Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
NCT number	NCT02970942
Sponsor trial ID:	NN9931-4296
Official title of study:	Investigation of efficacy and safety of three dose levels of subcutaneous semaglutide once daily versus placebo in subjects with non-alcoholic steatohepatitis
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16.1.1 Protocol and protocol amendments

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Protocol

Trial ID:NN9931-4296

Investigation of efficacy and safety of three dose levels of subcutaneous semaglutide once daily versus placebo in subjects with non-alcoholic steatohepatitis

A 72-week randomised, double-blind, placebo-controlled, six-armed parallel group, multi-centre, multinational trial

Redacted protocol
Includes redaction of personal identifiable information only.

Trial phase: Phase 2

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ClinOps 2, GLP-1 and Obesity

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List of abbreviations

ADA	American Diabetes Association
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUDIT	Alcohol Use Disorders Identification Test
BMI	body mass index
CAP	controlled attenuation parameter
CK-18	cytokeratin 18
CLAE	clinical laboratory adverse event
CMH	Cochran-Mantel-Haenszel
CRF	case report form
CRN	Clinical Research Network
CTR	clinical trial report
DUN	dispensing unit number
EAC	event adjudication committee
ECG	electrocardiogram
eCRF	electronic case report form
ELF	enhanced liver fibrosis
FAS	full analysis set
FGF-21	fibroblast growth factor 21

Fib-4	fibrosis 4
FPG	fasting plasma glucose
FSFV	first subject first visit
GCP	Good Clinical Practice
GGT	gamma glutamyltransferase
GLP-1	glucagon-like peptide-1
GLP-1 RA	glucagon-like peptide-1 receptor agonist
HbA_{1c}	glycosylated haemoglobin A1c
hCG	human chorionic gonadotrophin
HCV-RNA	hepatitis C virus Ribonucleic acid
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
HOMA-IR	homeostatic model assessment - insulin resistance
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IEC	independent ethics committee
IL-1R	interleukin-1 receptor
IMP	investigational medicinal product

INR	international normalized ratio
IRB	institutional review board
IWRS	interactive web response system
LDL	low-density lipoprotein
LLOQ	lower limit of quantification
LSLV	last subject last visit
MCP-1	monocyte chemoattractant protein 1
MedDRA	Medical Dictionary for Regulatory Activities
MELD	model for end-stage liver disease
MI	myocardial infarction
miR-122	microRNA 122
NAFLD	non- alcoholic fatty liver disease
NAS	NAFLD activity score
NASH	non- alcoholic steatohepatitis
NFS	NAFLD fibrosis score
NOAEL	no observable adverse effect level
PG	plasma glucose
PRO	patient reported outcome
SAE	serious adverse event
SAF	steatosis-activity-fibrosis
SAP	statistical analysis plan
SAS	safety analysis set

s.c.	subcutaneous(ly)
SF-36	short form 36
SGLT-2	sodium–glucose cotransporter 2
SMPG	self-measured plasma glucose
SUSAR	suspected unexpected serious adverse reaction
T2D	type 2 diabetes
TMM	trial materials manual
TSH	thyroid-stimulating hormone
UNL	upper normal limit
UTN	universal trial number
VLDL	very low density lipoprotein

1 Summary

Objectives and endpoints:

Primary objective

To compare the effect of semaglutide subcutaneous (s.c.) once daily versus placebo on histological resolution of non-alcoholic steatohepatitis (NASH).

Primary endpoint

- NASH resolution without worsening of fibrosis after 72 weeks (yes/no)

Key secondary objectives

- To investigate the dose-response relationship of three dose levels of semaglutide s.c. once daily (0.1 mg/day, 0.2 mg/day and 0.4 mg/day) on histological resolution of NASH.
- To compare the effects of semaglutide s.c. once daily to placebo on liver-related histological parameters and biomarkers of NASH disease.

Key secondary endpoints

- At least one stage of liver fibrosis improvement with no worsening of NASH after 72 weeks (yes/no) (worsening defined as an increase of at least one stage of either lobular inflammation or hepatocyte ballooning according to NASH clinical research network (CRN) criteria).

Change from baseline to week 72 in:

- Non-alcoholic fatty liver disease (NAFLD) activity score (NAS) (0-8)
- Stage of fibrosis according to the Kleiner fibrosis classification (0-4)
- Activity component of steatosis-activity-fibrosis (SAF) score (0-4)
- Fasting plasma glucose (FPG)
- Glycosylated haemoglobin A1c (HbA_{1c})
- Serum enhanced liver fibrosis (ELF)

Trial design:

This is a 72-week, randomised, double-blind, placebo-controlled, six-armed, parallel group, multi-centre, multi-national trial comparing once daily administration of semaglutide s.c. in three different doses (0.1 mg, 0.2 mg and 0.4 mg) with placebo in subjects with NASH. Subjects will be randomised in a 3:3:3:1:1:1 manner to receive daily dosing of semaglutide s.c. 0.1 mg, 0.2 mg, 0.4 mg or corresponding injection volumes of placebo once daily. To avoid bias in the assessment of the different semaglutide doses, the trial will be double-blinded within dose levels. The dose levels

will not be blinded between each other because of different dose escalations and different target doses and volumes required.

The total trial duration for the individual subject will be up to 85 weeks (maximum).

Randomisation will be stratified in five strata based on region (Japanese or non-Japanese) and, within the non-Japanese group, based on diabetes status at screening (with or without type 2 diabetes) and fibrosis stage for baseline liver biopsy (F2 or F3).

Trial population:

A total of 372 subjects are planned to be randomised. Based on an assumption of a 50% screening failure rate, 744 subjects are planned to be screened.

Key inclusion criteria

- 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.
- Male or female, aged 18-75 years (both inclusive) (for Japan: male or female aged 20-75 years (both inclusive)) at the time of signing informed consent.
- Local histological diagnosis of NASH followed by histological confirmation of NASH based on central pathologist evaluation of a liver biopsy obtained up to 21 weeks before screening.
- A histological NAS $\geq$ 4 with a score of 1 or more in each sub-component of the score based on central pathologist evaluation.
- NASH fibrosis stage 2 or 3 according to the NASH CRN fibrosis staging system based on central pathologist evaluation.

Key exclusion criteria

- Known or suspected abuse of alcohol (> 20 g/day for women or > 30 g/day for men), alcohol dependence* or narcotics. (* = assessed by the Alcohol Use Disorders Identification Test (AUDIT questionnaire)).
- Diagnosis of type 1 diabetes according to medical records.
- HbA_{1c} > 9% at screening.
- History or presence of pancreatitis (acute or chronic).
- Calcitonin $\geq$ 50 ng/L at screening.
- Family or personal history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma. Family is defined as a first degree relative.
- Body Mass Index (BMI) $\leq$ 25.0 or $\geq$ 45.0 kg/m^2 at the screening visit.

- Female who is pregnant, breast-feeding or intends to become pregnant or is of childbearing potential and not using an adequate contraceptive method (adequate contraceptive measures as required by local regulation or practice).

Assessments:

Efficacy

- Liver biopsy
- Liver enzymes (alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyltransferase (GGT))
- Fibroscan® measurements (liver stiffness and liver steatosis (with controlled attenuation parameter (CAP)))
- HbA_{1c}
- Body measurements (body weight in kg)
- Lipids (Total cholesterol, free fatty acids, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, very low density lipoprotein (VLDL) cholesterol)

Safety

- Adverse events
- Pulse
- Biochemistry and haematology
- Antibodies against semaglutide

Trial products:

The following trial products will be supplied by Novo Nordisk A/S:

- Semaglutide 1.0 mg/ml, solution for injection, 3.0 ml cartridge, for NovoPen® 4
- Semaglutide placebo, solution for injection, 3.0 ml cartridge, for NovoPen® 4

[redacted]

1.0

2 Flow chart

Trial Periods	Screening	Randomisation	Dose escalation/Maintenance period															EOT	FU	Trial product discontinuation 72 weeks FU[1]
Visit number	V1	V2	P3	V4	P5	V6	P7	V8	P9	V10	P11	V12	V13	V14	V15	V16	V17	V18	V19	V19A
Weeks in relation to visit 2	-6	0	2	4	6	8	10	12	14	16	18	20	28	36	44	52	62	72	79	72
Visit window, days	±7		±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±7	±7	±7	±7	±7	±7	-7	±7
SUBJECTS																				
Informed consent	x																			
In/exclusion criteria	x	x																		
AUDIT questionnaire	x																			
Medical history/ Concomitant illness	x																			
Concomitant medication	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Demography	x																			
Tobacco use	x																			
Hypoglycaemia unawareness	x[13]																			
Childbearing potential	x[14]																			
Criteria for premature discontinuation of trial product			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
EFFICACY																				
Height	x																			

Trial Periods	Screening	Randomisation	Dose escalation/Maintenance period															EOT	FU	Trial product discontinuation 72 weeks FU[1]
Visit number	V1	V2	P3	V4	P5	V6	P7	V8	P9	V10	P11	V12	V13	V14	V15	V16	V17	V18	V19	V19A
Weeks in relation to visit 2	-6	0	2	4	6	8	10	12	14	16	18	20	28	36	44	52	62	72	79	72
Visit window, days	±7		±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±7	±7	±7	±7	±7	±7	-7	±7
Body weight	x	x		x				x				x	x	x	x	x	x	x		x
Waist circumference		x		x				x				x	x	x	x	x	x	x		x
SF-36 questionnaire		x											x			x		x		x
Vital signs		x		x		x		x		x		x	x	x	x	x	x	x		x
Biochemistry	x	x		x				x				x	x	x	x	x	x	x		x
Fasting plasma glucose		x		x				x				x	x	x	x	x	x	x		x
HbA_{1c}	x	x		x				x				x	x	x	x	x	x	x		x
Fasting insulin and glucagon		x		x				x				x	x	x	x	x	x	x		x
Lipids		x		x				x					x			x		x		x
Liver biopsy	x[2]																	x[4]		x
Fibroscan®[3]		x											x			x		x[5]		x
Exploratory biomarkers[6]		x											x			x		x		x
SAFETY																				
ECG		x											x					x		x
Physical examination	x																	x		x
Haematology		x		x				x					x	x		x		x		x

Trial Periods	Screening	Randomisation	Dose escalation/Maintenance period															EOT	FU	Trial product discontinuation 72 weeks FU[1]
Visit number	V1	V2	P3	V4	P5	V6	P7	V8	P9	V10	P11	V12	V13	V14	V15	V16	V17	V18	V19	V19A
Weeks in relation to visit 2	-6	0	2	4	6	8	10	12	14	16	18	20	28	36	44	52	62	72	79	72
Visit window, days	±7		±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±7	±7	±7	±7	±7	±7	-7	±7
INR	x	x		x				x				x	x	x	x	x	x	x		x
Hepatitis B and C	x																			
HIV antigen/antibody screening test	x																			
TSH	x																			
Calcitonin	x	x		x						x		x	x	x	x	x	x	x		x
Pregnancy test[11]	x	x		x		x[12]		x		x		x	x	x	x	x	x	x	x[12]	
Anti-semaglutide antibodies[7]		x		x		x		x					x	x		x		x[8]	x	
Adverse events		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Hypoglycaemic episodes			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Technical complaints			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
OTHER ASSESSMENTS																				
Semaglutide plasma concentration				x		x		x		x		x	x	x		x		x[8]	x	
Biosamples for future analysis		x											x			x		x		x
Nutritional and physical		x		x		x		x		x		x	x	x	x	x	x	x	x	x

Trial Periods	Screening	Randomisation	Dose escalation/Maintenance period															EOT	FU	Trial product discontinuation 72 weeks FU[1]
Visit number	V1	V2	P3	V4	P5	V6	P7	V8	P9	V10	P11	V12	V13	V14	V15	V16	V17	V18	V19	V19A
Weeks in relation to visit 2	-6	0	2	4	6	8	10	12	14	16	18	20	28	36	44	52	62	72	79	72
Visit window, days	±7		±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±7	±7	±7	±7	±7	±7	-7	±7
activity counselling																				
TRIAL MATERIAL																				
Dispensing visit		x[9]		x		x		x		x		x	x	x	x	x	x			
Drug accountability		x		x		x		x		x		x	x	x	x	x	x	x		
IWRS session	x	x		x		x		x		x		x	x	x	x	x	x	x		
REMINDERS																				
Hand out ID card	x																			
Hand out and instruct in BG-meter use[10]		x																		
Training in trial product and pen handling		x		x										x						
Handout and instruct in subject diary		x		x		x		x		x		x	x	x	x	x	x	x		
Collect subject diary and record in eCRF				x		x		x		x		x	x	x	x	x	x	x	x	
Attend visit fasting		x		x				x				x	x	x	x	x	x	x	x	x

Abbreviations: P = Phone visit, V = Clinic visit, ECG = Electrocardiogram, FU = follow-up, IWRS = interactive web response system, SF-36 = Short Form 36, HbA1c = glycosylated haemoglobin, BG-meter = blood glucose meter, EOT = End of treatment

1) **Subjects prematurely discontinuing trial product should attend an end of treatment visit (V18) as soon as possible and a follow-up visit 7 weeks thereafter (visit 19). In addition they should follow the trial visit schedule as planned and attend the trial product discontinuation 72 weeks FU visit 72 weeks after randomisation. However the following should not be done after visit 19 for subjects prematurely discontinuing trial product: Semaglutide plasma concentration, anti-semaglutide antibody assessment, hypo reporting and handing out subject diaries.**
2) **A liver biopsy obtained 21 weeks or less before screening (visit 1) can be used. For subjects with no historical liver biopsy within 21 weeks prior to screening, a liver biopsy must be performed during the screening period.**
3) **In selected countries only at sites with Fibroscan® equipment available.**
4) **For subjects prematurely discontinuing trial product treatment, no biopsy at end of treatment visit (V18). Biopsy will be at visit 19A (trial product discontinuation 72 weeks FU).**
5) **For subjects prematurely discontinuing trial product treatment, no Fibroscan® assessment at end of treatment visit (V18). Fibroscan® will be at visit 19A (trial product discontinuation 72 weeks FU).**
6) **Exploratory biomarkers are: CK-18 fragments, ELF, miR-122, IL-1R antagonist, MCP-1, FGF-21.**
7) **Blood samples for measurement of anti-semaglutide antibodies must be drawn prior to trial product dose.**
8) **For subjects prematurely discontinuing trial product treatment a follow-up antibody sample and semaglutide plasma concentration sample must in addition to at the end of treatment vist (V18) be taken 7 weeks thereafter (visit 19).**
9) **Hand out directions for use**
10) **Only applicable for subjects with type 2 diabetes**
11) **For women of childbearing potential: urine pregnancy test should be performed at any time during the trial if a menstrual period is missed, or as required by local law**
12) **At these visits, urine pregnancy test will be performed**
13) **Only applicable for subjects with type 2 diabetes**
14) **Only applicable for female subjects**

3 Background information and rationale for the trial

The trial will be conducted in compliance with this protocol, ICH GCP[1] and applicable regulatory requirements, and in accordance with the Declaration of Helsinki[2].

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

3.1 Background information

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[3]. It is estimated that 70-90% of patients with obesity have some degree of steatosis, with the prevalence increasing with the severity of obesity. To that end, NAFLD is the most common chronic liver disorder in Western countries and in the USA 30% of the adult population suffers from NAFLD[4] [5]. Obesity is associated with an increased risk of NAFLD, the risk increasing with increasing BMI[6]. Furthermore the risk rises to as much as 70-75% in patients with type 2 diabetes (T2D)[7]. NASH represents a more advanced form of NAFLD and is reported in 3-5% of the Western population[8]. The prevalence of NASH is ~12% and ~22% in patients with obesity and T2D, respectively[9]. The incidence and prevalence of NASH is rising and it is estimated that 20-30% of patients with simple steatosis develop NASH[10]. Persistent inflammation can lead to the formation of fibrous scar tissue in the liver, which eventually causes cirrhosis and in some cases hepatocellular carcinoma[11].

An estimated 10% of patients with NASH develop cirrhosis[12]. Obesity-induced NASH leading to liver cirrhosis is the third most common cause of liver transplantation in the USA today and expected to be the primary cause of liver transplantation in 2030[13] [14] [15]. The pathophysiology of NASH is not well understood, but weight gain, insulin resistance, T2D and hypertension are all recognised as key factors[16].

In most patients NASH is asymptomatic, but non-specific symptoms such as right upper quadrant discomfort or fatigue can occur. Often, NASH is first suspected on the basis of elevated liver enzymes found at routine medical health checks or incidentally by imaging or bariatric surgery. Liver enzymes (e.g. alanine aminotransferase) are elevated in 50-80% of cases and typically around 1.5 times the upper limit of the normal[17].NASH is a histological diagnosis based on liver biopsy together with clinical exclusion of consumption of >20 g ethanol/day for women and >30g ethanol/day for men[18]. Histologically, NASH is defined by the presence of steatosis, lobular inflammation, portal inflammation, cellular ballooning and varying degrees of fibrosis. The degree of fibrosis is described by the Kleiner fibrosis staging system, ranging from F0 (absence of fibrosis), F1 (portal/perisinusoidal fibrosis), F2 (perisinusoidal and portal/periportal fibrosis), F3 (septal or bridging fibrosis) through F4 (cirrhosis)[19]. Several non-invasive biomarkers are available

for the assessment NASH and liver fibrosis, however, there are currently no non-invasive methods for diagnosis or assessment of disease prognosis approved for regulatory pivotal trials[20].

Currently, no drugs are approved for the treatment of NASH. First-line treatment is lifestyle intervention to achieve weight loss and treatment of comorbidities (e.g. hyperlipidaemia, hypertension and diabetes). In the case of progression to cirrhosis and liver failure, liver transplantation is the only treatment option. The current sparse epidemiological information on progression rates and predictive factors has limited the ability to calculate risk and possible benefit of treatments[21].

3.1.1 Glucagon-like peptide-1

Glucagon-like peptide-1 (GLP-1) is an incretin hormone secreted from the L-cells in the small intestine. GLP-1 has a glucose-dependent stimulatory effect on insulin and inhibitory effect on glucagon secretion from the pancreatic islets (i.e. when plasma glucose levels are above normal)[22] [23]. Furthermore, GLP-1 is a physiological regulator of appetite and food intake and GLP-1 receptors are present in several areas of the brain involved in appetite regulation. Physiologically, GLP-1 has a pronounced inhibitory effect on gastric emptying; however this effect seems to diminish upon chronic exposure[24] [25] [26]. Endogenous GLP-1 has a very short elimination half-life of <1.5 minutes after intravenous administration due to rapid degradation by ubiquitous dipeptidyl peptidase (DPP 4)[27]. Development of a GLP-1 receptor agonist (GLP-1 RA) with longer half-life has been necessary to enable effective treatment option for T2D and obesity.

Both human and animal studies have shown a beneficial effect of GLP-1 RA including liraglutide on liver lipid metabolism and progression of fatty liver to NASH [28] [29] [30] [31]. 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[29] [32]. Semaglutide effectively lowers body weight and have been shown to indirectly increase insulin sensitivity[31] [33] [34]. Additionally, semaglutide also increase insulin and lower glucagon levels, all of which may be beneficial in patients with NASH. Other mechanisms of actions based on the GLP-1 biology are anti-inflammation and lipid lowering effects[29].

In the liraglutide phase 3 programme for treatment of T2D, 50% of the more than 4000 subjectss had elevated ALT at baseline. Compared to placebo, liraglutide dose-dependently reduced ALT in these patients suggesting an improvement of hepatic steatosis[35].

The investigator sponsored study Liraglutide Efficacy and Action in NASH (LEAN), enrolled 52 overweight subjects with and without T2D, with biopsy-confirmed NASH to receive once daily liraglutide s.c or placebo. 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 [95% CI 1·0–17·7]; p=0·019) compared to placebo.

Furthermore, significantly fewer patients treated with liraglutide had worsening of fibrosis compared to placebo[34].

Semaglutide

Semaglutide is a potent human GLP-1 RA with a half-life of approximately 160 hours, suitable for both once daily (subcutaneous (s.c.) and oral) and once weekly s.c. administration. It is structurally similar to liraglutide (Victoza® and Saxenda®), a once daily GLP-1 RA developed by Novo Nordisk and approved in several countries for the treatment of T2D and weight management, respectively.

For the semaglutide molecule the principal mechanism of protraction is albumin binding facilitated by a large fatty acid derived chemical moiety attached to the lysine in position 26. The specific modifications in the molecule are: 1) a modification in position 8 (alanine to 2-aminoisobutyric acid) of the peptide backbone in order to further increase stability against DPP-4, and a change in position 34 from a lysine to an arginine in order to only have one (1) lysine in the sequence; 2) a large hydrophilic linker between the lysine in position 26 and the gamma glutamate whereto the fatty acid is attached; 3) a C18 fatty di-acid with a terminal acidic group. The latter two (2) contribute to increased albumin binding which results in decreased renal clearance. In addition to slowed degradation in plasma and decreased renal clearance, delayed absorption from subcutis possibly also contributes to a prolonged half-life t½ of 155-183 hours.

In vitro receptor studies have shown that semaglutide is a potent and selective GLP-1 analogue, and animal studies using non-diabetic rats, non-diabetic pigs and diabetic mice have shown lowering of BG and inhibition of food intake. A clinically relevant effect on glucose metabolism and body weight has also been observed in humans.

Nonclinical data

The nonclinical programme for semaglutide was designed according to the ICH M3[36] guideline to support the clinical development. The standard nonclinical data package required to support phase 3 clinical trials has been completed. In addition, 2-year carcinogenicity studies and a pre- and postnatal development toxicity study have been completed.

