could be part of the observations. Subjects can contact the investigator if they wish to be informed about results derived from stored biosamples obtained from their own body.

Appendix 8 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)[50]. 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[51]:

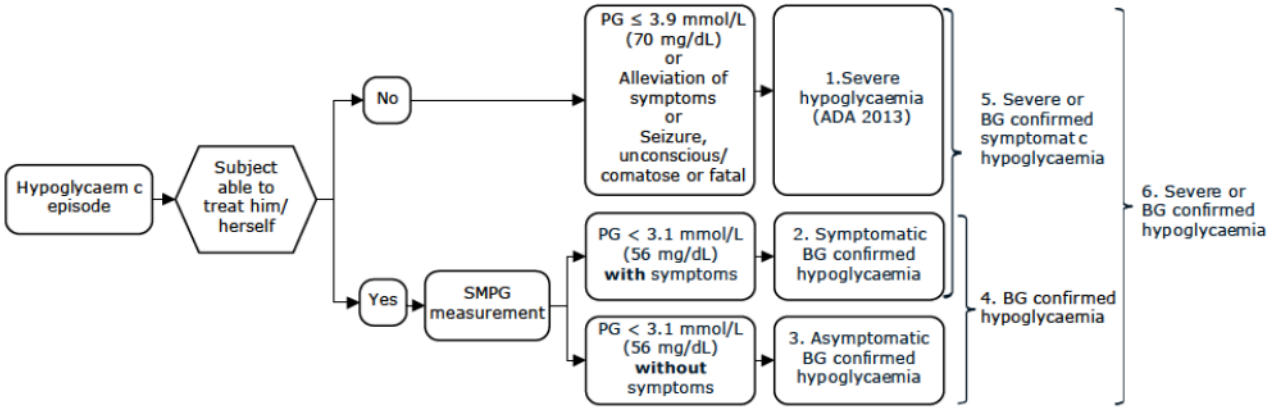
1. Severe hypoglycaemia according to the ADA classification[51].
2. Symptomatic BG confirmed hypoglycaemia: An episode that is BG confirmed by PG value <3.1 mmol/L (56 mg/dL) **with** symptoms consistent with hypoglycaemia.
3. Asymptomatic BG confirmed hypoglycaemia: An episode that is BG confirmed by PG value <3.1 mmol/L (56 mg/dL) **without** symptoms consistent with hypoglycaemia.
4. BG confirmed hypoglycaemia: The union of 2. and 3.
5. Severe or BG confirmed symptomatic hypoglycaemia: The union of 1. and 2.
6. 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[51] of hypoglycaemia

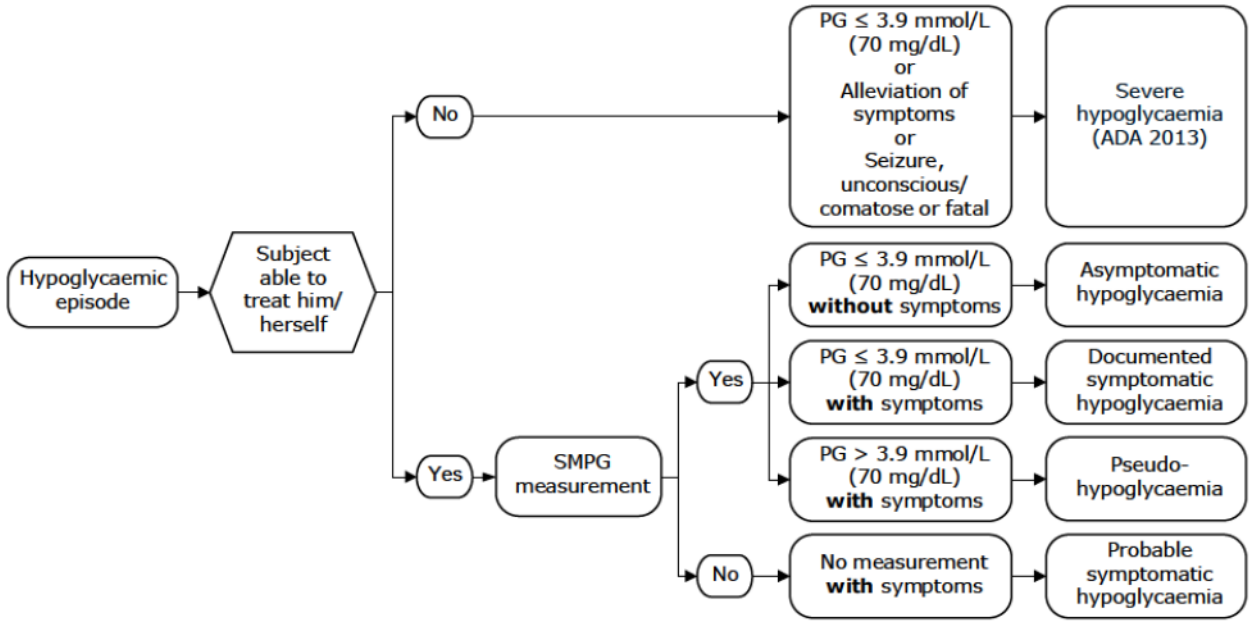
- Severe hypoglycaemia: An episode requiring assistance of another person to actively administer carbohydrate, glucagon or take other corrective actions. PG concentrations may not be available during an event, but neurological recovery following the return of PG to normal is considered sufficient evidence 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[51].

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 a 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), then investigator should report the hypoglycaemic episode directly in the CRF.

Upon onset of a hypoglycaemic episode the subject is recommended to measure PG every 15 minutes until the SMPG value is >3.9 mmol/L (70 mg/dL) and/or symptoms have been resolved in accordance with current guidelines[51].

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[51].

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[52, 53].

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 9 Country-specific requirements

Section 2 Flowchart

- **For Germany:** Subject's full Date of Birth is not allowed to be collected and must be shortened to Year of Birth.
- **For France:** Collection of race (Black/other) and age is needed for the calculation of eGFR (CKD-EPI)[36]. For France the race will not be collected in the CRF.

Section 9.4.6 Eye examination

- **For Germany:** In Germany the eye examination must be performed by an ophthalmologist.

Appendix 3, 5 Data protection

- **For United Kingdom:** The IRB/IEC do not have access to the patients' medical records.

Appendix 3, section 11 Retention of clinical trial documentation

- **For Spain:** Records and documents, including signed informed consent forms, pertaining to the conduct of this trial must be retained by the investigator for 25 years after end of trial.

Appendix 3, section 14 Indemnity statement

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

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