Semaglutide is generally well tolerated with expected GLP-1 effects on food intake and body weight being dose limiting in mice, rats and cynomolgus monkeys. Two potential safety issues have been identified.

Thyroid C-cell tumours in rodents

Treatment-related non-genotoxic proliferative changes in the thyroid C-cells of mice and rats were observed in 2-year carcinogenicity studies with semaglutide. Early C-cell changes were also identified in repeated dose toxicity studies with semaglutide in mice. However, this was not the case

in other species including a 52-week repeat dose study in non-human primates at exposure levels up to 36-fold above the expected clinical exposure. The observed pattern of effects in mice and rats (thyroid C-cell proliferation preceded by increase in serum calcitonin) and lack of these effects in the non-human primate and in man suggest that the mechanism by which semaglutide acts on the thyroid C-cells in rodents is the same as has been demonstrated for other GLP-1 RAs, including liraglutide. The relevance for human subjects is unknown. Recently published data have shown that the GLP-1 receptor 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[37].

Teratogenicity in rats

Semaglutide has been concluded teratogenic in rats, with exposure at no observable adverse effect level (NOAEL) below expected human exposure. This effect is regarded to be caused by impairment of nutrient supply to the embryo across the inverted yolk sac with placental function which is specific to rats.

Non-human primates and humans do not depend on a yolk sac with placental function to supply nutrients to the embryo early in pregnancy. The effect on rat embryo-foetal development is therefore not likely to be relevant to humans as described below. Preliminary and main embryofoetal development and pre- and postnatal development studies with doses corresponding to 12-15 fold expected clinical exposure in cynomolgus monkeys have been finalised. In the main embryofoetal development study sporadic abnormalities were reported across all dose groups and in the pre- and postnatal development study a dose-dependent increase in early pregnancy losses was observed. The findings observed across the three studies in cynomolgus monkeys are not indicative of a teratogenic potential of semaglutide in this species. The increase in early pregnancy losses is indicative of embryo-toxicity, which may be related to the maternal effect of semaglutide (marked body weight loss). A developmental toxicity NOAEL was determined at an exposure 1- to 2 fold the expected clinical exposure (1 mg/week). A risk for the developing human embryo or foetus cannot be definitely ruled out, but the absence of findings indicative of teratogenicity in the embryo-foetal development and pre- and postnatal development studies in cynomolgus monkey decreases the level of concern.

A comprehensive review of results from the nonclinical studies can be found in the current edition of semaglutide s.c. (NN9535), T2D, Investigator's Brochure (IB)[38] or any updates hereof.

Clinical data

Semaglutide s.c. is currently being investigated in the T2D development programme (please refer to the semaglutide s.c. IB for T2D or any updates hereof [38]) and in the obesity development programme. Novo Nordisk is also developing semaglutide for oral administration, and phase 3 trials with this formulation are ongoing.

As of 22 December 2015 (the cut-off date of the latest version of the semaglutide s.c. IB for T2D[38]), 13 clinical pharmacology trials and 1 phase 2 trial have been completed with semaglutide once-weekly s.c. In the completed once-weekly semaglutide s.c. trials, 802 subjects have been exposed to semaglutide: 411 healthy subjects (both single and multiple dosing), 313 subjects with type 2 diabetes (up to 12 weeks of treatment), 48 subjects with varying degrees of renal impairment (4 subjects had type 2 diabetes) (single dosing) and 30 subjects with obesity but otherwise healthy.

As of 22 December 2015, 8 therapeutic confirmatory trials with nearly 8000 subjects enrolled are ongoing including a 104-week trial comparing the long-term safety (including cardiovascular risk) and efficacy of semaglutide once-weekly s.c.

Doses up to 1.6 mg with weekly dosing have been tested and doses up to 0.4 mg with daily dosing are being tested in the NN9536-4153 trial for the weight management indication.

A recent finalised trial (not described in the current version of the semaglutide s.c. IB for T2D[38]), investigated subjects with hepatic impairment. Following administration of a single dose of semaglutide 0.5 mg, semaglutide pharmacokinetics were compared between subjects with mild, moderate and severe hepatic impairment and subjects with normal hepatic function. The primary endpoint, total exposure in terms of area under curve (AUC), met the criterion for 'no effect' for all 3 hepatic impairment groups versus the group with normal hepatic function. Hence, exposure of semaglutide was not affected by hepatic impairment, and semaglutide pharmacokinetic properties for subjects with hepatic impairment were similar to those with normal function. No new safety or tolerability issues were observed for semaglutide following single dose administration to this subject group.

Efficacy

As of 22 December 2015, efficacy of semaglutide in subjects with T2D has been investigated in one phase 2 dose range finding trial (NN9535-1821). The trial was a 12-week, randomised, double-blind, placebo- and active-controlled trial in which 411 adults with T2D received once-weekly s.c. injection of 1 of 5 semaglutide dose levels (0.1-1.6 mg), once-daily injection of open label liraglutide (1.2 mg or 1.8 mg) or once-weekly placebo.

12 weeks of treatment, equivalent to 5-7 weeks in steady state on maintenance dose, provided statistically significant and clinically relevant improvement in glycaemic control for dose levels of 0.2 mg and above. Mean changes in glycosylated haemoglobin (HbA_{1c}) from baseline was up to -1.19% (placebo adjusted estimated treatment difference). Dose-dependent improvements in fasting plasma glucose (FPG) and postprandial PG were also observed. The improvement in glycaemic control was accompanied by weight loss for semaglutide doses of 0.8 mg and above (estimated treatment difference compared to placebo up to a mean value of -3.64 kg).

Safety

From the clinical trials completed so far the following safety observations have been made. In consistency with the findings obtained from evaluating other GLP-1 RAs, common adverse events (AEs) included nausea and vomiting; most of them were mild to moderate in severity.

Hypoglycaemia has occurred in subjects receiving semaglutide and these events have mainly been minor. As with other GLP-1 RAs, an increase in heart rate has been observed in subjects exposed to semaglutide. The implications of this increase are unknown. As with all protein based pharmaceuticals, subjects treated with semaglutide may develop immunogenic and allergic reactions. Few allergic reactions have been reported in connection with semaglutide. These have mainly been mild and transient however, more generalised reactions may occur, including urticaria, rash, pruritus and rare cases of angioedema have been observed. Injection site reactions have been infrequently reported. These have mainly been mild and transient in nature.

Please see the current edition of semaglutide s.c. (NN9535), T2D, Investigator's Brochure (IB)[38] or any updates hereof for further details.

For an assessment of benefits and risks of the trial, see Section 18.1.

3.2 Rationale for the trial

Currently, first-line treatment of NASH is lifestyle interventions to provide weight loss and to treat comorbidities (e.g. hyperlipidaemia, hypertension and diabetes) as no specific pharmaceutical therapies are approved and, thus, there is a substantial unmet medical need for effective treatment of NASH.

The results from the LEAN trial[34] showed beneficial treatment effects of liraglutide in overweight subjects with biopsy-confirmed NASH. Data from semaglutide trials, a human GLP-1 analogue structurally similar to liraglutide with similar mechanism of action, has suggested a more pronounced effect on glycaemic control and body weight loss compared to liraglutide. Therefore semaglutide is considered to have an even better potential as treatment for NASH.

The purpose of the present trial is to investigate the potential of semaglutide s.c. once daily at three dose levels to resolve NASH compared to placebo. Furthermore, the trial is designed to explore the dose response relationship for semaglutide in NASH in order to inform dose selection for phase 3. Furthermore, safety and tolerability including the formation of anti-semaglutide antibodies will be investigated.

4 Objectives and endpoints

4.1 Objectives

Primary objective

To compare the effect of semaglutide s.c. once daily versus placebo on histological resolution of NASH.

Secondary efficacy objectives

To investigate the dose-response relationship of three dose levels of semaglutide s.c. once daily (0.1 mg/day, 0.2 mg/day and 0.4 mg/day) on histological resolution of NASH.

To compare the effects of semaglutide s.c. once daily to placebo on liver-related histological parameters and biomarkers of NASH disease.

To investigate the effects of semaglutide s.c. once daily versus placebo in subjects with NASH on:

- Weight-related parameters
- Glucose metabolism related parameters
- Cardiovascular risk factors
- Patient reported outcomes

Secondary safety objectives

To evaluate the safety and tolerability of three dose levels of semaglutide s.c. once daily in subjects with NASH.

4.2 Endpoints

4.2.1 Primary endpoint

- NASH resolution* without worsening of fibrosis** after 72 weeks (yes/no)

*) Resolution of NASH as defined by comprehensive interpretation by two independent pathologists (central reading) blinded to treatment allocation and with complete resolution captured by terms such as “no fatty liver disease” or “simple steatosis or isolated steatosis” and defined by the NASH Clinical research network (CRN) as “no more than mild residual inflammatory cells and no ballooning”

**) worsening defined by an increase of at least one stage of the Kleiner fibrosis classification

4.2.2 Secondary endpoints

4.2.2.1 Supportive secondary efficacy endpoints

Liver-related histological parameters

- At least one stage of liver fibrosis improvement with no worsening of NASH after 72 weeks (yes/no) (worsening defined as an increase of at least one stage of either lobular inflammation or hepatocyte ballooning according to NASH CRN criteria [19] [39]).*

Change from baseline to week 72 in:

- NAFLD activity score (NAS)*
- Stage of fibrosis according to the Kleiner fibrosis classification*
- Activity component of steatosis-activity-fibrosis (SAF) score*

Biomarkers of NASH disease

Change from baseline to week 72 in:

Algorithms:

- Fibrosis-4 score (Fib-4 score)
- NAFLD Fibrosis Score (NFS)

Blood samples:

- Liver enzymes
  - ALT, AST and GGT
- Liver synthesis function
  - Albumin, INR
- Exploratory biomarkers
  - Serum enhanced liver fibrosis (ELF)*
  - CK-18 fragments
  - miR-122
  - IL-1R antagonist
  - MCP-1
  - FGF-21

Imaging:

- Liver stiffness and liver steatosis (with controlled attenuation parameter) measurement by Fibroscan®

Weight related parameters

- Weight loss of ≥ 5% of baseline body weight at 72 weeks (yes/no)
- Weight loss of ≥ 10% of baseline body weight at 72 weeks (yes/no)

Change from baseline to 72 weeks in:

- Body weight (% and kg)
- Waist circumference
- Body mass index (BMI)

Glucose metabolism related parameters

Change from baseline to 72 weeks in:

- Glycosylated haemoglobin type A1c (HbA_{1c})*
- Fasting plasma glucose (FPG)*
- Fasting glucagon
- Homeostatic model assessment of insulin resistance (HOMA-IR)

Cardiovascular risk factors

Change from baseline to 72 weeks in:

- Systolic and diastolic blood pressure
- Lipids (total cholesterol, low density lipoprotein cholesterol (LDL cholesterol), high density lipoprotein cholesterol (HDL cholesterol), very low density lipoprotein cholesterol (VLDL cholesterol), triglycerides, free fatty acids)
- High sensitivity C reactive protein (hsCRP)

Patient reported outcomes

Change from baseline to 72 weeks in:

- Short form 36 (SF-36): Physical and mental component summary scores and scores on the individual sub-domains: Physical functioning, role functioning, bodily pain, general health, vitality, social functioning, role emotional and mental health.

4.2.2.2 Supportive secondary safety endpoints

- Number of treatment-emergent adverse events during the trial
- Number of treatment-emergent hypoglycaemic episodes during the trial
- Number of treatment-emergent severe or BG confirmed symptomatic hypoglycaemic episodes during the trial
- Number of treatment-emergent severe hypoglycaemic episodes during the trial
- Number of subjects discontinuing treatment due to gastrointestinal adverse events

Occurrence of anti-semaglutide antibodies during and after 72 weeks treatment (yes/no):

- Anti-semaglutide binding antibodies
- Anti-semaglutide binding antibodies with *in vitro* neutralising effect
- Anti-semaglutide binding antibodies cross reacting with native GLP-1
- Cross-reacting anti-semaglutide binding antibodies with *in vitro* neutralising effect to native GLP-1

Anti-semaglutide antibody binding level during and after 72 weeks treatment

Change from baseline to 72 weeks in:

- Pulse
- ECG
- Physical examination
- Haematology (haemoglobin, haematocrit, thrombocytes, erythrocytes, leucocytes, differential count)
- Biochemistry (creatinine, creatinine phosphokinase, urea, bilirubin (total), alkaline phosphatase, ferritin, sodium, potassium, calcium (total), amylase, lipase)
- Hormones (calcitonin)

Key supportive secondary endpoints prospectively selected for disclosure (e.g. clinicaltrials.gov and EudraCT) are marked with an asterisk (*).

5 Trial design

5.1 Type of trial

This is a 72-week, randomised, double-blind, placebo-controlled, six-armed, parallel group, multi-centre, multi-national trial comparing once daily administration of semaglutide s.c. in three different doses (0.1 mg, 0.2 mg and 0.4 mg) with placebo in subjects with NASH.

A planned total of 372 subjects will be randomised. Based on an assumption of a 50% screening failure rate, 744 subjects will be screened. Subjects will be randomised in a 3:3:3:1:1:1 manner to receive daily dosing of semaglutide s.c. 0.1 mg, 0.2 mg, 0.4 mg or corresponding injection volumes of placebo once daily (for details see Figure 5–1). To avoid bias in the assessment of the different semaglutide doses, the trial will be double-blinded within dose levels. The dose levels will not be blinded between each other because of different dose escalations and different target doses and volumes required. It is expected that 15% will withdraw from the trial or prematurely discontinue treatment with trial product.

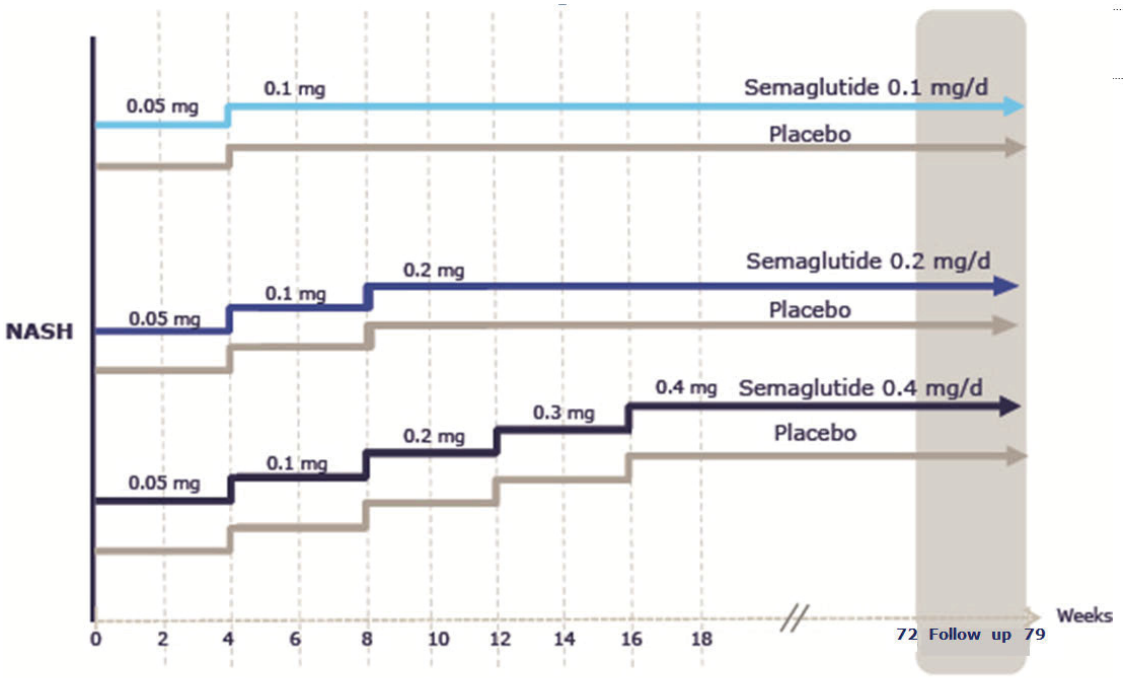


Figure 5–1 Trial design

Subjects in all treatment groups including placebo will receive nutritional and physical activity counselling by a member of the study team according to local site practice.

The randomisation of subjects to treatment will be stratified in five groups as described in section 5.2 and section 11).

The diagnosis of NASH as well as the histology based scores will be subject to central pathologist evaluation.

Subjects who prematurely discontinue the trial product treatment should continue with the originally scheduled site visits/contacts including a liver biopsy and final assessments 72 weeks after randomisation (visit 19A). However the following should not be done after visit 19 for subjects prematurely discontinuing trial product: Semaglutide plasma concentration, anti-semaglutide antibody assessment, hypo reporting and handing out subject diaries.

Subjects who prematurely discontinue trial product treatment will continue to receive nutritional and physical exercise counselling throughout their trial participation.

The total trial duration for the individual subject will be up to 85 weeks (maximum).

5.2 Rationale for trial design

Trial duration of 72 weeks is considered adequate in terms of assessing the primary endpoint. Furthermore, a 72-week trial period is considered to be sufficient to characterise the semaglutide safety and tolerability profile in patients with NASH.

Randomisation will be stratified in five strata based on region (Japanese or non-Japanese) and, within the non-Japanese group, based on diabetes status at screening (with or without type 2 diabetes) and fibrosis stage for baseline liver biopsy (F2 or F3). This is to ensure an even distribution of the treatment arms within the specified strata. Balance of treatment arms with respect to region can help an evaluation of consistency of treatment effect between the entire population and Japanese subjects. Diabetes status and fibrosis stage for baseline liver biopsy are considered important prognostic covariates and including them in the stratification may enhance the credibility of the results of the trial as well as improve the precision of the estimated treatment effect. Stratification based on diabetes status and fibrosis stage is not feasible within the Japanese group due to small sample sizes.

As gastrointestinal AE rates are anticipated to increase with higher doses and with large excursions in the semaglutide plasma concentration, semaglutide is dosed once daily to ensure less variability in concentrations. Dose escalation every fourth week is chosen to reach steady state at each dose level before increasing the dose. This could potentially reduce gastrointestinal AEs.

The trial design and protocol has been developed with harmonised advice from the regulatory authorities of the USA and Germany, and based on the recommendation of the Liver Forum[40] [41].

5.3 Treatment of subjects

The dosing of semaglutide or placebo will be once daily with increase to the next dose step every four weeks until the randomised dose level is reached. During the dose escalation period subjects will be allowed to stay up to one extra week on each dose level, if the dose is not tolerable due to gastrointestinal events or for other reasons as judged by the investigator.

Table 5–1 Duration of dose escalation period

Target dose	Scheduled time to target dose	Flexibility allowed if not tolerated	Maximum time to target dose
Semaglutide 0.4 mg/day	16 weeks	4 weeks	20 weeks
Semaglutide 0.2 mg/day	8 weeks	2 weeks	10 weeks
Semaglutide 0.1 mg/day	4 weeks	1 week	5 weeks

Once the randomised target dose is reached the subject should not change the dose. In case the dose escalation regimen or the target dose cannot be tolerated the subject must be discontinued from treatment.

The following investigational medicinal products (IMP) will be supplied by Novo Nordisk A/S, Denmark:

- Semaglutide 1.0 mg/ml, solution for injection, 3.0 ml cartridge, for NovoPen® 4
- Semaglutide placebo, solution for injection, 3.0 ml cartridge, for NovoPen® 4

Auxiliaries to IMP will be supplied by Novo Nordisk e.g. needles.

The NovoPen® 4 device that will be used in this trial will display a value and not mg.

The conversion table below shows the connection between each volume matched dose level and the value shown in the display on the NovoPen® 4. Subjects must be instructed to administer the value shown in the display.

Table 5–2 Dose conversion table

Value shown in display	Semaglutide (mg)	µL
5	0.05 mg	50 µL
10	0.10 mg	100 µL
20	0.20 mg	200 µL
30	0.30 mg	300 µL
40	0.40 mg	400 µL

Throughout the trial subjects cannot initiate treatment with:

- Glucose-lowering agents other than trial product
- Vitamin E
- Drugs with potential effect on steatosis (corticosteroids (topical and inhaled 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 subjects participate in any organised weight reduction programme throughout the trial.

5.3.1 Subjects treated with basal insulin

The following basal insulins are allowed:

- Insulin glargine
- Insulin detemir
- Insulin degludec
- Neutral protamine Hagedorn (NPH) insulin

Subjects treated with basal 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 dose-escalation should be avoided, unless required to control acute hyperglycaemia and acute diabetic complications.

Subjects treated with basal insulin with $HbA_{1c} \leq 8.0$ % at screening:

Subjects with $HbA_{1c} \leq 8.0$ % at screening (visit 1) should have the insulin dose reduced by 30 % at start of trial product treatment to limit the potential risk of hypoglycaemia induced by the combination of insulin and semaglutide.

5.3.2 Missed dose

If a subject forgets to inject a trial product dose, the dose can be administered as soon as the subject remembers. However, if it is more than 12 hours since the subject should have administered the dose, the subject should skip the missed dose and take the next dose as usual on the following day.

If a subject has missed several consecutive doses of trial product, trial product can be continued. Please refer to guidance document describing recommendations on how to re-initiate trial product.

5.3.3 Nutritional and physical activity counselling

All subjects will receive nutritional and physical activity counselling (see section 8.6.3).

5.4 Treatment after discontinuation of trial product

When discontinuing trial products, either at the scheduled end of treatment visit or if trial product is discontinued prematurely, the investigator should discuss other potential treatment options with the subject. For subjects with type 2 diabetes investigator should also discuss potential treatment options for type 2 diabetes.

5.5 Rationale for treatment

Subjects are enrolled for a treatment period of 72 weeks in order to be able to evaluate the full effect of treatment on the primary and secondary endpoints as well as to be able to make a reasonable safety assessment. This is based on the knowledge from the LEAN study (investigator sponsored study) where a statistically significant greater number of patients had resolution of NASH after 48 weeks of treatment with liraglutide 1.8 mg compared with placebo in patients with biopsy confirmed NASH. 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 [95% CI 1·0–17·7]; p=0·019) compared to placebo[34]. Thus, given the relatively long time required to reach the target dose of the highest semaglutide doses, and in order to see the full effect of the different doses, trial duration of 72 weeks was chosen.

The comparator in the trial is placebo. Placebo is used in order to evaluate the absolute safety and efficacy of once-daily semaglutide. Currently, there are no approved therapies for NASH.

The semaglutide dose levels of 0.1 mg/day to 0.4 mg/day have been chosen to get a wide range of exposure. This will allow for dose-response modelling which in combination with safety information related to the individual doses, will form the basis for selecting the optimal semaglutide dose for patients with NASH.

6 Trial population

6.1 Number of subjects

Number of subjects planned to be screened: 744.

Number of subjects planned to be randomised: 372 (50% screen failure rate).

Number of subjects expected to complete the trial on or off trial product: 335 (10% trial withdrawal rate).

Number of subjects expected to complete the trial on trial product: 316 (15% total trial product discontinuation rate).

The aim is that between 30 and 70% of subjects should have NASH and type 2 diabetes.

6.2 Inclusion criteria

For an eligible subject, all inclusion criteria must be answered "yes".

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) (for Japan: male or female aged 20-75 years (both inclusive)) at the time of signing informed consent.

3. Stable body weight (defined as less than 5% self-reported change in body weight in the period from 28 days prior to screening or if recent biopsy is used from 28 days prior to baseline liver biopsy until time of screening).

4. Accept to have one liver biopsy performed during the screening period (if no biopsy within 21 weeks before screening is available) and one at 72 weeks after randomisation.

5. Local histological diagnosis of NASH followed by histological confirmation of NASH based on central pathologist evaluation of a liver biopsy obtained up to 21 weeks before screening.

6. A histological NAS $\geq$ 4 with a score of 1 or more in each sub-component of the score based on central pathologist evaluation.

7. NASH fibrosis stage 2 or 3 according to the NASH CRN fibrosis staging system based on central pathologist evaluation.

6.3 Exclusion criteria

For an eligible subject, all exclusion criteria must be answered "no".

Liver-related:

1. Documented causes of chronic liver disease other than NASH.
2. Positive HBsAg, positive anti-HIV, positive HCV-RNA.
3. AST greater than 5 times upper normal limit (UNL) at screening.
4. ALT greater than 5 times UNL at screening.
5. Elevated total bilirubin (> 1.5 mg/dL) at screening.
6. Prothrombin time (INR) > 1.3 at screening.
7. Known or suspected abuse of alcohol (> 20 g/day for women or > 30 g/day for men), alcohol dependence* or narcotics. (* = assessed by the Alcohol Use Disorders Identification Test (AUDIT questionnaire)).
8. Treatment with vitamin E which has not been at a stable dose in the period from 28 days prior to screening or if recent biopsy is used from 28 days prior to baseline liver biopsy until time of screening.
9. Treatment with drugs with potential effect on steatosis; Corticosteroids (topical and inhaled are allowed), Methotrexate, Tamoxifen, Valproic acid, Amiodarone or Tetracycline in the period from 28 days prior to screening or if recent biopsy is used from 28 days prior to baseline liver biopsy until time of screening.

Glycaemia related:

10. HbA_{1c} > 9% at screening.
11. Treatment with GLP-1 RAs or SGLT-2 inhibitors in the period from 90 days prior to screening or if recent biopsy is used from 90 days prior to baseline liver biopsy until time of screening.
12. Treatment with bolus (fast-acting) insulin in the period from 28 days prior to screening or if recent biopsy is used from 28 days prior to baseline liver biopsy until time of screening.
13. Treatment with other glucose lowering agent(s) (apart from what is listed in exclusion criterion 11 and 12) not stable in the period from 28 days prior to screening or if recent

biopsy is used from 28 days prior to baseline liver biopsy until time of screening. Changes without clinical relevance in the opinion of the investigator are allowed.

14. Diagnosis of type 1 diabetes according to medical records.

    Obesity related:

15. Body Mass Index (BMI) ≤ 25.0 or ≥ 45.0 kg/m^2 at the screening visit (visit 1).

16. TSH > 6 mIU/L or < 0.4 mIU/L at screening.

17. Treatment with orlistat, zonisamide, topiramate, phentermine, lorcaserin, bupropion and naltrexone alone or in combination or any other medication that could promote weight loss in the opinion of the investigator in the period from 28 days prior to screening or if recent biopsy is used from 28 days prior to baseline liver biopsy until time of screening.

18. Participation in an organised weight reduction program (e.g. WeightWatchers®) in the period from 28 days prior to screening or if recent biopsy is used from 28 days prior to baseline liver biopsy until time of screening.

19. Previous surgical treatment for obesity. However (1) liposuction and/or abdominoplasty if performed > 6 months before baseline liver biopsy is allowed or 2) lap banding where the band has been removed > 6 months before baseline liver biopsy is allowed 3) intragastric balloon where the balloon has been removed > 6 months before baseline liver biopsy is allowed.

    General safety:

20. Proliferative retinopathy or maculopathy requiring acute treatment verified by fundus photography or dilated fundoscopy performed within the past 90 days prior to randomisation.

21. History or presence of pancreatitis (acute or chronic).

22. Calcitonin ≥ 50 ng/L at screening.

23. Family or personal history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma. Family is defined as a first degree relative.

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

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

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

27. Language barrier, mental incapacity, unwillingness or inability to adequately understand or comply with study procedures.

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

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

30. Participation in any clinical trial of an approved or non-approved investigational medicinal product within 90 days before screening.

31. Female who is pregnant, breast-feeding or intends to become pregnant or is of childbearing potential and not using an adequate contraceptive method (adequate contraceptive measures as required by local regulation or practice).

For EU countries: The following contraceptive measures are considered adequate:

- Combined estrogen and progestogen containing hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation :
  - oral
  - injectable
  - implantable
- Placement of an
  - intrauterine device (IUD)
  - intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Barrier methods of contraception (condom or occlusive cap with spermicidal foam/gel/film/cream/suppository) **(not applicable for Belgium, Denmark, Finland, Greece, Spain, Sweden)**
- Vasectomised partner (where partner is sole partner of subject) **(not applicable for Denmark)**
- True sexual abstinence **(not applicable for Denmark)**. Sexual abstinence is defined as refraining from heterosexual intercourse during the entire period of risk associated with the

study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

6.4 Criteria for premature discontinuation of trial product

Efforts must be made so that subjects attend and complete all scheduled visit procedures. However the following should not be done after visit 19 for subjects prematurely discontinuing trial product: Semaglutide plasma concentration, anti-semaglutide antibody assessment, hypo reporting and handing out subject diaries. Subjects should stay in the trial irrespective of lack of adherence to randomised treatment, lack of adherence to visit schedule or missing assessments. Only subjects who decline any further contact with the site in relation to the trial will be considered as withdrawn from the trial (see section 6.5).

The subject may be prematurely discontinued from trial product at the discretion of the investigator due to a safety concern.

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

1. Included in the trial in violation of the inclusion and/or exclusion criteria
2. Pregnancy
3. Intention of becoming pregnant
4. Simultaneous participation in another clinical trial of an approved or non-approved investigational medicinal product.
5. In case of code break
6. If the target treatment dose of the randomised trial product is not tolerated by the subject
7. Diagnosis of acute pancreatitis
8. Diagnosis of medullary thyroid carcinoma
9. Surgical treatment for obesity
10. Treatment with other GLP-1 receptor agonists, SGLT-2 inhibitors or bolus (fast-acting) insulin

See section 8.1.5 for procedures to be performed for subjects discontinuing trial product prematurely.

6.5 Withdrawal from trial

The subject may withdraw consent at will at any time. The subject's request to withdraw from the trial must always be respected.

Please see section 8.1.6 for procedures to be performed for subjects withdrawing consent.

6.6 Subject replacement

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

6.7 Rationale for trial population

Patients with NASH have an increased risk of all cause and liver related mortality. As there is currently no established, safe and effective pharmacological treatment for NASH there is a significant unmet medical need.

As the prevalence of NASH is high in patients with T2D (approximately 25% of patients with T2D have NASH) and considering the glycaemic properties of semaglutide it is appropriate not to exclude patients with T2D in the trial. Hence both patients with and without T2D can be included as it is the aim to include a broad NASH population.

The trial population will consist of patients with NASH and a fibrosis stage of F2-F3. Patients with F0 and F1 will be excluded as they do not have fibrosis (F0) or are less progressed in the disease spectrum, why less benefit may be achieved on fibrosis (F1). Furthermore, subjects with fibrosis stage 4 (cirrhosis) will be excluded from the trial as an important endpoint addressing worsening in fibrosis cannot be addressed in this population (the Kleiner classification has a maximum score of 4).

7 Milestones

Planned duration of recruitment period: 51 weeks

End of trial is defined as LSLV

Recruitment:
The screening and randomisation rate will be followed closely via the interactive web response system (IWRS) in order to estimate when to stop screening. All investigators will be notified immediately when the recruitment period ends, after which no further subjects may be screened and the IWRS will be closed for further screening. All subjects screened during the recruitment period and found eligible for randomisation can be randomised within the timelines specified in the flowchart (see section 2).

Trial registration:

Information of the trial will be disclosed at clinicaltrials.gov and novonordisk-trials.com. According to the Novo Nordisk Code of Conduct for Clinical Trial Disclosure[42], it will also be disclosed according to other applicable requirements such as those of the International Committee of Medical Journal Editors (ICMJE)[43], the Food and Drug Administration Amendment Act (FDAAA)[44], European Commission Requirements[45] [46] 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.

8 Methods and assessments

The following sections describe the assessments and procedures that must be performed during this trial. The overview of when they must be performed is included in the flow chart (section 2).

8.1 Visit procedures

8.1.1 Screening, re-screening and screen failures

Informed consent must be obtained before any trial related activity, see section 18.2. Separate informed consent forms for long-term storage of human samples and genotyping are available and informed consent must be obtained before activities related to any of these are undertaken.

At screening (visit 1), subjects will be provided with a card stating that they are participating in a trial and giving contact address(es) and telephone number(s) of relevant trial site staff. Subjects should be instructed to return the card to the investigator at the last trial visit or to destroy the card after the last visit.

Each subject will be assigned a unique 6-digit subject number which will remain the same throughout the trial.

The investigator must keep a subject screening log, a subject identification code list and a subject enrolment log. Only subjects who have signed the informed consent form should be included on the logs. The subject screening log and subject enrolment log may be combined in one log and may be generated from the IWRS (see section 10).

Screening failures

For screening failures the screening failure form in the electronic case report form (eCRF) must be completed with the reason for not continuing in the trial. Serious and non-serious adverse events from screening failures must be transcribed by the investigator into the eCRF. Follow-up on serious adverse events (SAEs) must be carried out according to section 12.
A screening failure session must be made in the IWRS. The case book in the eCRF must be signed.

Re-screening

Re-screening of screening failures is allowed only once within the limits of the recruitment period. However, re-screening is NOT allowed if the subject has failed one of the inclusion/exclusion criteria related to laboratory parameters (histological NAS, NASH fibrosis stage, HBsAg, anti-HIV, HCV-RNA, AST, ALT, total bilirubin, INR, HbA_{1c}, calcitonin or TSH). In the event of re-screening, a new informed consent must be obtained and a new subject number must be allocated. All assessments and laboratory samples must be repeated.

8.1.2 AUDIT questionnaire

The AUDIT questionnaire is used to assess the frequency of alcohol consumption and screen out alcohol-related problems, and dependence symptoms.

8.1.3 Fasting visits

Subjects must attend some of the clinic visits in a fasting state (see section 2).

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 blood sampling has been performed. 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. Fasting procedures include body weight, Fibroscan® measurements and blood sampling.

Prior to Fibroscan® measurements, only two hours of fasting is required.

At visit 19, the subject must be fasting for two hours prior to the anti-semaglutide antibody sampling (see section 8.5.3.7).

8.1.4 Missed visits

If an entire visit is missed and it is not possible to re-schedule the visit within the time window, every effort should be made to re-schedule the visit at the earliest possible date before the next visit.

8.1.5 Premature discontinuation of trial product

If a subject prematurely discontinues trial product treatment, the investigator must undertake procedures similar to those for visit 18 (end of treatment) as soon as possible and the follow up visit (visit 19) must be performed 7 weeks later. **Females only:** All female subjects using an adequate contraceptive method must be reminded to continue this for 7 weeks after discontinuation of trial product treatment.

Following visit 19, subjects should continue with the originally scheduled site visits/contacts up to and including visit 19A. Visit 19A should take place 72 weeks (± 7 days) after their randomisation date (for details refer to section 2). However the following should not be done after visit 19 for subjects prematurely discontinuing trial product: Semaglutide plasma concentration, anti-semaglutide antibody assessment, hypo reporting and handing out subject diaries.

If a subject is not willing to attend one or more of the above mentioned visits, it should be documented in the subject's medical record that the subject has refused to attend the visit and why.

For subjects discontinued from trial product, final drug accountability must be performed and a treatment discontinuation session must be made in the IWRS. The primary reason for premature discontinuation of trial product must be specified in subject's medical records and the eCRF.

8.1.6 Withdrawn subjects

If a subject withdraws consent, the investigator must aim to undertake procedures similar to those for visit 18 (end of treatment) as soon as possible. If the subject agrees, the follow up visit (visit 19) must be performed 7 weeks later.

The end-of-trial form must be completed, and final drug accountability must be performed even if the subject is not able to come to the trial site. A treatment discontinuation session must be made in the IWRS. The case book must be signed.

Although a subject is not obliged to give his/her reason(s) for withdrawing consent, 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 withdrawing consent must be specified in the end-of-trial form in the eCRF.

8.1.7 Subject training

Subject diaries

The subject must be provided with diaries at the specified visits (section 2). The investigator should instruct the subjects in filling in the diary according to the provided diary instructions (see section 8.4.7 and 8.6.2). The diaries dispensed to subjects should be collected at the specified visits (section 2).

Trial product

Trial product must be dispensed to subjects at the specified visits (see section 2). Trial product will be dispensed to the subject by the site. At the visits specified in section 2 and as needed, the subjects will be instructed in the handling of trial product and trained in the use of the pen-injector and in the administration of s.c. injection of trial product.

Subjects must be instructed to administer the value shown in the display, see Table 5–2.

Hypoglycaemic episodes recognition

The investigator or delegate will train the subjects in symptom recognition and handling of hypoglycaemia.

Suspected pregnancy

Female subjects must be instructed to contact site if a menstrual period is missed so they can come in for urine pregnancy test.

8.2 Subject related information/assessments

8.2.1 Demography

Demography will be recorded at screening and consists of:

- Date of birth (according to local regulation)
- Sex
- Ethnicity (according to local regulation)
- Race (according to local regulation)

8.2.2 Concomitant illness and medical history

A **concomitant illness** is any illness that is present at the start of the trial (i.e. at visit 1) or found as a result of a screening procedure or other trial procedures performed before exposure to trial product.

Any change to a concomitant illness should be recorded during the trial. A clinically significant worsening of a concomitant illness must be reported as an AE.

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.

It must be possible to verify the subject's medical history in source documents such as subject's medical record. If a subject is not from the investigator´s own practice; the investigator must make reasonable effort to obtain a copy of the subject's medical record from any relevant party e.g. primary physician. The investigator must document any attempt to obtain external medical information by noting the date(s) when information was requested and who has been contacted.

8.2.3 Concomitant medication

A **concomitant medication** is any medication, other than the trial product(s), which is taken during the trial, including the screening and follow-up periods.

Details of any concomitant medication must be recorded at the first visit. Changes in concomitant medication must be recorded at each visit as they occur.

The information collected for each concomitant medication includes trade name or generic name, indication, start date and stop date or continuation.

If a change is due to an AE, then this must be reported according to section 12. If the change influences the subject's eligibility to continue in the trial, the monitor must be informed.

8.2.4 Hypoglycaemia unawareness

For subjects with type 2 diabetes information on hypoglycaemia unawareness will be recorded at screening according to Clarke's questionnaire, question 8[47]. The investigator must ask the subject in the following way: "To what extent can you tell by your symptoms that your blood glucose is low?" The subject can answer never, rarely, sometimes, often or always.

Subjects answering 'never, rarely or sometimes' are considered as having impaired awareness of hypoglycaemia.

8.2.5 Childbearing potential

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

Pregnancy testing must be performed on female subjects of childbearing potential as described in section 8.5.3.6. Female subjects of childbearing potential must be instructed to use adequate contraceptive methods throughout the trial and until 7 weeks after end of treatment.

Female of non-childbearing potential is defined as:

- Female who has undergone a hysterectomy, bilateral oophorectomy or bilateral tubal ligation
- Postmenopausal defined as no menses for 12 months without an alternative medical cause
- Other medical reasons preventing childbearing potential

8.2.6 Tobacco use

Details of tobacco use must be recorded at the first visit. Smoking is defined as smoking at least one cigarette or equivalent daily.

Smoking status:

- Never smoked
- Previous smoker
- Current smoker

8.3 Efficacy assessments

8.3.1 Liver biopsy

Liver biopsies must be performed according to site standard procedures.

To be randomised, subjects must have a local histological diagnosis of NASH followed by histological confirmation of NASH diagnosis based on central pathologist evaluation of a liver biopsy. Confirmation of NASH diagnosis can be based on a liver biopsy obtained up to 21 weeks prior to screening. For subjects with no historical liver biopsy within 21 weeks prior to screening, a liver biopsy must be performed during the screening period. The local NASH diagnosis and the confirmation of NASH diagnosis by central pathologist evaluation of the liver biopsy must be available prior to randomisation of the subject. The local NASH diagnosis and the confirmation of NASH diagnosis by central pathologist evaluation can be done on the same liver biopsy sample.

In case the liver biopsy obtained during the screening period or up to 21 weeks prior to screening cannot be used for confirmation of NASH diagnosis 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 should have a liver biopsy performed at end of treatment (if the 72 weeks treatment period is completed) or at 72 weeks after randomisation (if trial product has been prematurely discontinued). 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.

Tissue samples will be returned to the relevant sites no later than at finalisation of the clinical trial report (CTR).

8.3.1.1 Central pathologist evaluation

The NASH diagnosis and histology based scores will be centrally assessed by two independent pathologists with expertise and experience in NASH.

The central pathologist evaluation will include the following:

- Presence or absence of NASH
- NAFLD Activity Score (NAS) components (steatosis, lobular inflammation and hepatocyte ballooning)
- Stage of fibrosis (according to Kleiner fibrosis classification)

The pathologists will be blinded to the subject and treatment and to each other's assessment of the tissue until both have reached a final conclusion. Both pathologists have to agree on the outcome of the assessment. In case of misalignment of the conclusions, a consensus needs to be reached by discussion or joint assessment of the two pathologists. If not possible a third independent, qualified pathologist will make the final decision.

8.3.2 Fibroscan® measurements

At sites where Fibroscan® equipment is not available, no assessment should be done.

Liver stiffness

At sites with Fibroscan® equipment available, measurements of liver stiffness must be performed at the specified visits (section 2). A result measured in kPa must be available. The same equipment should preferably be used for all measurements throughout the trial.

All randomised subjects should have a liver stiffness measurement performed 72 weeks after randomisation regardless of whether trial product has been discontinued prematurely or not.

The liver stiffness measurements must be performed in fasting state (see section 8.1.3) and according to site standard procedures. The result of the measurement must be documented and investigator evaluation of the result must be documented either on the actual report or in the subject´s medical record.

Liver steatosis

At sites with Fibroscan® equipment available with Controlled Attenuation Parameter (CAP) option available, measurements of liver steatosis must be performed at the specified visits (section 2). A result measured in dB/m must be available. The same equipment should preferably be used for all measurements throughout the trial.

All randomised subjects should have a liver steatosis measurement performed 72 weeks after randomisation regardless of whether trial product has been discontinued prematurely or not.

The liver steatosis measurements must be performed in fasting state (see section 8.1.3) and according to site standard procedures. The result of the measurement must be documented and investigator evaluation of the result must be documented either on the actual report or in the subject´s medical record.

8.3.3 Body measurements

8.3.3.1 Body weight

Body weight must be measured in a fasting state (except at visit 1), see flowchart (section 2) and will only be measured at visits where subjects are fasting due to blood sampling.

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

8.3.3.2 Height

Height is measured at screening (visit 1) without shoes in centimetres or inches (one decimal).

8.3.3.3 Body mass index

Body mass index will be calculated by the eCRF from visit 1 height data and must be in accordance with exclusion criterion 15.

8.3.3.4 Waist circumference

The waist circumference is defined as the abdominal circumference located midway between the lower rib margin and the iliac crest and will be measured at the specified visits (section 2).

One waist measurement must be performed and is measured in the horizontal plane with one decimal using a non-stretchable measuring tape. The same measuring tape should preferably be used throughout the trial.

The subject should be measured in a standing position with an empty bladder and wearing light clothing. The subject should be standing, feet together with arms at the side and waist accessible. 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.

8.3.3.5 Vital signs

Systolic and diastolic blood pressure

One measurement of blood pressure must be performed at the visits specified in section 2.

The method for measuring systolic and diastolic blood pressure needs to follow the standard clinical practice at site, but as a minimum, the following guideline must be adhered to:

- Avoid caffeine, smoking and exercise at least 30 minutes prior to measuring the blood pressure
- Blood pressure should be measured in a sitting position, with the legs uncrossed, the back and arms supported
- The subject should be sitting for five minutes before the measurement is taken
  The same arm and an appropriate cuff size should be used for blood pressure measurement at all visits

Pulse

Pulse (beat/min) will be recorded in a sitting position after resting for five minutes at the specified visits (section 2).

8.3.4 SF-36 questionnaires

The Short Form 36 (SF-36) should be completed by subjects at the visits specified in section 2.

The questionnaires must be completed by the subject and should preferably be completed after conclusion of all fasting-related activities, but before any other visit-related activities. Subjects must be given the opportunity to complete the questionnaires by themselves without interruption.

SF-36 measures the individual's overall health-related quality of life (HRQoL) on 8 domains: physical functioning, role functioning, bodily pain, general health, vitality, social functioning, role emotional and mental health.

Review of the questionnaires must be documented either on the documents and/or in the subject's medical record. If clarification of entries or discrepancies in the patient reported outcomes questionnaires is needed, the subject must be questioned and a conclusion made in the subject's medical record. Care must be taken not to bias the subject.

It is the responsibility of the investigator or delegated staff to review the questionnaires to report possible AEs immediately following completion.

All results from the SF-36 questionnaires must be transferred into the eCRF.

8.4 Safety assessments

8.4.1 Physical examination

Physical examination will be performed at the specified visits (section 2) according to local procedure. Physical examination must be recorded in the subject´s medical record and should include:

- General appearance
- Thyroid gland
- Respiratory system
- Cardiovascular system
- Gastrointestinal system including mouth
- Musculoskeletal system
- Central and peripheral nervous system
- Skin
- Lymph node palpation
- Head, ears, eyes, nose, throat and neck

Any abnormal, clinically significant findings at visit 1 must be recorded as a concomitant illness (see section 8.2.2).

8.4.2 Electrocardiogram

A 12-lead ECG will be performed at the visits specified in the flow chart (section 2). The investigator or delegate must sign, date and interpret the ECG by using the following categories:

- Normal
- Abnormal
    - Was the result clinically significant? (Yes/No)

All ECGs will in addition undergo central evaluation. Sites will be informed of the central ECG evaluation in case this evaluation reveals an abnormal ECG reading. If the abnormality, in the opinion of the investigator, represents an unreported AE, such finding must be reported by the investigator (see section 12.2).

If the central ECG evaluation of a post-baseline ECG is suggestive of new MI, a confirmatory ECG should be performed. All findings suggestive of new MI detected by the central ECG reading will be adjudicated by the event adjudication committee (EAC) (see section 12.7.2).

Additional unscheduled ECG recordings can be performed at the investigator's discretion at other visits than the planned ECG visits. If unscheduled ECGs are recorded and submitted for central assessment the reason should be documented and an AE reported (if applicable).

8.4.3 Adverse events

Adverse events (AEs) must be reported at each visit in accordance with the procedures outlined in section 12.

8.4.4 Medication error

If a medication error is observed during the trial, the following information is required and a specific event form must be completed in the eCRF in addition to the AE form:

- Trial product(s) involved
- Classification of medication error
- Whether the subject experienced any hypoglycaemic episodes and/or adverse event(s) as a result of the medication error
- Suspected primary reason for the medication error

For definition of medication errors, see section 12.1.4.

8.4.5 Adverse events requiring additional data collection

For the following AEs additional data collection is required and specific event forms must be completed in the eCRF in addition to the AE form:

- Acute coronary syndrome (myocardial infarction, silent myocardial infarction or unstable angina pectoris)
- Cerebrovascular event (stroke or transient ischaemic attack)
- Heart failure requiring hospitalisation or urgent unscheduled visit
- Acute pancreatitis
- Acute gallbladder disease
- Neoplasm
- Hepatic event

See appendix B for details about the additional information to report.

In case any of these events fulfil the criteria for a serious adverse event, please report accordingly, see section 12.2. For events requiring adjudication, please see Table 12–1.

8.4.6 Self-measured plasma glucose

At the randomisation visit (visit 2) subjects with type 2 diabetes will be provided with a blood glucose meter (BG-meter) including auxiliaries as well as instructions for use. The subjects will be instructed in how to use the device and the instruction will be repeated at regular intervals as needed. Subjects must be instructed to measure their blood glucose in connection with symptoms of hypoglycaemia.

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

Only the blood glucose meter provided by Novo Nordisk should be used for the measurements required in the protocol.

Subjects without type 2 diabetes at the randomisation visit will not be provided with BG-meters and hypoglycaemic episodes will only be identified by subjects via symptoms of hypoglycaemia.

In case a subject is diagnosed with type 2 diabetes during trial participation, the subject must be provided with a BG-meter and must be instructed in how to use the device and to measure their blood glucose in connection with symptoms of hypoglycaemia in the remaining trial period.

Subjects with type 2 diabetes should be instructed in how to record the results of the SMPG values in the diaries. The record of each SMPG value should include date, time and value. All data from the diary must be transcribed into the eCRF during or following the contact. If obtained via phone and a discrepancy is later detected, the values in the eCRF must be corrected.

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

8.4.7 Hypoglycaemic episodes

All subjects will at randomisation be instructed in symptom recognition and handling of hypoglycaemia.

All subjects will be provided with diaries for capturing information related to hypoglycaemic episodes throughout the trial from visit 2 to visit 19 (7 weeks after end of treatment visit (visit 18)).

For subjects with type 2 diabetes plasma glucose should always be measured and recorded when a hypoglycaemic episode is suspected.

All plasma glucose 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 in the diary according to the instructions below throughout the trial from visit 2 to visit 19 (7 weeks after end of treatment visit (visit 18)).

Upon onset of a hypoglycaemic episode the subject is recommended to measure plasma glucose every 15 minutes until the SMPG value is >3.9 mmol/L (70 mg/dL) and/or symptoms have been resolved in accordance to current guidelines[48].

An SMPG value ≤ 3.9 mmol/L (70 mg/dL) or hypoglycaemic symptoms must trigger a hypoglycaemic episode form to be completed by the subject. Repeated SMPG measurements and/or symptoms, occurring within a period of 60 min after onset on a hypoglycaemic episode, 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 and should be reported on one hypoglycaemic episode form. SMPG measurements ≤ 3.9 mmol/L (70 mg/dL) or hypoglycaemic symptoms after the 60 min period shall trigger the reporting of a new hypoglycaemia episode and prompt the subject to fill out a new hypoglycaemic episode form until a succeeding measurement is > 3.9 mmol/L (70 mg/dL) and/or symptoms have been resolved.

In case of several low SMPG values within the 60 minutes interval, 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 SMPG value and/or symptom.

For all subjects the records on hypoglycaemic episodes should include the following information (in subject diaries):

- Start date and time of the hypoglycaemic episode.
- Stop date and time of the hypoglycaemic episode (stop time is the first time the plasma glucose value is > 3.9 mmol/L (70 mg/dL) (only applicable for subjects with type 2 diabetes) and/or symptoms have been resolved).
- The plasma glucose level before treating the episode (if available) and any follow up measurements (only applicable for subjects with type 2 diabetes).
  The lowest value measured during the hypoglycaemic episode will be reported as the plasma glucose value for the episode, the remaining values will be kept as source data in the diary.
- Whether the episode was symptomatic (Yes/No).
  A hypoglycaemic episode starting without symptoms should be updated to symptomatic if the subject experiences symptoms later during the episode.
- Whether the subject was able to treat him/herself.

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

- Date, time and dose of last trial product administration prior to the episode.
- Date and time of last main meal (not including snacks) prior to the episode.
- Whether the episode occurred in relation to physical activity.
- Change in any concomitant illness.
- Any sign of fever and/or other acute disease.
- Whether the subject was asleep when the episode occurred.
  - If yes, whether the symptoms of the episode woke up the subject

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. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration[48].

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

If the question "Was the subject able to treat him/herself?" is answered "No", the following information should be recorded by the subject:

- Who assisted in the treatment of the hypoglycaemic episode (i.e. medical person or non-medical person, please specify)?
- Where the treatment was administered (in clinic/emergency room/hospital or other. If the subject was treated in clinic/emergency room/hospital, whether they were transported in an ambulance or not, please specify)
- Type of treatment provided by another person (i.e. oral carbohydrates, glucagon, intravenous (IV) glucose or other, please specify)
- Were symptoms alleviated after administration of treatment?
- Factors contributing to the episode (i.e. physical activity, missed meal, diet change, medication error (i.e. overdose, mix-up between products, incorrect use of device), miscalculation of dose of antidiabetic medication, other factors not listed or unknown)
- Did the subject experience seizure?
- Was the subject unconscious/comatose?
- Did the subject experience any of the following symptoms[49] (layman term used in the diary is specified in brackets if different from the protocol term)?
  - Autonomic: sweating, trembling, hunger or palpitations (rapid or irregular heart beat)
  - Neuroglycopenic: confusion, drowsiness, speech difficulty, visual disturbances, odd behaviour, impaired balance or incoordination (reduced ability to coordinate movement)
  - General malaise: headache or malaise (feeling discomfort/unease)

- Other symptoms

If the hypoglycaemic episode fulfils the criteria for an SAE then an AE form and a safety information form must also be filled in, see section 12.

8.4.8 Hyperglycaemic episodes

Self-measured plasma glucose values or central laboratory FPG values > 16.7 mmol/L (300 mg/dL) must be reported as adverse events (see section 12.2). Subjects should be instructed to contact site staff in case of hyperglycaemia. **Applicable for subjects with type 2 diabetes only**: Whenever a hyperglycaemic episode is suspected, plasma glucose should be measured with the BG-meter handed out.

8.5 Laboratory assessments

The laboratory analyses will be performed by a central laboratory except for analysis of anti-semaglutide antibodies and semaglutide plasma concentration analysis and some exploratory biomarkers which will be performed at specialised laboratories. The central laboratory may utilise subcontractors for their analyses.

Descriptions of laboratory supplies, procedures for obtaining samples, handling, storage and shipments of samples, will be given in the trial-specific laboratory manual provided by the central laboratory.

Only laboratory samples specified in the protocol must be sent to the central laboratory for analysis; if additional laboratory sampling is needed, e.g. to follow up on AEs, this must be done at a local laboratory.

The laboratory provides results to the trial sites in the units preferred by the trial sites while the results that are transferred to the trial database will always be in SI units.

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 and report these according to section 8.2.2 and section 12.

Laboratory samples may be drawn on another day than the day of the actual visit, as long as it is within the visit window outlined in the flow chart (see section 2).

Laboratory results will be made available to the investigator on an on-going basis except for the anti-semaglutide antibody results, the results of the semaglutide plasma concentration analysis and the exploratory biomarker results. Anti-semaglutide antibody results and the results of the

semaglutide plasma concentration analysis 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 will not be provided to the investigator, as these results will not be used for any clinical evaluation during the trial.

Laboratory samples, including specific safety assessments, will be destroyed no later than at finalisation of the clinical trial report (CTR).

Antibody samples and biosamples for future analysis will be stored as described in section 24.2.

8.5.1 Review of laboratory reports

Review of laboratory reports must be documented either on the documents and/or in the subject's medical record.

For laboratory report values outside the reference range, the investigator must specify whether the value is clinically significant or not. The evaluation of screening results must be documented prior to visit 2 (randomisation), for the subsequent visits preferably on the day of evaluation.

It is the responsibility of the investigator or delegated staff to review the laboratory reports and to report possible AEs immediately following completion of the review.

8.5.2 Laboratory assessments for efficacy

8.5.2.1 Biochemistry

- ALT
- AST
- GGT
- hsCRP
- Lipids (Total cholesterol, free fatty acids, HDL cholesterol, LDL cholesterol, triglycerides, VLDL cholesterol)
- Fib-4 and NFS (refer to section 17.4.1.1)

8.5.2.2 Glucose metabolism

- FPG
- HbA_{1c}
- Fasting insulin
- Fasting glucagon
- HOMA-IR (refer to section 17.4.1.1)

FPG is measured to evaluate metabolic control. The subjects must attend these visits fasting (for definition of fasting, see section 8.1.3). An FPG result ≤3.9 mmol/L (70 mg/dL) should not be reported as a hypoglycaemic episode but as a clinical laboratory adverse event (CLAE) at the discretion of the investigator (see section 12.1.1).

8.5.2.3 Exploratory biomarkers

- CK-18 fragments
- ELF (refer to section 17.4.1.1)
- miR-122
- IL-1R antagonist
- MCP-1
- FGF-21

8.5.2.4 Biosamples for future analysis:

Biosamples for future analysis must be drawn/collected and shipped to the central lab at the visits specified in section 2. The details and instructions around these samples are described in the trial-specific central laboratory manual. Please refer to section 24.2 for more information about the planned use of the samples.

8.5.3 Laboratory assessments for safety

Blood samples for haematology and biochemistry must be collected at the specified visits (section 2).

8.5.3.1 Biochemistry

- Bilirubin, total
- Calcium
- Creatinine phosphokinase
- Creatinine
- Lipase
- Potassium
- Sodium
- Alkaline phosphatase
- Amylase
- Albumin
- Ferritin
- Urea
- MELD score[50]

8.5.3.2 Hormones

- Calcitonin (see Appendix A)
- Thyroid-stimulating hormone (TSH)

8.5.3.3 Haematology

- Erythrocytes
- Haematocrit
- Haemoglobin
- Leucocytes
- Thrombocytes
- Differential count:
  - Eosinophils
  - Basophils
  - Lymphocytes
  - Monocytes
  - Neutrophils

8.5.3.4 Coagulation marker

- International Normalised Ratio (INR) of prothrombin time

8.5.3.5 HIV and hepatitis

- Hepatitis B
- Hepatitis C
- HIV antigen/antibody screening test

8.5.3.6 Pregnancy test

Females of childbearing potential will have a human chorionic gonadotropin (hCG) serum pregnancy test performed at the specified visits in the flow chart (see section 2).

Urine pregnancy tests (dipstick) will be performed for females of childbearing potential at the visits specified in the flowchart (section 2). If a female subject misses a menstrual period, she should contact site to come in for a urine pregnancy test (dipstick). Urine pregnancy tests will be supplied by the central laboratory. The test will be performed at the site.

Pregnancy testing is not required for women who are of non-childbearing potential as defined in section 8.2.5.

For Austria: Urine pregnancy test must be done once a month for women of childbearing potential.

8.5.3.7 Anti-semaglutide antibodies

Blood samples will be drawn during the trial and analysed at a specialised laboratory for determination of serum antibodies against semaglutide, including cross reactivity to endogenous GLP-1 (see flow chart, section 2).

Subjects must be instructed to withhold their trial product dose in the morning until blood sampling has been performed at the visit.

Samples taken at the follow-up visit (visit 19) must be taken fasting (as a minimum by only having consumed water for at least 2 hours). Samples taken at the follow-up visit which are positive for anti-semaglutide antibodies will be further characterised for *in vitro* neutralising effect towards semaglutide. In addition, samples taken at the follow-up visit which are positive for cross-reactivity against endogenous GLP-1 will be analysed for *in vitro* neutralising effect towards endogenous GLP-1.

8.6 Other assessments

8.6.1 Semaglutide plasma concentration

For all subjects a single blood sample for measurement of plasma semaglutide concentration will be drawn at selected visits (see section 2).

Subjects must be instructed to withhold their trial product dose in the morning until blood sampling is performed on the visit. In addition subjects must be instructed to complete their diary (see section 8.6.2) and bring it to the visits.

8.6.2 Subject diaries

Review of subject diaries must be documented either on the documents and/or in the subject's medical record. If clarification of entries or discrepancies in the diary is needed, the subject must be questioned and a conclusion made in the subject's medical record. Care must be taken not to bias the subject.

The following information will be captured in subject diaries:

- Information regarding first trial product dose (date, time, dose, injection site)
- Information regarding trial product doses (prior to each visit with blood sampling for measurement of semaglutide plasma concentration after randomisation until the end of treatment visit)
- Information regarding hypoglycaemic episodes

Trial product dosing information

The subject must record the date, time, dose and injection site of the last trial product injection prior to the clinic visit. Furthermore, the subject must fill in if any trial product doses were not taken in the previous two weeks. This information will be collected at all visits with blood sampling for measurement of semaglutide plasma concentration until the end of treatment visit. The information will be transcribed to the eCRF by the investigator or delegate together with the exact date and time for blood sampling, when applicable.

Hypoglycaemic episodes

For information to be captured regarding hypoglycaemic episodes, please refer to section 8.4.7.

8.6.3 Nutritional and physical activity counselling

Subjects will recieve nutritional and physical activity counselling in accordance with site practice at the visits specified in section 2.

8.7 Specific safety requirements

8.7.1 Suspicion of acute pancreatitis

Assessments in case of suspicion of acute pancreatitis

The diagnosis of acute pancreatitis requires two of the following three features:

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

Abdominal pain

Most patients with acute pancreatitis experience abdominal pain that is located generally in the epigastrium and radiates to the back. The onset of the pain may be swift reaching maximum intensity within 30 minutes, it is frequently unbearable and characteristically persists for more than 24 hours without relief. The pain is often associated with nausea and vomiting. Physical examination usually reveals severe upper abdominal tenderness at times associated with guarding.

Lipase and amylase

In general, both amylase and lipase are elevated during the course of acute pancreatitis. The serum lipase may remain elevated slightly longer than amylase. The level of the serum amylase and/or

lipase does not correlate with the severity of acute pancreatitis. In general, serum lipase is thought to be more sensitive and specific than serum amylase in the diagnosis of acute pancreatitis.

In case of suspicion of acute pancreatitis, the trial product should promptly be interrupted (NO treatment discontinuation call should be made in IWRS before diagnosis of acute pancreatitis is confirmed). A ppropriate additional examinations must be performed, including local measurement of amylase and lipase.

If acute pancreatitis is ruled out, trial product should be re-initiated.

If acute pancreatitis is confirmed, appropriate treatment and careful monitoring of the subject should be initiated. The subject must be discontinued from trial product (treatment discontinuation call) , but should remain in the trial (see section 6.4) . The event should be reported as an AE requiring additional data collection (see section 8.4.5 and Appendix B) and will undergo assessment by the EAC (see section 12.1.5) .

8.7.2 Assessments in case of increased levels of liver blood parameters

In case of any of the below:

- ALT or AST > 5x UNL
- ALT or AST > 3x baseline value
- ALT or AST > 3x UNL and total bilirubin > 2x UNL, where no alternative aetiology exists (Hy's Law)
- Total bilirubin > 1.5 mg/dL
- INR > 1.3

report the event according to section 12.1.2 and Appendix B.

For all such events prompt repeat testing (at central laboratory) including ALT, AST, alkaline phosphatase, total bilirubin and INR should be done and discontinuation of trial product considered. Thereafter, repeat testing (at central laboratory) of ALT, AST, alkaline phosphatase and total bilirubin should be done regularly until the abnormalities return to normal or baseline state. Additional clinical information should be gathered to seek a possible cause of the observed laboratory test abnormalities.

8.7.3 Training in the delivery device (NovoPen® 4)

Trial product must be dispensed to subjects at the specified visits (see section 2). At the visits specified in section 2 and as needed, the subjects will be instructed in the handling of trial product and trained in the use of NovoPen® 4 and in the administration of s.c. injection of trial product.

The subjects must be trained in how to handle the delivery device (NovoPen® 4) and in use of the pen-injector when handed out the first time. Training must be repeated during the trial at regular intervals and as needed in order to ensure correct use of the device.

The following should be emphasised:

- Always use a new needle for each injection as this will prevent contamination and blocked needles
- Priming the pen to ensure product flow
- The needle should be kept in the skin while counting slowly to 6 after the dose counter has returned to zero after injection. If the needle is removed too early then the full dose may not have been delivered.

8.8 Subject 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. If the subject continues to be non-compliant the investigator may discontinue the subject from trial product (see section 6.4).

Treatment compliance: will be assessed by monitoring of drug accountability. Prior to visits where drug accountability is performed the subject will be asked to return all used, partly used and unused trial products. The investigator must assess the amount of trial products returned compared to what was dispensed at the last dispensing visit and, in case of discrepancies, question the subject.

9 Trial supplies

Trial supplies comprise trial products and auxiliary supplies. Additional details regarding trial supplies can be found in the trial materials manual (TMM).

Trial products must not be dispensed to any person not included in the trial.

Trial product must not be used, if it does not appear clear and colourless.

9.1 Trial products

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

Table 9–1 Trial products

Trial product	Strength	Dosage form	Route of administration	Container/delivery device
Semaglutide 1.0 mg/mL (Investigational medicinal product (IMP))	1.0 mg/mL	Solution for injection	Subcutaneous (s.c.) injection	3 mL Cartridge for NovoPen® 4
Semaglutide placebo (Investigational medicinal product (IMP))	N/A			

Semaglutide 1.0 mg/mL and semaglutide placebo are visually identical.

9.2 Labelling

The trial products will be labelled in accordance with Annex 13[51], local regulations and trial requirements.

Each trial site will be supplied with sufficient trial products for the trial on an on-going basis controlled by the IWRS.

Each dispensing unit (DU) is uniquely numbered with a Dispensing Unit Number (DUN).

NovoPen® 4 is a CE-marked, US FDA and Japan MHLW (Ministry of Health, Labour and Welfare) approved pen injector device for subcutaneous administration of insulin. This trial is investigating

an indication outside the approved intended use or indication for use and the NovoPen® 4 will therefore be labelled "exclusively for clinical investigations" worded in accordance with national legislation. A description of the device is included in the Investigator's Brochure.

The investigator must document that direction for use (DFU) is given to the subject orally and in writing at the first dispensing visit (visit 2). At the later dispensing visits the investigator or delegate should ensure that subjects comply with injection procedures and re-dispense DFU, if needed.

9.3 Storage

Table 9–2 Storage conditions

Trial product	Storage conditions (not-in-use)	In-use conditions	In-use time[a]
Semaglutide 1.0 mg/mL	Store in a refrigerator between 2°C - 8°C (36°F – 46°F) Do not freeze Protect from light	Store below 30°C (86°F) Do not refrigerate Do not freeze Protect from light	Use within 28 days
Semaglutide placebo			

[a] In-use time starts when the product is taken out of the refrigerator at subjects home

The investigator must ensure that trial product is kept under proper storage conditions and record and evaluate the temperature. The investigator must inform Novo Nordisk **immediately** if any trial product has been stored outside specified conditions (e.g. outside temperature range). Additional details regarding handling of temperature deviations can be found in the trial materials manual (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 must take appropriate action to ensure correct storage.

9.4 Drug accountability and destruction

Drug accountability of all trial products received at site is the responsibility of the investigator.

Returned trial product (used/partly used and/or unused), expired or damaged trial product can be stored at room temperature and must be stored separately from non-allocated trial product.

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

The trial products will be dispensed to each subject as required according to treatment group. The IWRS will allocate trial product to the subject at randomisation and each dispensing visit. The correct dispensing unit number(s) (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.

Subjects must be instructed to return all used, partly used and unused trial product including empty packaging material at each dispensing visit and at end of treatment visit.

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

9.5 Auxiliary supplies

The following auxiliary supplies will be provided by Novo Nordisk in accordance with the TMM:

- Needles for NovoPen® 4 pen injector (maximum length to be used is 8 mm)
- Direction for use for NovoPen® 4 pen injector
- Blood glucose meters (including lancets, plasma-calibrated test strips and control solutions). User manual will be provided along with the blood glucose meter.

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

10 Interactive voice/web response system

A trial-specific IWRS will be set up which can be accessed at any time via the internet or telephone. Access to the IWRS must be restricted to and controlled by authorised persons.

In this trial, the IWRS is used for:

- Screening
- Screening failure
- Randomisation
- Medication arrival
- Dispensing
- Treatment discontinuation
- Completion
- Code break
- Drug accountability
- Data change

IWRS user manuals will be provided to each trial site. DUNs will be allocated using the IWRS. It is important to dispense the exact allocated DUNs to a subject.

11 Randomisation procedure and breaking of blinded codes

The trial is a double-blinded trial. A randomisation session will be carried out for all subjects using the IWRS.

At the randomisation visit (visit 2), eligible subjects will be randomised in a 3:3:3:1:1:1 manner to receive daily dose of:

- semaglutide 0.1, 0.2 or 0.4 mg (dose escalation every fourth week) or
- placebo (matching each of the active treatment arms with corresponding injection volumes)

Randomisation will be controlled by the IWRS and stratified in five strata defined by region, diabetes status and fibrosis stage for baseline liver biopsy according to the criteria below:

- Japanese
- Non-Japanese, with type 2 diabetes, fibrosis stage 2
- Non-Japanese, with type 2 diabetes, fibrosis stage 3
- Non-Japanese, without type 2 diabetes, fibrosis stage 2
- Non-Japanese, without type 2 diabetes, fibrosis stage 3

This is to ensure an even distribution of the treatment arms within the five strata.

11.1 Breaking of blinded codes

The IWRS will notify Novo Nordisk (monitor and the Global Safety department) immediately after the code is broken.

The code for a particular subject may be broken in a medical emergency if knowing the actual treatment would influence the treatment of the subject. Whenever a code is broken the person breaking the code must print the Code Break Confirmation Notification generated by the IWRS, record the reason, and sign and date the document.

When the code 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 code break the IWRS helpdesk should be contacted. Contact details are listed in Attachment I.
If the code has been broken, the subject must discontinue treatment with trial product and a treatment discontinuation session must be completed in IWRS.

12 Adverse events, technical complaints and pregnancies

12.1 Definitions

12.1.1 Adverse event

An adverse event (AE) is any untoward medical occurrence in a subject administered a medicinal product, and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a product, whether or not considered related to the product.

An AE includes:

- A clinically significant worsening of a concomitant illness.
- A clinical laboratory adverse event (CLAE): a clinical laboratory abnormality which is clinically significant, i.e. an abnormality that suggests a disease and/or organ toxicity and is of a severity that requires active management. Active management includes active treatment or further investigations, for example change of medicine dose or more frequent follow-up due to the abnormality.

The following should **not** be reported as AEs:

- Pre-existing conditions, including those found as a result of screening or other trial procedures performed before exposure to trial product (pre-existing conditions should be reported as medical history or 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.
- Non-serious hypoglycaemia is an AE, but is reported on a hypoglycaemic episode form instead of on an AE form, see section 8.4.7.

The following three definitions are used when assessing an AE:

- **Severity**
  - **Mild –** no or transient symptoms, no interference with the subject's daily activities.
  - **Moderate** – marked symptoms, moderate interference with the subject's daily activities.
  - **Severe** – considerable interference with the subject's daily activities; unacceptable.
- **Causality**
  Relationship between an AE and the relevant trial product*(s)*:
  - **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.

- **Final outcome**
  - **Recovered/resolved** - The subject has fully recovered, or by medical or surgical treatment the condition has returned to the level observed at the first trial-related activity after the subject signed the informed consent.
  - **Recovering/resolving** - The condition is improving and the subject is expected to recover from the event. This term is only applicable if the subject has completed the trial or has died from another AE.
  - **Recovered/resolved with sequelae** - The subject has recovered from the condition, but with lasting effect due to a disease, injury, treatment or procedure. If a sequela meets an SAE criterion, the AE must be reported as an SAE.
  - **Not recovered/not resolved** - The condition of the subject has not improved and the symptoms are unchanged, or the outcome is not known.
  - **Fatal** - This term is only applicable if the subject died from a condition related to the reported AE. Outcomes of other reported AEs in a subject before he/she died should be assessed as "recovered/resolved", "recovering/resolving", "recovered/resolved with sequelae" or "not recovered/not resolved". An AE with fatal outcome must be reported as an SAE.
  - **Unknown** - This term is only applicable if the subject is lost to follow-up.

12.1.2 Serious adverse event

A serious adverse event (SAE) is an experience that at any dose results in any of the following:

- Death.
- A life-threatening[a] experience.
- In-patient hospitalisation[b] or prolongation of existing hospitalisation.
- A persistent or significant disability or incapacity[c].
- A congenital anomaly or birth defect.
- Important medical events that may not result in death, be life threatening[a] or require hospitalisation[b] may be considered an SAE when - based on appropriate medical judgement - they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition of SAE[d].

a. The term "life threatening" in the definition of SAE 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 was more severe.

b. The term "hospitalisation" is used when a subject:

- Is admitted to a hospital or in-patient, irrespective of the duration of physical stay, or
- Stays at the hospital for treatment or observation for more than 24 hours

Medical judgement must always be exercised, and when in doubt, the hospital contact should be regarded as a hospitalisation. 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.

[c.] A substantial disruption of a subject's ability to conduct normal life functions (e.g. following the event or clinical investigation the subject has significant, persistent or permanent change, impairment, damage or disruption in his/her body function or structure, physical activity and/or quality of life).

[d.] For example intensive treatment in an emergency room or at home of allergic bronchospasm, blood dyscrasia or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

The following adverse events must always be reported as an SAE using the important medical event criterion if no other seriousness criteria are applicable:

- suspicion of transmission of infectious agents via the trial product
- risk of liver injury defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 x UNL and total bilirubin >2 x UNL, where no alternative aetiology exists (Hy's law).

12.1.3 Non-serious adverse event

A non-serious AE is any AE which does not fulfil the definition of an SAE.

12.1.4 Medication errors

A medication error concerning trial products is defined as:

- Administration of wrong drug or use of wrong device.
  Note: Use of wrong DUN is not considered a medication error.
- Wrong route of administration, such as intramuscular instead of subcutaneous.
- Administration of an overdose with the intention to cause harm (e.g. suicide attempt), misuse or abuse of trial product.
- Accidental administration of a lower or 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.

Medication errors must be reported on an AE form and a specific event form, see section 8.4.4.

12.1.5 Adverse events requiring additional data collection

AEs requiring additional data collection are AEs where the additional data will benefit the evaluation of the product safety. Some events in this trial will be adjudicated by an independent external committee as described in section 12.7.2.

Table 12–1 lists AEs that require completion of specific event forms in the eCRFs and/or are subject to event adjudication.

For further information regarding definitions and which data to collect for the events that require additional data collection, please see Appendix B.

Table 12–1 Adverse events requiring completion of specific eCRF event forms and/or are subject to event adjudication

Event	Specific event form	Event adjudication
Fatal event	No	Yes
Acute coronary syndrome (myocardial infarction, silent myocardial infarction or unstable angina pectoris)	Yes	Yes
Cerebrovascular event (stroke or transient ischaemic attack)	Yes	Yes
Heart failure (requiring hospitalisation or urgent unscheduled visit)	Yes	Yes
Acute pancreatitis	Yes	Yes
Acute gallbladder disease	Yes	No
Neoplasm	Yes	No
Hepatic event	Yes	No

For details about specific event forms, see appendix B.

Identification and reporting of events relevant for adjudication is the responsibility of the investigator including but not limited to the following:

- Identification of adverse events relevant for adjudication according to the protocol.
- Completing the "Adjudication" form in the Novo Nordisk eCRF system within the required timelines.
- Providing alternative aetiology for events initially not reported as an event relevant to adjudication, identified via for example the Novo Nordisk Event Adjudication Group, a centralised ECG reading or the event adjudication committee.
- Uploading redacted copies of source data as specified on the adjudication form directly into the source document collection database, provided by the event adjudication supplier. This

responsibility also covers uploading of clinical data for events identified in the preferred term (PT) search and evaluated to be relevant to adjudication by the event adjudication supplier or the committee chair or appointed delegate. In case copies of source data cannot be retrieved or are pending for a long time, the investigator should prepare and provide a narrative describing the event based on the information which the investigator has access to.

12.1.6 Technical complaints

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:

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

12.2 Reporting of adverse events

All events meeting the definition of an AE must be collected and reported. This includes events from the first trial-related activity after the subject has signed the informed consent until the end of the post-treatment follow-up period (visit 19) or visit 19A for subjects discontinuing trial product prematurely. The events must be recorded in the applicable eCRF forms in a timely manner, see timelines below and Figure 12–1.

During each contact with the trial site staff, the subject must be asked about AEs and technical complaints, for example by asking: “Have you experienced any problems since the last contact?”

All AEs, either observed by the investigator or subject, must be reported by the investigator and evaluated.

All AEs must be recorded by the investigator on an AE form. The investigator should report the diagnosis, if available. If no diagnosis is available, the investigator should record each sign and symptom as individual AEs using separate AE forms.

For SAEs, a safety information form must be completed in addition to the AE form. If several symptoms or diagnoses occur as part of the same clinical picture, one safety information form can be used to describe all the SAEs.

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.

Timelines for initial reporting of AEs:

The investigator must complete the following forms in the CRF/eCRF within the specified timelines:

- **SAEs:** The AE form **within 24 hours** and the safety information form **within 5 calendar** days of the investigator's first knowledge of the SAE.

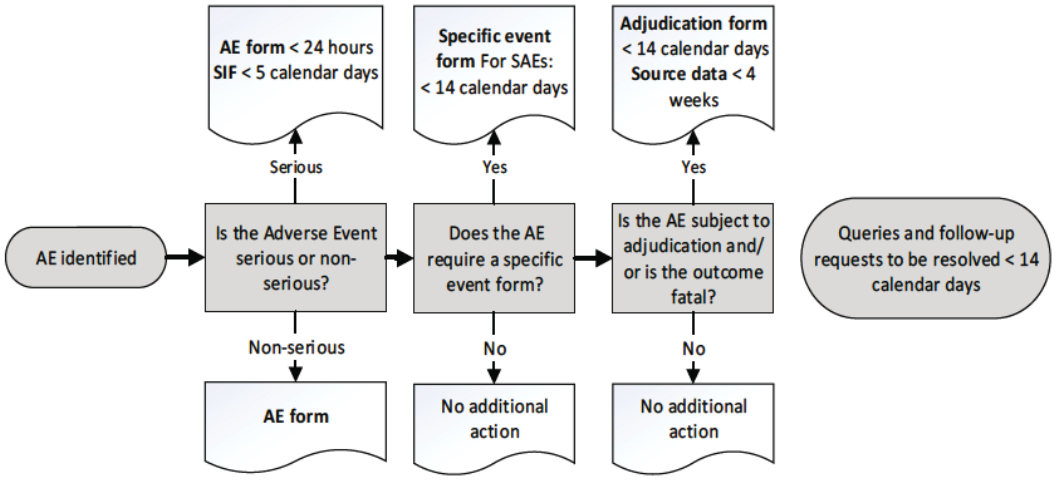
Both forms must be signed within 7 calendar days from the date the information was entered in the eCRF.

For SAEs requiring reporting on a specific event form: In addition to the above the specific event form within 14 calendar days from the investigator's first knowledge of the AE.

Events for Adjudication: The adjudication form should be completed within 14 calendar days of the investigator's first knowledge of the AE and all relevant predefined documents provided within 4 weeks, see Section 12.7.2.

If the eCRF is unavailable, the concerned AE information must be reported on a paper AE form and sent to Novo Nordisk by fax, e-mail or courier within the same timelines as stated above. When the eCRF becomes available again, the investigator must enter the information on the form into the eCRF.

Contact details (fax, telephone, e-mail and address) are provided in the investigator trial master file.



Timelines are for the completion of forms from the time of investigator's awareness
AEs requiring specific event forms are descibed in Section 12.1.4 and 12.1.5
AEs for adjudication are described in Section 12.1.5
AE: Adverse event **SIF:** Safety information form

Figure 12–1 Reporting of AEs

Novo Nordisk assessment of AE expectedness:

Novo Nordisk assessment of expectedness is performed according to the following reference documents: Semaglutide Investigator´s Brochure, s.c., T2D[38], current version and any updates thereto.

Reporting of trial product-related SUSARs by Novo Nordisk:

Novo Nordisk will notify the investigator of trial product-related suspected unexpected serious adverse reactions (SUSARs) in accordance with local requirements and ICH GCP[1]. In addition, the investigator will be informed of any trial-related SAEs that may warrant a change in any trial procedure.

In accordance with regulatory requirements, Novo Nordisk will inform the regulatory authorities, including EMA, of trial product-related SUSARs. In addition, Novo Nordisk will inform the IRBs/IECs of trial product-related SUSARs in accordance with local requirement and ICH GCP[1], unless locally this is an obligation of the investigator.

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.

12.3 Follow-up of adverse events

The investigator must record follow-up information by updating the forms in the eCRF.

Follow-up information must be reported to Novo Nordisk according to the following:

- **SAEs:** All SAEs must be followed until the outcome of the event is "recovered/resolved", "recovered/resolved with sequelae" or "fatal", and until all queries have been resolved. Cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE) may be closed with the outcome "recovering/resolving" or "not recovered/not resolved". Cases can be closed with the outcome of "recovering/resolving" when the subject has completed the follow-up period and is expected by the investigator to recover.

  The SAE follow-up information should only include new (e.g. corrections or additional) information and must be reported **within 24 hours** of the investigator's first knowledge of the information. This is also the case for previously non-serious AEs which subsequently become SAEs.

- **Non-serious AEs:** Non-serious AEs must be followed until the outcome of the event is "recovering/resolving", "recovered/resolved" or "recovered/resolved with sequelae" or until the end of the follow-up period stated in the protocol, whichever comes first, and until all queries related to these AEs have been resolved. Cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE) may be closed with the outcome "recovering/resolving" or "not recovered/not resolved". Cases can be closed with the outcome of "recovering/resolving" when the subject has completed the follow-up period and is expected by the investigator to recover.

The investigator must ensure that the recording of the worst case severity and seriousness of an event is kept throughout the trial. A worsening of an unresolved AE must be reported as follow up with re-assessment of severity and/or seriousness of the event.

Queries or follow-up requests from Novo Nordisk must be responded to **within 14 calendar days** from the date of receipt of the request, unless otherwise specified in the follow-up request.

SAEs after end of trial: If the investigator becomes aware of an SAE with a suspected causal relationship to the investigational medicinal product occurring to a subject after the subject has

ended the trial, the investigator should report this SAE within the same timelines as for SAEs during the trial.

12.4 Technical complaints and technical complaint samples

12.4.1 Reporting of technical complaints

All technical complaints on any of the following products:

- Semaglutide 1.0 mg/mL or semaglutide placebo, 3 mL cartridge
- NovoPen® 4
- Novo Nordisk needles

which occur from the time of first usage of the product until the time of the last usage of the product, must be collected and reported to Customer Complaint Center, Novo Nordisk.

Contact details (fax, e-mail and address) are provided in Attachment I to the protocol.

The investigator must assess whether the technical complaint is related to any AEs and/or SAEs.

Technical complaints must be reported on a separate technical complaint form:
- One technical complaint form must be completed for each affected DUN
- If DUN is not available, a technical complaint form for each batch, code or lot number must be completed

The investigator must complete the technical complaint form in the eCRF within the following timelines of the trial site obtaining knowledge of the technical complaint:
- Technical complaint assessed as related to an SAE **within 24 hours**
- All other technical complaints **within 5 calendar days**

If the eCRF 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 eCRF becomes available again, the investigator must enter the information on the technical complaint form in the eCRF.

12.4.2 Collection, storage and shipment of technical complaint samples

The investigator must collect the technical complaint sample and notify the monitor **within 5 calendar days** of obtaining the sample at trial site. The monitor must coordinate the shipment to Customer Complaint Center, Novo Nordisk (the address is provided in Attachment I) and ensure that the sample is sent as soon as possible. A copy of the technical complaint form must be included

in the shipment of the sample. If several samples are returned in one shipment, the individual sample and the corresponding technical complaint form must be clearly separated.

The investigator must ensure that the technical complaint sample contains the batch, code or lot number and, if available, the DUN. All parts of the DUN should be returned.

If the technical complaint sample is unobtainable, the investigator must specify on the technical complaint form why it is unobtainable.

Storage of the technical complaint sample must be done in accordance with the conditions prescribed for the product.

12.5 Pregnancies

12.5.1 Pregnancies in female subjects

Female subjects must be instructed to notify the investigator immediately if they become pregnant during the trial. The investigator must report any pregnancy in subjects who have received trial product(s).

The investigator must follow the pregnancy until the pregnancy outcome and the newborn infant is one month of age.

The investigator must report information about the pregnancy, pregnancy outcome, and health of the newborn infant(s), as well as AEs in connection with the pregnancy, and AEs in the foetus and newborn infant.

The following must be collected and reported by the investigator to Novo Nordisk - electronically (e.g. in PDF format), or by fax or courier:

1. **Reporting of pregnancy information**
   Information about the pregnancy and pregnancy outcome/health of the newborn infant(s) has to be reported on Maternal Form 1A and 1B, respectively.

   When the pregnancy outcome is abnormal (i.e. congenital anomalies, foetal death including spontaneous abortion and/or any anomalies of the foetus observed at gross examination or during autopsy), and/or when a congenital anomaly is diagnosed within the first month, further information has to be reported for the female subject on Maternal Form 2. In addition, information from the male partner has to be reported on the Paternal Form, after an informed consent has been obtained from the male partner.

   Initial reporting and follow-up information must be reported **within 14 calendar days** of the investigator's first knowledge of initial or follow-up information.

2. Reporting of AE information

The investigator has to report AEs in connection with the pregnancy as well as in the foetus and newborn infant(s). The SAEs that must be reported include abnormal outcome, such as foetal death (including spontaneous abortion), and congenital anomalies (including those observed at gross examination or during autopsy of the foetus), as well as other pregnancy complications fulfilling the criteria of an SAE.

Forms and timelines for reporting AEs:

Non-serious AEs:

- AE form[a] **within 14 calendar days** of the investigator's first knowledge of the initial or follow-up information to the non-serious AE.

SAEs:

- AE form[a] **within 24 hours** of the investigator's first knowledge of the SAE.
- Safety information form **within 5 calendar days** of the investigator's first knowledge of the SAE.
- **SAE follow-up information** to the AE form and/or safety information form **within 24 hours** of the investigator's first knowledge of the follow-up information.

[a] It must be clearly stated in the AE diagnosis field on the AE form if the event occurred in the subject, foetus or newborn infant. If the AE occurred in the foetus or newborn infant, the AE can only be reported on paper AE and safety information form.

Any queries or follow-up requests from Novo Nordisk to non-serious AEs, SAEs and pregnancy forms must be responded to by the investigator **within 14 calendar days** from the date of receipt of the request, unless otherwise specified in the follow-up request.

12.6 Precautions and/or overdose

Limited data are available with regard to overdose and semaglutide. Expected adverse events in connection to an overdose of subcutaneous semaglutide are gastrointestinal AEs and hypoglycaemia (if combined with SU and insulin). Events of nausea, vomiting and headache have been reported in connection with accidental administration of up to 4 mg semaglutide. No symptoms of hypoglycaemia have been reported in connection with overdose of semaglutide. In the event of overdosage, appropriate supportive treatment should be initiated according to the subject's clinical signs and symptoms.

12.7 Committees related to safety

12.7.1 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.

12.7.2 Event adjudication committee

An independent external event adjudication committee is established to perform validation of selected AEs according to pre-defined diagnostic criteria. The validation is based on review of pre-defined clinical source data related to the specific AE. The pre-defined clinical source data consist of copies of source documents collected and delivered by the investigational sites.

The EAC is composed of permanent members covering required medical specialities. The EAC members must disclose any potential conflicts of interest and must be independent of Novo Nordisk.

The events are reviewed by the event adjudication committee in a blinded manner. The EAC will have no authorisation to impact on trial conduct, trial protocol or amendments.

The EAC works in accordance with written guidelines included in the EAC Charter describing in details the composition, tasks, responsibilities and work processes of the committee.

The AEs for adjudication are listed in Table 12–1. In addition, cardiovascular events are being adjudicated according to FDA requirements[1, 52].

There are different processes for capturing events for adjudication:

1. Direct reporting by investigator:

All AEs need to be assessed by the investigator if any AE category is applicable. If the AE category selected is in scope for adjudication, the adjudication form in the eCRF will be populated for sites to complete. For AEs with fatal outcome the Fatal Adjudication form will appear in the eCRF when a fatal outcome is selected for an AE.

2. Screening:

All AEs will be screened by Novo Nordisk for potential missed events for adjudication and if needed, the investigator will be asked to provide additional information such as an alternative aetiology, underlying cause(s) and/or clinical details.

All ECGs will be centrally read. If the central reading conclusion is suggestive of new MI, the ECG adjudication form will be populated for sites to complete for all post-baseline ECGs.

3. EAC identified events:

The EAC can decide to have an AE adjudicated even if not initially reported as an event for adjudication by the investigator.

Event adjudication will be performed for AEs in randomised subjects including AEs with an onset date during the screening period. Event adjudication will not be performed for AEs in screening failures.

AEs for adjudication must be reported according to section 12.2. In addition the specific adjudication form should be completed within 14 calendar days of the investigator's first knowledge of the AE, and all relevant predefined documents provided within 4 weeks according to instructions in the event adjudication site manual.

The EAC will review copies in English (translated if necessary) of medical documentation received in the adjudication packages (e.g. x-ray, ECGs, ultrasound images, discharge summaries, pathology reports and death certificates). The investigator must provide medical documentation as soon as possible, when they receive the request from Novo Nordisk or the event adjudication vendor.

The assessment made by the event adjudication committee will be included in the clinical trial report as well as the assessments made by the investigator. However, the adjudication made by the event adjudication committee, given its independent analysis of each event, will be attributed with greater importance of the two. The outcome of adjudication will be kept in the clinical trial database.

13 Case report forms

For this trial a combination of electronic case report forms (eCRFs) and paper CRFs will be used.

Novo Nordisk will provide a system for the electronic case report forms (eCRF). This system and support services to the system will be provided by an external supplier.

Ensure that all relevant questions are answered, and that no empty data field exists. If a test or an assessment has not been done and will not be available, or if the question is irrelevant (e.g. is not applicable), indicate this according to the data entry instructions.

The following will be provided as paper CRFs:

- Pregnancy forms

The following will be provided as paper CRFs to be used when access to the eCRF is revoked or if the eCRF is 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)

On the paper CRF forms print legibly, using a ballpoint pen. Ensure that all questions are answered, and that no empty data blocks exist. Ensure that no information is recorded outside the data blocks. If a test/assessment has not been done and will not be available, indicate this by writing “ND” (not done) in the appropriate answer field in the CRF. If the question is irrelevant (e.g. is not applicable) indicate this by writing “NA” (not applicable) in the appropriate answer field. Further guidance can be obtained from the instructions in the CRF.

The investigator must ensure that all information is consistent with the source documentation. By electronically signing the case book in the eCRF, the investigator confirms that the information in the eCRF and related forms is complete and correct.

13.1 Corrections to case report forms

Corrections to the eCRF data may be made by the investigator or the investigator’s delegated staff. An audit trail will be maintained in the eCRF 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 the investigator has signed the case book, the case book must be signed and dated again by the investigator.

13.2 Case report form flow

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

Site specific eCRF data (in an electronic readable format) will be provided to the trial site before access to the eCRF is revoked. This data must be retained at the trial site.

14 Monitoring procedures

During the course of the trial, the monitor will visit the trial site to ensure that the protocol is adhered to, that all issues have been recorded, to perform source data verification and to monitor drug accountability. The first monitoring visit will be performed as soon as possible after FSFV at the trial site and no later than 4 weeks after. The monitoring visit intervals will depend on the outcome of the remote monitoring of the eCRFs, the trial site's recruitment rate and the compliance of the trial site to the protocol and GCP, but will not exceed 8 weeks during recruitment and 12 weeks after end of recruitment until LSLV at the trial site for sites with subjects between visit 1 and visit 19/19A.

The monitor must be given direct access to all source 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).

All data must be verifiable in source documentation other than the eCRF.

For all data recorded the source document must be defined in a source document agreement at each trial site. There must only be one source defined at any time for any data element.

Source data generated by the trial site can be corrected by another person than the person entering the source data if accepted by local regulations; any correction must be explained, signed and dated by the person making the correction.

The original of the completed diaries and PROs must not be removed from the trial site.

The monitor will ensure that the eCRFs are completed and that paper CRFs are collected.

`The following data will be source data verified for screening failures:

- Date for obtaining informed consent.
- Reason for screening failure
- Serious adverse events (if any)

Monitors will review the subject's medical records and other source data (e.g. the diaries and PROs) to ensure consistency and/or identify omissions compared to the eCRF. If discrepancies are found, the investigator must be questioned about these.

A follow-up letter (paper or electronic) will be sent to the investigator following each monitoring visit. They should address any action to be taken.

15 Data management

Data management is the responsibility of Novo Nordisk. Data management may be delegated under an agreement of transfer of responsibilities to a contract research organisation (CRO).

Appropriate measures, including encryption of data files containing person identifiable data, will be used to ensure confidentiality of subject data, when they are transmitted over open networks.

Data from central laboratories will be transferred electronically. In cases where data is transferred via non-secure electronic networks, data will be encrypted during transfer.

The subject and any biological material obtained from the subject will be identified by subject number and trial ID. Appropriate measures such as encryption or leaving out certain identifiers will be enforced to protect the identity of subjects in all presentations and publications as required by local, regional and national requirements.

16 Computerised systems

Novo Nordisk will capture and process clinical data using computerised systems that are described in Novo Nordisk Standard Operating Procedures and IT architecture documentation. The use and control of these systems are documented.

Investigators working on the trial may use their own electronic systems to capture source data.

17 Statistical considerations

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

The estimand addressing the primary objective is defined as the de-facto (effectiveness) treatment effect on NASH resolution without worsening in fibrosis for all randomised subjects after 72 weeks. All post-baseline scheduled visit data will be included in the statistical analysis, including data collected after discontinuation of trial product. The chosen estimand assesses the difference in resolution of NASH in a future population that results from initiating treatment with semaglutide as compared to placebo. Generalisation of this estimand depends among other things on the extent to which treatment adherence in this trial reflects clinical practice.

The three different placebo arms will be pooled into one placebo treatment arm in all planned analyses. This pooling assumes that there is no substantial effect of different semaglutide placebo volumes on the efficacy and safety endpoints. The validity of this assumption will be checked for the primary endpoint and treatment-emergent adverse events by evaluating summaries for each placebo arm. Should the placebo arms demonstrate substantial differences, appropriate sensitivity analyses will be included.

The statistical analyses will in general consist of the following three pairwise treatment comparisons:

- semaglutide 0.4 mg versus placebo
- semaglutide 0.2 mg versus placebo
- semaglutide 0.1 mg 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. The problem of multiple testing will be taken into account with respect to the primary endpoint (see section 17.2) but not for any of the secondary endpoints.

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 (see the definition of the sets in section 17.2).

The baseline measurement is defined as the latest available measurement at or prior to the randomisation visit. An exception is made for identifying abnormal laboratory findings (including ALT, AST, GGT, bilirubin and INR) in which case the baseline value is defined as the mean of the available measurements at the screening and randomisation visits.

Laboratory values below the lower limit of quantification (LLOQ) will be set to ½LLOQ.

17.1 Sample size calculation

The sample size calculation is based on an aim to detect a difference in the probability of achieving NASH resolution (without worsening in fibrosis) between the highest semaglutide dose and the pooled placebo arm at 5% significance level, using Pearson chi-square test with normal approximation. The power is set to 90%.

It is expected that some subjects will respond to standard care. In the LEAN trial, 2 (9%) of 22 placebo subjects had improvement in liver histology. In the FLINT[53] and PIVENS[54] trials, clearance of NASH was a secondary endpoint and the corresponding numbers were 13 (13%) of 98 subjects and 17 (21%) of 83 subjects, respectively. However, these figures also included patients that had worsening of fibrosis. As a conservative assumption, it is anticipated that up to 20% of the placebo completers will achieve resolution of NASH with no worsening of fibrosis.

It is uncertain how many subjects on semaglutide should be expected to achieve resolution of NASH. In the LEAN trial, an improvement was found in 9 (39%) of 23 subjects who received liraglutide 1.8 mg. In communication with medical advisers, a treatment difference of 20-30 percentage points was deemed to be a realistic target as well as clinically relevant. Therefore, it is assumed that 45% of the subjects who complete treatment with semaglutide 0.4 mg achieve resolution of NASH.

Based on the previous NASH trials, 15% of the randomised subjects are anticipated to prematurely discontinue trial product before week 72. These will be included in the main analysis either by using the observed outcome at week 72 (if the outcome is known) or by using imputation (if the outcome is not known). In either case, it is assumed that none of these subjects will achieve resolution of NASH.

Based on the assumptions above, the required number of randomised subjects per arm for the 3 semaglutide arms and the pooled placebo arm is found to be 91. Since the number in the pooled placebo arm needs to be divisible by 3, the number of subjects in each arm is adjusted to 93. Hence, the total number of subjects to be randomised is 372.

In order to investigate the influence of the values of the model parameters such as treatment difference and rate of premature discontinuation of trial product on the calculation, sample sizes have been calculated for different alternative scenarios. The results can be seen in Table 17–1.

Table 17–1 Sample size calculations for different scenarios - number of subjects per arm

Probability of achieving resolution of NASH			
Semaglutide completers	Placebo completers	Rate of premature discontinuation	N per arm
50%	20%	10%	61
		15%	66
		20%	72
45%	20%	10%	84
		15%	91
		20%	99
40%	20%	10%	126
		15%	137
		30%	176

17.2 Definition of analysis sets

The following analysis sets are defined in accordance with the ICH-E9 guidance[55]:

- 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".

Before data are locked for statistical analysis, a review of all data will take place. Any decision to exclude a subject or single observations from the statistical analysis is the joint responsibility of the trial statistician, the international trial manager and the medical specialist. Exclusion of data from analyses will be used restrictively and normally no data should be excluded from the FAS. If any data is excluded, the decision will be justified and documented. The subjects and observations excluded from analysis sets, and the reason for their exclusion, will be described in the clinical trial report.

Observation periods

Data will be evaluated based on different observation periods which will be derived individually for each subject. The following two observation periods are defined:

- In-trial: This period starts on the date of the randomisation visit and ends on the date of the last trial-related procedure/assessment whether or not the subject has stopped taking trial product.

- 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 (V19), or c) end of the in-trial period. For evaluation of all other data, the period ends at the date of the last dose of trial product +1 day in order to ensure specificity to reversible effects of treatment.

The statistical analyses of the efficacy endpoints will primarily be based on the in-trial period. The on-treatment period is used for some supportive efficacy analyses and all statistical analyses of safety endpoints. Summary statistics will in general be presented for both observation periods.

Data collected after the observation period in question will be excluded from any summary or analysis based on that observation period.

Missing data

With respect to the primary analysis of the primary endpoint, missing week 72 data will be imputed as no resolution of NASH. Sensitivity analyses will be performed using imputation methods based on treatment adherence and unconditional reference, respectively (see section 17.3). For the secondary endpoints, the handling of missing data depends on the type of endpoint and analysis (see section 17.4).

In the analyses based on the in-trial period, the proportion of missing data is expected to be maximum 10%. These data would be missing due to subjects withdrawing from trial or being lost to follow-up. In the analyses based on the on-treatment period, the proportion of missing data is expected to be higher (15%) since data collected after discontinuation of trial product will be excluded. The most common reasons for premature discontinuation of trial product are anticipated to be AEs, ineffective therapy, and noneligibility (subjects randomised although not fulfilling inclusion/exclusion criteria). AEs leading to treatment discontinuation are expected to be equally common across treatment arms except possibly for a higher incidence of AEs due to gastrointestinal side effects in the semaglutide arms. On the other hand, more subjects in the placebo arms may be expected to drop out due to an experienced lack of effect with respect to body weight loss. Overall, the proportion of missing data is expected to be similar across treatment arms.

17.3 Primary endpoint

The primary endpoint is the binary outcome NASH resolution without worsening in fibrosis after 72 weeks (yes/no).The primary analysis will be based on the Cochran-Mantel-Haenszel (CMH) test[54] which will be performed separately for the comparisons between each of the semaglutide arms and placebo. The test will adjust for baseline diabetes status (with or without T2D) and baseline fibrosis stage (F2 or F3). The response data will consist of the outcomes of the week 72 biopsy including assessments taken after premature discontinuation of trial product. Missing response data will be

imputed as no resolution of NASH. This approach does not rely on an assumption of missing at random and should be considered conservative for estimating the treatment effect.

The result of each comparison will be presented as the p-value for testing the null hypothesis of no treatment difference versus a two-sided alternative. The asymptotic p-value obtained from a chi-square distribution will be used unless it is not considered a valid approximation based on the Mantel-Fleiss criterion[55], in which case the exact p-value will be calculated. Besides the p-value, the common odds ratio will be estimated together with a 95% confidence interval using the Mantel-Haenszel estimator associated with the CMH test.

Hierarchical testing procedure

In order to confirm the effect of semaglutide without risk of inflation of the type 1 error, the comparisons will be evaluated hierarchically according to descending semaglutide dose using a family-wise error rate of 5%. The testing procedure will start with the comparison of semaglutide 0.4 mg versus placebo and then continue by in turn comparing semaglutide 0.2 mg versus placebo and semaglutide 0.1 mg versus placebo. Each test will use a local two-sided significance level of 5%. If one of the tests fails to reject the null hypothesis, the testing procedure will stop and no further conclusions will be made.

Sensitivity analyses

To investigate the sensitivity of the results of the primary analysis with regard to the handling of missing data, the following four sensitivity analyses will be performed:

- Analysis using imputation based on treatment adherence: An analysis based on the same type of non-parametric method as for the primary analysis but with missing data handled by a multiple imputation (MI) method which assumes that the unobserved outcomes are well described by the observed outcomes from subjects who at week 72 are similar in terms of treatment adherence. This will be done as follows:

1. Missing data are imputed by sampling with replacement from the empirical distribution of observed outcomes separately within the 8 groups of subjects defined by randomised treatment arm and whether subjects complete the 72-week treatment or not. If a group completely lacks observed outcomes, missing data within this group will be imputed as no resolution of NASH. Multiple (1000) replicates of a complete data set are generated in this way.

2. For each complete data set, the log odds ratios are estimated using the same method as in the primary analysis.

3. The estimates and standard errors for the 1000 complete data sets are pooled using Rubin's rule[56]:

$$m_{MI} = \frac{1}{N}\sum_{i=1}^{N} m_i\,, \qquad SE_{MI} = \sqrt{\frac{1}{N}\sum_{i=1}^{N} SE_i^2 + \left(1+\frac{1}{N}\right)\left(\frac{1}{N-1}\right)\sum_{i=1}^{N}(m_i - m_{MI})^2},$$

where m_i and SE_i are the estimated log odds ratios and standard errors for the $N = 1000$ data sets, and m_{MI} and SE_{MI} are the pooled estimates. From m_{MI} and SE_{MI}, the 95% confidence intervals for the odds ratios and associated p-values are calculated.

This analysis differs from the primary analysis in that it assumes that subjects with missing week 72 data have the same chances of NASH resolution as subjects with week 72 data in the same treatment group, accounting for whether they completed or discontinued the randomised treatment. This is a less conservative assumption than the one used in the primary analysis since it includes the possibility that subjects with missing week 72 data may have NASH resolution. The analysis intends to address missing data relative to what the measurements would have been had the measurements been taken.

- 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 of the subjects in the placebo arm 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. 1000 replicates of a complete data set will be generated that will then be analysed in the same way as in the MI analysis based on treatment adherence. This analysis differs from the primary analysis in that it assumes that subjects with missing week 72 data have the same chances of NASH resolution as subjects with week 72 data in the placebo group. If there are more missing week 72 data in the semaglutide group than in the placebo group, this analysis is less conservative than the primary analysis and probably gives better estimate of the treatment effect. Compared to the first sensitivity analysis, this analysis is more conservative since it assumes that subjects with missing week 72 data in the semaglutide group have the same chance of NASH resolution as subjects in the placebo group.
- Complete case in-trial analysis: The same as the primary analysis but where subjects with missing week 72 data are excluded from the analysis.
- Complete case on-treatment analysis: The same as the primary analysis but where subjects with missing week 72 data or for whom the data were collected after the on-treatment period are excluded from the analysis.

The two complete case analyses are included as benchmarks. They are not based on the randomisation principle and do not estimate any causal effect of semaglutide treatment. The results are expected to be biased in favour of semaglutide and must be interpreted with extreme caution.

The adjustment for covariates in the primary analysis does not exactly match the stratification used for the randomisation. The rationale is that it will not be possible to adjust for region (Japanese or non-Japanese) and, at the same time, adjust for diabetes status and baseline fibrosis stage within the Japanese group due to small sample sizes. Adjustment for region is not expected to influence the overall results but is included in the stratification to facilitate an evaluation of consistency of treatment effect between the entire population and Japanese subjects. Region has therefore been excluded from the primary analysis. However, a CMH test stratified according to the five strata used for the randomisation will be performed as a sensitivity analysis.

Adjustment for baseline body weight as a continuous covariate may potentially give more precise estimates of the treatment effects. To investigate the influence of such an adjustment, a sensitivity analysis will be performed using a logistic regression model which includes treatment, baseline diabetes status, baseline fibrosis stage and diabetes-by-fibrosis interaction as factors and baseline body weight as a covariate.

Exploratory analysis

The dose-response relationship with respect to the primary endpoint will be further explored by fitting a modified logistic regression model with baseline diabetes status, baseline fibrosis stage and diabetes-by-fibrosis interaction as factors and the log-transformed dose level and baseline body weight as covariates. The model may be expressed as

$$\boldsymbol{p_i} = \boldsymbol{c_1} + \frac{(\boldsymbol{c_2} - \boldsymbol{c_1})}{\mathbf{1} + \boldsymbol{e}^{-\boldsymbol{\beta}\cdot \mathbf{X}_i}}$$

where $\boldsymbol{p_i}$is the probability of NASH resolution for subject *i*, $\boldsymbol{c_1}$and $\boldsymbol{c_2}$ are the asymptotic probabilities of NASH resolution at zero and infinite dose levels, respectively, and $\boldsymbol{\beta}\cdot\mathbf{X}_i$ is the linear prediction function of factors and covariates. The response in the placebo arm will be included in the analysis to help estimate $\boldsymbol{c_1}$. If the model does not describe the dose-response relationship well or if there are convergence problems, a different approximation may be investigated.

17.4 Secondary endpoints

17.4.1 Supportive secondary endpoints

17.4.1.1 Efficacy endpoints

Liver-related histological parameters

The following secondary histological endpoint will be analysed:

- At least one stage of liver fibrosis improvement with no worsening of NASH after 72 weeks (yes/no)

The analysis of this binary endpoint will be based on a logistic regression model which includes treatment, baseline diabetes status, baseline fibrosis stage and diabetes-by-fibrosis interaction as factors and baseline body weight as a covariate. The analysis will include all assessments taken during the in-trial period. Missing week 72 data will be imputed as no improvement in fibrosis.

In addition, separate analyses will be performed for the change from baseline to week 72 in the following histological feature scores:

- Total NAS (0-8) and each of the components:
    - Steatosis (0-3)
    - Lobular inflammation (0-3)
    - Hepatocyte ballooning (0-2)
- Stage of fibrosis according to the Kleiner fibrosis classification (0-4)
- Activity component of SAF score (0-4)

The activity component of the SAF score is defined as the unweighted sum of hepatocyte ballooning and lobular inflammation. The definition of the lobular inflammation score is modified in this calculation so that the scores 2 and 3 on the original scale are merged to a score 2. The possible range of the sum is thus 0 to 4. For all scores, a higher value indicates a more severe state of disease.

The histological feature scores will be analysed by an ordered logistic regression model (also known as a proportional odds model) with the score at week 72 as response; treatment, baseline diabetes status, baseline fibrosis stage, diabetes-by-fibrosis interaction and corresponding baseline score as factors; and baseline body weight as a covariate. The analyses will be based on the in-trial period and missing week 72 data will be imputed as no change from baseline in agreement with the analyses of the binary histological endpoints. The results will be presented as an estimate of the cumulative odds ratio for each treatment comparison together with the associated 95% confidence intervals and p-values.

Biomarkers of NASH disease

Analyses will be performed for the change from baseline to week 72 in the following biomarkers for NASH disease:

- Algorithms
  - Fibrosis-4 score
  - NAFLD Fibrosis Score
- Blood samples
  - Liver enzymes
    - ALT
    - AST
    - GGT
  - Liver synthesis function
    - Albumin
    - INR
  - Exploratory biomarkers
    - ELF
    - CK-18 fragments
    - miR-122
    - IL-1R antagonist
    - MCP-1
    - FGF-21
- Imaging
  - Liver stiffness
  - CAP (liver steatosis)

The Fib-4 score will be derived according to the formula[57]:

$$\text{Fib-4} = \frac{\text{Age (years)} \times \text{AST (U/L)}}{\text{Thrombocyte count } (10^9/\text{L}) \times \sqrt{\text{ALT (U/L)}}}$$

The derivation will be performed at each visit where ALT, AST and thrombocyte count have been assessed. If any of the three laboratory parameters is missing at a specific visit, the Fib-4 score will be considered missing as well.

The NAFLD Fibrosis Score will be derived according to the linear regression formula[58]:

$$\text{NFS} = -1.675 + 0.037 \times \text{Age (years)} + 0.094 \times \text{BMI (kg/m}^2\text{)} + 1.13 \times \text{Hyperglycaemia (yes/no)} + 0.99 \times \text{AST/ALT} + 0.013 \times \text{Thrombocyte count (10}^9\text{/L)} + 0.66 \times \text{Albumin (g/dL)}$$

Hyperglycaemia (yes/no) is a binary variable defined as 1 if FPG ≥ 6.1 mmol/L (110 mg/dL) at the corresponding visit of assessment or the subject has been diagnosed with T2D at screening; otherwise, the variable is defined as 0. NFS will be derived at each visit where body weight, FPG, ALT, AST, thrombocyte count and albumin have been assessed.

The ELF discriminant score will be derived as a log-linear combination of the markers hyaluronic acid (HA), amino-terminal propeptide of type III collagen (PIIINP) and tissue inhibitor of metalloproteinase 1 (TIMP1) according to the formula[59]:

$$\text{ELF} = -7.412 + 0.681 \times \ln(\text{HA (ng/mL)}) + 0.775 \times \ln(\text{P3NP (ng/mL)}) + 0.494 \times \ln(\text{TIMP1 (ng/mL)})$$

Analyses of liver stiffness and CAP (liver steatosis) will only be applicable to sites where these assessments were possible. Subjects at sites which did not have capability to assess liver stiffness or CAP (liver steatosis) will be excluded from the corresponding analysis.

All biomarkers except for NFS, ELF and CAP (liver steatosis) will be logarithmically transformed before the statistical analysis. The treatment differences will subsequently be back-transformed to the original scale and expressed as treatment ratios.

The main analysis of each of the biomarkers will be analysis of covariance (ANCOVA) with missing data handled by unconditional reference-based imputation. This will be done as follows:

1. An ANCOVA model with baseline diabetes status, baseline fibrosis stage and diabetes-by-fibrosis interaction as factors and baseline body weight and baseline value of the corresponding biomarker as covariates is fitted to the change from baseline to 72 weeks for the placebo group only.

2. 1000 sets of values of the model parameters are drawn from the posterior distribution. For each replicated set of parameter values, the model is used to generate a complete data set by imputing missing values at 72 weeks for subjects in all treatment groups based on their baseline diabetes status, baseline fibrosis stage, baseline body weight and baseline value of the corresponding biomarker.

3. For each complete data set, the change from baseline to 72 weeks is analysed using an ANCOVA model with treatment, baseline diabetes status, baseline fibrosis stage and diabetes-by-fibrosis interaction as factors and baseline body weight and baseline value of the corresponding biomarker as covariates.

4. The estimated treatment differences and standard errors for the 1000 complete data sets are pooled using Rubin's rule. From the pooled estimates and standard errors, the 95% confidence intervals for the treatment differences and associated p-values are calculated.

A supportive on-treatment analysis using a mixed model for repeated measurements (MMRM) will be performed for each of the biomarkers. In this model, all scheduled post-baseline measurements taken during the individual subject's on-treatment period will enter as response; treatment, baseline diabetes status, baseline fibrosis stage and diabetes-by-fibrosis interaction will be included as factors; and baseline body weight and baseline value of the corresponding biomarker will be included as covariates. All factors and covariates will be nested within visit and an unstructured covariance matrix for measurements within subject will be employed. There will be no explicit imputation of missing values. As for the main analysis, the estimated treatment differences at week 72 with associated 95% confidence intervals and p-values will be presented.

Whereas the main analysis attempts to estimate the de-facto treatment effect (in agreement with the chosen estimand for the primary objective), the supportive analysis aims to estimate the de-jure effect that would have been observed if all subjects had remained on treatment and completed all visits. The latter analysis relies on the assumption that data are missing at random, which means that given the observed data, the events that lead to data being missing are independent of the unobserved data.

Additional exploratory analyses will be conducted to evaluate the performance of the biomarkers as predictors of NASH (yes/no), fibrosis (stage ≥2, ≥3 and 4, respectively) and/or steatosis (score ≥1, ≥2 and 3, respectively) as applicable using the liver biopsy as the gold-standard reference. Separate analyses will be performed at baseline and week 72 for each predictor. A measurement will be classified as "positive" if the value of the predictor exceeds a chosen cut-point. The performance will be illustrated by the receiver operating characteristic (ROC) curve which describes the relationship of the true positive rate (sensitivity) versus the false positive rate (1 - specificity) as one moves the cut-point. The area under the ROC curve will be used to summarise the overall performance of a predictor and the optimal cut-point will be determined by finding the maximum of Youden's index (sensitivity + specificity - 1). In addition, new algorithms may be explored by constructing a logistic regression model which includes a large set of potential predictors and then selecting the most useful ones using stepwise backward elimination.

Weight-related parameters

The secondary endpoints related to weight are defined as change from baseline to 72 weeks in:

- Body weight (% and kg)
- Waist circumference
- BMI

These endpoints will be analysed separately using the same type of ANCOVA with MI as for the biomarkers with treatment, baseline diabetes status, baseline fibrosis stage and diabetes-by-fibrosis interaction as factors and corresponding baseline value as a single covariate. Supportive on-treatment analyses will be performed based on MMRM in the same way as for the biomarkers with factors and covariates specified as in the ANCOVA model.

In addition to the continuous endpoints, the following binary endpoints related to weight will be analysed separately:

- Weight loss of ≥ 5% of baseline body weight at 72 weeks (yes/no)
- Weight loss of ≥ 10% of baseline body weight at 72 weeks (yes/no)

The binary endpoints will be compared between treatment arms using an MI approach similar to the continuous endpoints but based on logistic regression. The 1000 data sets with imputed values for percent change in body weight will be reused to derive an equal number of complete data sets for the binary outcomes. For each data set, the binary outcomes will be analysed using a logistic regression model which includes treatment, diabetes status, baseline fibrosis stage and diabetes-by-fibrosis interaction as factors and baseline body weight as a covariate. The estimated log odds ratios and standard errors for the 1000 complete data sets are then pooled using Rubin's rule. From the pooled estimates and standard errors, the 95% confidence intervals for the odds ratios and associated p-values are calculated.

Glucose metabolism related parameters

The secondary endpoints related to glucose metabolism are defined as change from baseline to 72 weeks in:

- HbA_{1c}
- FPG
- Fasting glucagon
- HOMA-IR, derived through the approximation formula[60]:

$$\text{HOMA-IR} = \text{FPG (mmol/L)} \times \text{Fasting insulin (mmol/L)}/22.5$$

These endpoints will be analysed using the same type of ANCOVA with MI as for the biomarkers. For each endpoint, the ANCOVA will be performed separately for subjects with and without type 2 diabetes at screening. The model will include treatment and baseline fibrosis stage as factors and

corresponding baseline value as covariate. Supportive on-treatment analyses will be performed based on MMRM in the same way as for the biomarkers with factors and covariates specified as in the ANCOVA model. Fasting glucagon and HOMA-IR will be logarithmically transformed before analysis.

Cardiovascular risk factors

The secondary endpoints related to cardiovascular risk factors are defined as change from baseline to 72 weeks in:

- Systolic and diastolic blood pressure
- Lipids (total cholesterol, LDL cholesterol, HDL cholesterol, VLDL cholesterol, triglycerides, free fatty acids)
- hsCRP

These endpoints will be analysed separately using the same type of ANCOVA with MI as for the biomarkers with treatment, baseline diabetes status, baseline fibrosis stage and diabetes-by-fibrosis interaction as factors and corresponding baseline value as a single covariate. Supportive on-treatment analyses will be performed based on MMRM in the same way as for the biomarkers with factors and covariates specified as in the ANCOVA model. The lipids and hsCRP will be logarithmically transformed before analysis.

Patient reported outcomes

The results from SF-36 questionnaire will be analysed as the change from baseline to 72 weeks in overall mental and physical scores, respectively, as well as the change in each of the 8 domains:

- Physical functioning
- Role functioning
- Bodily pain
- General health
- Vitality
- Social functioning
- Role emotional
- Mental health

The change in score will be analysed as a continuous endpoint using the same type of ANCOVA with MI as for the biomarkers with treatment, baseline diabetes status, baseline fibrosis stage and diabetes-by-fibrosis interaction as factors and corresponding baseline score as a single covariate. Supportive on-treatment analyses will be performed based on MMRM in the same way as for the biomarkers with factors and covariates specified as in the ANCOVA model.

17.4.1.2 Safety endpoints

The following secondary endpoints are used to support the safety objectives:

- Number of treatment-emergent adverse events during the trial
- Number of treatment-emergent hypoglycaemic episodes during the trial
- Number of treatment-emergent severe or BG confirmed symptomatic hypoglycaemic episodes during the trial
- Number of treatment-emergent severe hypoglycaemic episodes during the trial
- Number of subjects discontinuing treatment due to gastrointestinal adverse events
- Change from baseline to 72 weeks in:
    - Pulse
    - ECG
    - Physical examination
    - Haematology (haemoglobin, haematocrit, thrombocytes, erythrocytes, leucocytes, differential count)
    - Biochemistry (creatinine, creatinine phosphokinase, urea, bilirubin (total), alkaline phosphatase, ferritin, sodium, potassium, calcium (total), amylase, lipase)
    - Hormones (calcitonin)
- Occurrence of anti-semaglutide antibodies during and after 72 weeks treatment (yes/no):
    - Anti-semaglutide binding antibodies
    - Anti-semaglutide binding antibodies with *in vitro* neutralising effect
    - Anti-semaglutide binding antibodies cross reacting with native GLP-1
    - Cross-reacting anti-semaglutide binding antibodies with *in vitro* neutralising effect to native GLP-1
- Anti-semaglutide antibody binding level during and after 72 weeks treatment

Adverse events

AEs will be coded using the most recent version of the Medical Dictionary for regulatory Activities (MedDRA) coding. A treatment emergent adverse event (TEAE) is defined as an event that has onset date during the on-treatment period (see section 17.2).

AE data will be displayed in terms of the number of subjects with at least one event, the percentage of subjects with at least one event, the number of events and the event rate per 100 patient years of exposure. The main AE summaries will only contain TEAEs. Non-treatment emergent AEs will be included in listings and overview summaries.

Hypoglycaemic episodes

Hypoglycaemic episodes will be classified and then summarised descriptively in terms of the number of subjects with at least one event, the percentage of subjects with at least one event, the

number of events and the event rate per 100 patient years of exposure. The summaries will be made separately for subjects with and without type 2 diabetes at randomisation.

For subjects with type 2 diabetes at randomisation, the severe or BG confirmed symptomatic hypoglycaemic episodes will be analysed using a negative binomial regression model with the number of treatment emergent episodes as response, the logarithmic function as link function and the logarithm of the time period during which episodes are considered treatment emergent as offset. The model will include treatment and baseline fibrosis stage as factors and baseline HbA_{1c} as a covariate. The results will be described by the rate ratio for the comparison of each semaglutide dose versus placebo with the associated 95% confidence interval and two-sided p-value.

Classification of Hypoglycaemia:

Treatment emergent: hypoglycaemic episodes will be defined as treatment emergent if the onset of the episode occurs during the on-treatment period (see section 17.2).

Nocturnal hypoglycaemic episodes: episodes occurring between 00:01 and 05.59 both inclusive.

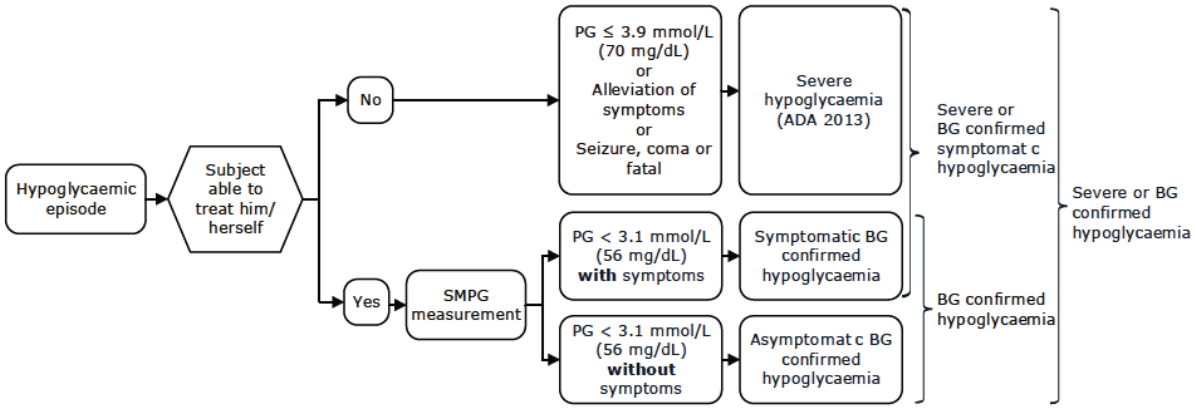
Hypoglycaemic episodes are classified according to the Novo Nordisk classification of hypoglycaemia (see Figure 17–1) and the ADA classification of hypoglycaemia (see Figure 17–2). For subjects without type 2 diabetes, the episodes will only be classified as either severe or probable symptomatic according to the ADA classification.

Novo Nordisk classification of hypoglycaemia

In normal physiology, symptoms of hypoglycaemia occur below a plasma glucose level of 3.1 mmol/L (56 mg/dL)[63]. Therefore, Novo Nordisk has included hypoglycaemia with plasma glucose levels below this cut-off point in the definition of blood glucose (BG) confirmed hypoglycaemia.

Novo Nordisk uses the following classification (see Figure 17–1) in addition to the ADA classification:

- Severe hypoglycaemia according to the ADA classification[48].
- Symptomatic BG confirmed hypoglycaemia: An episode that is BG confirmed by plasma glucose value <3.1 mmol/L (56 mg/dL) **with** symptoms consistent with hypoglycaemia.
- Asymptomatic BG confirmed hypoglycaemia: An episode that is BG confirmed by plasma glucose value <3.1 mmol/L (56 mg/dL) **without** symptoms consistent with hypoglycaemia.
- Severe or BG confirmed symptomatic hypoglycaemia: An episode that is severe according to the ADA classification[48] or BG confirmed by a plasma glucose value <3.1 mmol/L (56 mg/dL) **with** symptoms consistent with hypoglycaemia.
- BG confirmed hypoglycaemia: An episode that is BG confirmed by a plasma glucose value <3.1 mmol/L (56 mg/dL) **with** or **without** symptoms consistent with hypoglycaemia.
- Severe or BG confirmed hypoglycaemia: An episode that is severe according to the ADA classification[48] or BG confirmed by a plasma glucose value <3.1 mmol/L (56 mg/dL) **with** or **without** symptoms consistent with hypoglycaemia.



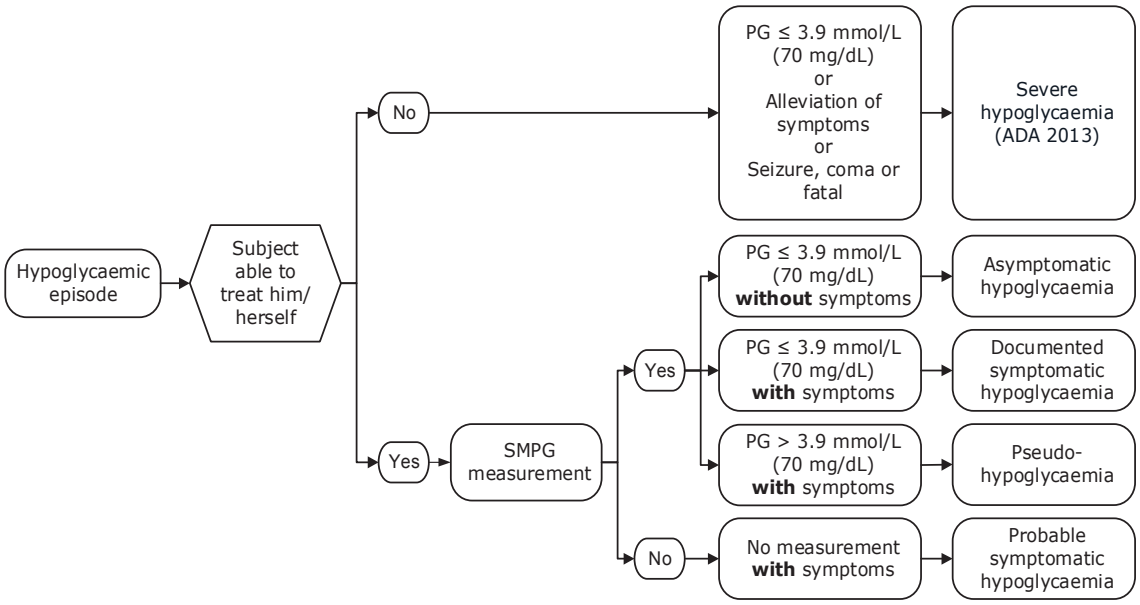
Note: Glucose measurements are performed w th capillary blood calibrated to plasma equivalent glucose values

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

Figure 17–1 Novo Nordisk classification of hypoglycaemia

ADA classification[48] of hypoglycaemia

- Severe hypoglycaemia: An episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.
- Asymptomatic hypoglycaemia: An episode not accompanied by typical symptoms of hypoglycaemia, but with a measured plasma glucose concentration ≤ 3.9 mmol/L (70 mg/dL).
- Documented symptomatic hypoglycaemia: An episode during which typical symptoms of hypoglycaemia are accompanied by a measured plasma glucose 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 plasma glucose 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 plasma glucose determination but that was presumably caused by a plasma glucose concentration ≤ 3.9 mmol/L (70 mg/dL).



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

PG: plasma glucose SMPG: Self-measured plasma glucose

Figure 17–2 ADA classification of hypoglycaemia

Pulse

Pulse will be summarised by descriptive statistics and analysed using the same type of MMRM as for the on-treatment analyses of the biomarkers with treatment, baseline diabetes status, baseline fibrosis stage and diabetes-by-fibrosis interaction as factors and baseline pulse as a covariate.

ECG

ECG will be described by summarising the number and percentage of subjects with normal and abnormal readings (separated into clinically significant and not clinically significant). The summaries will be presented by visit and as shift tables from baseline to week 72.

Physical examination

The results of the physical examination will be summarised descriptively in the same way as ECG.

Laboratory assessments

The haematology and biochemistry parameters will be summarised and evaluated by descriptive statistics.

Amylase and lipase will be analysed separately using the same type of MMRM as for the on-treatment analyses of the biomarkers with treatment, baseline diabetes status, baseline fibrosis stage and diabetes-by-fibrosis interaction as factors and the baseline value of the corresponding laboratory parameter as a covariate. A logarithmic transformation will be applied for both amylase and lipase

Calcitonin will be summarised in tables including number and percentage of observations > and ≤ LLOQ, quartiles, minimum and maximum. Persistent and incidental abnormal elevation of calcitonin will further be displayed in terms of the number and percentage of subjects and the event rate per 100 patient years of exposure.

Antibodies

The occurrence of anti-semaglutide antibodies will be described by summarising the number and percentage of subjects with antibodies in the different treatment arms. The antibody binding level will be presented in listings.

In addition, a comparison of the change in HbA_{1c} and body weight between antibody-positive and antibody-negative subjects will be performed using descriptive statistics and graphs. The impact of anti-semaglutide antibodies on safety will be similarly assessed by descriptive statistics.

17.4.1.3 Pharmacokinetic endpoints

The plasma concentrations of semaglutide will be summarised by descriptive statistics. In addition, the data will be used for population pharmacokinetic (PK) modelling, see section 17.6.

17.5 Interim analysis

No interim analyses or other analyses of unblinded data will be performed before the database is locked.

17.6 Pharmacokinetic and/or pharmacodynamic modelling

Exploratory population PK and PK/PD modelling will be used to evaluate the semaglutide dose-exposure, the effects of pre-specified covariates on the exposure and the semaglutide exposure-response on selected efficacy and safety parameters. It will follow a modelling analysis plan that is to be finalised before database lock, describing criteria for inclusion of data, pre-specification of covariates and criteria for presentation of results.

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

17.7 Health economics and/or patient reported outcomes

The PRO questionnaire SF-36 will be used to evaluate the effects on quality of life, see section 17.4.1.1 for the details of the statistical analysis. The results will be included in the CTR.

18 Ethics

18.1 Benefit-risk assessment of the trial

Risks and precautions for semaglutide

The sections below describe potential risks associated with semaglutide treatment, based on findings with other GLP-1 RAs and observations in nonclinical and clinical trials with semaglutide administered s.c. once weekly. For each of these risks, mitigating actions have been implemented to minimise the risks for subjects enrolled in this trial.

The nonclinical safety programme of semaglutide has revealed no identified safety issues for humans based on conventional studies of safety pharmacology, repeat-dose toxicity or genotoxicity.

Identified risks

Gastrointestinal adverse events

Consistent with findings from other GLP-1 RAs, the most frequently reported AEs in the clinical trials with semaglutide thus far have been gastrointestinal (GI) disorders (nausea, vomi ting, diarrhoea, dyspepsia and constipation). However, based on a completed clinical trial (NN9535-3819) where slower dose escalation substantially improved the GI tolerability profile, a 4-week dose escalation regimen has been developed and is used in the ongoing clinical phase 3 programme for semaglutide s.c. administered once weekly as well as in this trial.

Potential risks

Thyroid C-cell tumour

The human relevance of the proliferative C-cell changes found in rodents is unknown, but data suggest that rodents are more sensitive to the mode of action for induction of C-cell tumours with GLP-1 RAs. However, as a precaution subjects with a family or personal history of Multiple Endocrine Neoplasia type 2 (MEN 2) , familial medullary thyroid carcinoma (MTC), pe rsonal history of non-familial medullary thyroid carcinoma, and subjects with a screening calcitonin ≥50 ng/L will be excluded from trial. During the trial calcitonin will be measured on a regular basis and guidance for investigators of further evaluation and action on elevated plasma calcitonin is provided in appendix A.

Allergic reactions and injection site reactions

As is the case with all protein based pharmaceuticals, subjects treated with semaglutide risk developing immunogenic and allergic reactions. These may include localised injection site reactions

or generalised reactions including urticaria, rash or pruritus. Severe allergic reactions such as anaphylactic reactions could potentially also pose a risk for subjects treated with semaglutide.

Hypoglycaemia

Based on current knowledge about the GLP-1 RA drug class, there is a risk of hypoglycaemic episodes. Hypoglycaemic episodes have mainly been observed when a GLP-1 RA is combined with sulphonylurea (SU) or insulin in patients with T2D. The risk for development of hypoglycaemia specifically with semaglutide in combination with SU and insulin is unknown due to limited data. To reduce the risk of hypoglycemia the insulin dose will be reduced by 30% in subjects with HbA_{1c} $\leq$ 8.0% at screening.

Altered renal function

Based on current knowledge about the GLP-1 RA drug class, there is a risk of volume depletion, resulting from nausea, vomiting and dehydration, such as acute renal failure have been observed in subjects treated with other GLP-1 RAs. As a precaution serum creatinine is measured regularly.

Acute pancreatitis

Based on current knowledge about the GLP-1 RA drug class, there is a risk of acute pancreatitis, including severe necrotising and haemorrhagic forms. As a precaution patients with a history of acute or chronic pancreatitis will be excluded from the trial. Subjects will be monitored for elevated activity levels of amylase and lipase and be informed of the characteristic symptoms of acute pancreatitis.

Pancreatic cancer

There is currently no support from non-clinical or clinical trials or post-marketing data that GLP-1-based therapies increase the risk of pancreatic cancer. However, as the long-term effects of stimulation of β-cells and suppression of α-cells are largely unknown, pancreatic cancer is considered a potential risk by the European Medicine Agency (EMA).

Other safety considerations

Teratogenicity (nonclinical embryo-foetal toxicity)

Semaglutide has been concluded teratogenic in rats. This effect is regarded to be caused by impairment of nutrient supply to the embryo across the inverted yolk sac with placental function. As the yolk sac does not play such a role for nutrition of the embryo in humans, this effect is unlikely to be relevant for humans. However, as a precaution subjects fulfilling exclusion criterion 31 will be excluded from trial participation. Furthermore, as specified in the flowchart, female subjects

included in the trial will have pregnancy testing performed frequently during the entire duration of the trial.

General risks and precautions

All subjects will be included after a thorough evaluation in regards to in- and exclusion criteria defined in order to ensure that subjects are eligible for trial treatment.

All subjects will have one or two liver biopsies performed as part of participation in the trial. Pain is the most common complication of percutaneous liver biopsy, occurring in up to 84% of patients, including those with relatively mild discomfort. The most important complication of liver biopsy is bleeding. Severe bleeding may require hospitalization blood transfusion, or even radiological intervention or surgery. Such bleeding has been estimated to occur in between 1 in 2500 to 1 in 10,000 biopsies after an intercostal percutaneous liver biopsy. Mortality after liver biopsy is usually related to hemorrhage. It is very uncommon after percutaneous biopsy, but precise figures vary widely. The most commonly quoted mortality rate is less than or equal to 1 in 10,000 liver biopsies[64]. The risk of liver biosy is minimised by excluding patients with liver cirrhosis and coagulopathy, and by requiring that liver biopsy is performed according to standard practice.

Benefits

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

In the LEAN trial significantly more patients who received liraglutide 1.8 mg/day had resolution of NASH compared with patients in the placebo group. Further, significantly fewer patients in the liraglutide had progression of fibrosis compared to the placebo group[34]. Currently the standard of care of NASH is weight loss, and reduction of body weight was speculated to be one of the modes of action of liraglutide by the authors of the LEAN study[34]. In a phase 2 trial (NN9535-1821), semaglutide resulted in a clinical meaningful and dose-dependent weight loss. Doses ≥ 0.8 mg/week semaglutide provided a greater weight loss than liraglutide 1.8 mg/day. In clinical studies with liraglutide 3.0 mg/day, approximately 2/3 of the subjects lost more than 5% of their initial body weight and approximately 1/3 lost more than 10% of their initial body weight. Additionally, semaglutide also increase insulin, lower glucagon levels and improves insulin sensitivity and blood lipids, all of which are beneficial in patients with NASH. Finally, semaglutide may have anti-inflammatory effects.

Although subjects will have to spend time on site visits and procedures required by trial participation, it is expected that all subjects (including those subjects randomised to placebo) will benefit from participation through close contact with the trial site, with close follow-up of their NASH and general metabolic state, and a careful medical examination. Furthermore, all subjects

will receive nutritional and physical activity counselling throughout the trial. All of which will probably result in a better management of their NASH.

Conclusion

The trial products may be associated with AEs, but relevant precautions have been implemented in the design and planned conduct of the trial in order to minimise the risks and inconveniences of participation in the trial. These precautions include thorough information regarding the correct administration of the trial products and gradual dose adjustment. Furthermore, subjects are informed about possible AEs and inconveniences and will be instructed to contact the investigator in case of any concerns regarding the trial participation.

When treatment with trial products ends, the subject and investigator will decide on the best available treatment.

It is concluded that the potential benefits from participating in the trial outweigh the potential risks including the risk related to the liver biopsy. The safety profile of semaglutide generated from the clinical and nonclinical development programme in T2D has not revealed any safety issues that would prohibit administration of once weekly doses of 0.5 mg or 1.0 mg semaglutide. Based on the nature and frequency of the AEs in the T2D trials, it appears to be safe to investigate daily doses of up to 0.4 mg as in the current trial. Additional safety surveillance will be instituted in all treatment arms during the dose escalation period until 4 weeks after last target dose is reached (steady state). It is concluded that the risk to the subjects in this trial is low and acceptable in view of the potential benefits a long-acting GLP-1 analogue would provide subjects with NASH.

18.2 Informed consent

In seeking and documenting informed consent, the investigator must comply with applicable regulatory requirement(s) and adhere to ICH GCP[1] and the requirements in the Declaration of Helsinki[2].

Before any trial-related activity, the investigator must give the subject verbal and written information about the trial and the procedures involved in a form that the subject can read and understand. This includes the use of an impartial witness where required.

The subjects must be fully informed of their rights and responsibilities while participating in the trial as well as possible disadvantages of being treated with the trial products.

The investigator must ensure the subject ample time to come to a decision whether or not to participate in the trial.

A voluntary, signed and personally dated informed consent must be obtained from the subject before any trial-related activity.

Separate informed consent forms for long-term storage of human biosamples and genotyping are available for this trial, and informed consent must be obtained before activities related to any of these are undertaken.

The responsibility for seeking informed consent must remain with the investigator, but the investigator may delegate the task to a medically qualified person, in accordance with local requirements. The written informed consent must be signed and personally dated by the person who seeks the informed consent before any trial-related activity.

If information becomes available that may be relevant to the subject's willingness to continue participating in the trial, the investigator must inform the subject in a timely manner, and a revised written subject information must be provided and a new informed consent must be obtained.

18.3 Data handling

If the subject withdraws from the trial or is lost to follow up, then the subject's data will be handled as follows:

- Data already collected and any data collected at the end-of-trial visit including follow up visits will be retained by Novo Nordisk, entered into the database and used for the clinical trial report.
- Safety events will be reported to Novo Nordisk and regulatory authorities according to local/national requirements.

If data is used, it will always be in accordance with local regulations and IRBs/IECs.

18.4 Information to subjects during trial

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

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.

18.5 Premature termination of the trial and/or trial site

Novo Nordisk, the IRBs/IECs or a regulatory authority may decide to stop the trial, part of the trial or a trial site at any time, but agreement on procedures to be followed must be obtained.

If the trial is suspended or prematurely 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.

If, after the termination of the trial, the benefit-risk analysis changes, the new evaluation must be provided to the IRBs/IECs in case it has an impact on the planned follow-up of subjects who have participated in the trial. If it has an impact, the actions needed to inform and protect the subjects should be described.

19 Protocol compliance

19.1 Protocol deviations

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 eCRF or via listings from the trial database. Novo Nordisk will monitor protocol deviations on an on-going basis throughout the trial followed by appropriate actions (e.g. re-training of site staff).

Documentation on protocol deviations must be kept in the investigator trial master file and sponsor trial master file.

19.2 Prevention of missing data

The importance of subject retention will be addressed by Novo Nordisk in the training and communication with the trial sites.

The subjects will be carefully informed about the trial procedures before signing informed consent, so that they know the implications of participating in the trial.

Close surveillance of subject retention will be performed throughout the trial by Novo Nordisk with focus on reasons for premature discontinuation of trial product or withdrawal of consent to secure early mitigations in collaboration with the trial sites. The investigator will make every effort to

ensure that all assessments are performed and data is collected (see section 8.1.5). If missing data does occur the reason will be collected via the protocol deviation process described in section 19.1.

20 Audits and inspections

Any aspect of the clinical trial may be subject to audits conducted by Novo Nordisk or inspections from domestic or foreign regulatory authorities or from IRBs/IECs. Audits and inspections may take place during or after the trial. The investigator and the site staff as well as Novo Nordisk staff have an obligation to cooperate and assist in audits and inspections. This includes giving auditors and inspectors direct access to all source documents and other documents at the trial site relevant to the clinical trial. This includes permission to examine, analyse, verify and reproduce any record(s) and report(s) that are relevant to the evaluation of the trial.

21 Critical documents

Before a trial site is allowed to start screening subjects, written notification from Novo Nordisk must be received and the following documents must be available to Novo Nordisk:

- Regulatory approval and/or acknowledgement of notification as required
- Approval/favourable opinion from IRBs/IECs clearly identifying the documents reviewed as follows: protocol, any protocol amendments, subject information/informed consent form, any other written information to be provided to the subject and subject recruitment materials
- List of IRB/IEC members and/or constitution (or a general assurance number/statement of compliance)
- Curricula vitae of investigator and sub-investigator(s) (current, dated and signed - must include documented GCP training or a certificate)
- Signed receipt of Investigator's Brochure
- Signed and dated Agreement on Protocol
- Signed and dated Agreement on Protocol Amendment, if applicable
- Contract, signed by the investigator and/or appropriate parties on behalf of the investigator's site and Novo Nordisk
- Source document agreement
- Central laboratory certification and normal ranges
- Insurance statement, if applicable
- Financial disclosure form from investigator and sub-investigator(s)

Only applicable for US trial sites:

- For US trial sites: verification under disclosures per Code of Federal Regulations (CFR) of Financial Conflict of Interest
- For US trial sites: FDA form 1572 must be completed and signed by the investigator at each site

FDA form 1572:

For US sites:

- Intended for US sites
- Conducted under the IND
- All US investigators, as described above, will sign FDA Form 1572

For sites outside the US:

- Intended for participating sites outside of the US
- Not conducted under the IND
- All investigators outside of the US will not sign FDA form 1572

Novo Nordisk will analyse and report data from all sites together if more than one site is involved in the trial.

By signing the protocol agreement, each investigator agrees to comply fully with ICH GCP[1] applicable regulatory requirements and the Declaration of Helsinki[2].

By signing the protocol agreement, each investigator also agrees to allow Novo Nordisk to make investigator's name and information about site name and address publically available if this is required by national or international regulations.

22 Responsibilities

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

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

The investigator will follow instructions from Novo Nordisk when processing data.

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 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).

23 Reports and publications

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 physicians 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 investigator will be appointed by Novo Nordisk to review and sign the clinical trial report (signatory investigator) on behalf of all participating investigators. The signatory investigator will be appointed based upon the criteria defined by the International Committee of Medical Journal Editors for research publications[65].

23.1 Communication of results

Novo Nordisk commits to communicating, and otherwise making available for public disclosure, results of trials regardless of outcome. Public disclosure includes publication of a paper in a

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, as reflected in the Novo Nordisk Code of Conduct for Clinical Trial Disclosure[42].

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

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.

Novo Nordisk maintains the right to be informed of plans by any investigator to publish and to review any scientific paper, presentation, communication or other information concerning the investigation described in this protocol. Any such communication must be submitted in writing to Novo Nordisk before submission for comments. Comments will be given within four weeks from receipt of the planned communication.

23.1.1 Authorship

Authorship of publications should be in accordance with the Uniform Requirements of the International Committee of Medical Journal Editors[65] (sometimes referred to as the Vancouver Criteria).

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

For a multi-centre 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. It is a Novo Nordisk policy that

such individual reports do not precede the primary manuscript and should always reference the primary manuscript of the trial.

Novo Nordisk reserves the right to prior review of such publications. Further to allow for the primary manuscript to be published as the first, Novo Nordisk asks for deferment of publication of individual site results until the primary manuscript is accepted for publication. As Novo Nordisk wants to live up to the industry publication policy, submission of a primary publication will take place no later than 18 months after trial completion.

23.2 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.

24 Retention of clinical trial documentation and human biosamples

24.1 Retention of clinical trial documentation

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

The investigator must agree to archive the documentation (this includes both electronic and paper-based records) pertaining to the trial in an archive after completion or discontinuation of the trial if not otherwise notified. The investigator should not destroy any documents without prior permission from Novo Nordisk. If the investigator cannot archive the documents at the trial site, Novo Nordisk can refer the investigator to an independent archive provider that has a system in place to allow only the investigator to access the files.

The investigator must be able to access his/her trial documents without involving Novo Nordisk in any way. Site-specific CRFs and other subject data (in an electronic readable format or as paper copies or prints) will be provided to the investigator before access is revoked to the systems and/or electronic devices supplied by Novo Nordisk. These data must be retained by the trial site. If the provided 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.

Novo Nordisk will maintain Novo Nordisk documentation pertaining to the trial for at least 20 years after discontinuation of the marketing authorisation, termination of the trial or cancellation of the research project whichever is longest.

The files from the trial site/institution must be retained for 15 years after end of trial as defined in section 7), or longer if required by local regulations or Novo Nordisk. In any case trial files cannot be destroyed until the trial site/institution is notified by Novo Nordisk. The deletion process must ensure confidentiality of data and must be done in accordance with local regulatory requirements.

24.2 Retention of human biosamples

24.2.1 Antibody samples

Antibody samples may be retained for later analysis for further characterisation of antibody responses towards drug if required by health authorities or for safety reasons. The samples will not be used for other purposes.

The samples will be stored at a bio-repository after end of trial and until marketing authorisation approval or until the research project terminates, but no longer than 15 years from end of trial after which they will be destroyed.

The subject's identity will remain confidential and the antibody 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.

Only Novo Nordisk staff and bio-repository personnel will have access to the stored antibody samples.

Subjects can contact the investigator if they wish to be informed about results derived from stored antibody samples obtained from their own body.

24.2.2 Samples for future analysis

As new biomarkers related to the disease and/or safety, efficacy, or mechanism of action of semaglutide may evolve during the conduct of the trial or after end of trial, the analyses of the stored biosamples may also include biomarkers that are unknown at present or have not been included in the scientific hypotheses at initiation of the trial. Likewise if genetic high risk population or populations are described for NASH, Novo Nordisk may want to investigate if such genetic predispositions are associated with different response to semaglutide.

Subjects must sign and date a separate informed consent form before biosamples to be stored for future analysis are drawn/collected (refer to section 8.1.1).

After trial completion the biosamples will be stored at a central storage facility contracted by Novo Nordisk A/S. Only Novo Nordisk and storage facility employees will be able to access the stored biosamples. The biosamples may be transferred to other countries for analysis and will be destroyed at the latest 15 years after end of trial.

The subject may request the stored biosamples to be destroyed by withdrawing consent. The results obtained from any already performed analyses of the samples will still be used.

In the event that the collected biosamples (blood and urine) 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.

25 Institutional Review Boards/Independent Ethics Committees and regulatory authorities

IRB/IEC:

Written approval or favourable opinion must be obtained from IRB/IEC prior to commencement of the trial.

During the trial, the investigator or Novo Nordisk, as applicable, must promptly report the following to the IRB/IEC, in accordance with local requirements: updates to Investigator's Brochure, unexpected SAEs where a causal relationship cannot be ruled out, protocol amendments according to local requirements, deviations to the protocol implemented to eliminate immediate hazards to the subjects, new information that may affect adversely the safety of the subjects or the conduct of the trial (including new benefit-risk analysis in case it will have an impact on the planned follow-up of the subjects), annually written summaries of the trial status, and other documents as required by the local IRB/IEC.

The investigator must ensure submission of the clinical trial report synopsis to the IRB/IEC.

Protocol amendments must not be implemented before approval or favourable opinion according to local regulations, unless necessary to eliminate immediate hazards to the subjects.

The investigator must maintain an accurate and complete record of all submissions made to the IRB/IEC. The records must be filed in the investigator trial master file and copies must be sent to Novo Nordisk.

Regulatory Authorities:

Regulatory authorities will receive the clinical trial application, protocol amendments, reports on SAEs, and the clinical trial report according to national requirements.

26 Indemnity statement

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

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

Novo Nordisk accepts liability in accordance with:

For Netherlands only: Wetgeving betreffende geneesmiddelen; geneesmiddelenwet 1 juli 2007 (Medicines Law, 1 July 2007). De Wet Medisch-wetenschappelijk Onderzoek met mensen (WMO), 1 maart 2006 (Medical Research Involving Human Subjects Act, 1 March 2006). Besluit verplichte verzekering bij medisch-wetenschappelijk onderzoek met mensen 2015, 24 november 2014 (Decree compulsory insurance in medical research involving human subjects 2015, 24 November 2014)." The national protocol requirement is also here under compliance: http://globeshare.novonordisk.com/rd/gd/gdareas/qrd/gcc/Pages/Default.aspx

For France only: 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. "The sponsor is responsible for identification of the harmful consequences of the biomedical research for the person lending himself thereto and for indemnification of his beneficiaries, except in case of proof, incumbent on it, that the prejudice is not attributable to his fault of or the fault of any intervening party, without the sponsor's being entitled to call on acts by a third party or the voluntary withdrawal of the person who had initially consented to cooperating in the research.

For Austria only: Arzneimittelgesetz (BGBI. Nr. 185/1983) last amended with BGBI Nr. 105/2015.

For Russia only: Federal law of 12 April 2010 No. 61-FZ 'On Medicinal Drugs' Circulation.

For Belgium only: Law concerning experiments on the human person of 07 May 2004 - Article 29:

§1. Even if without fault, the sponsor is liable for the damage which the subject and/or his rightful claimants sustain and which shows either a direct or an indirect connection with the trial.

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Protocol

Trial ID:NN9931-4296

Investigation of efficacy and safety of three dose levels of subcutaneous semaglutide once daily versus placebo in subjects with non-alcoholic steatohepatitis

A 72-week randomised, double-blind, placebo-controlled, six-armed parallel group, multi-centre, multinational trial

Updated protocol including:

- Original protocol, version 1.0, dated 20 June 2016
- Global protocol amendment number 1, version 1.0, dated 26 August 2016
- Global protocol amendment number 2, version 1.0, dated 29 November 2016
- Global protocol amendment number 3, version 1.0, dated 25 August 2017
- Global protocol amendment number 4, version 1.0, dated 01 March 2018
- Local protocol amendment number 5 in Sweden, version 1.0, dated 09 January 2018

Trial phase: Phase 2

Protocol originator
[redacted] Senior International Trial Manager
TrialOps 2, GLP-1 Diabetes, NADs & Complications

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List of abbreviations

ADA	American Diabetes Association
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUDIT	Alcohol Use Disorders Identification Test
BMI	body mass index
CAP	controlled attenuation parameter
CK-18	cytokeratin 18
CLAE	clinical laboratory adverse event
CMH	Cochran-Mantel-Haenszel
CRF	case report form
CRN	Clinical Research Network
CTR	clinical trial report
DILI	drug induced liver injury
DUN	dispensing unit number
EAC	event adjudication committee
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ELF	enhanced liver fibrosis

FAS	full analysis set
FGF-21	fibroblast growth factor 21
Fib-4	fibrosis 4
FPG	fasting plasma glucose
FSFV	first subject first visit
GCP	Good Clinical Practice
GGT	gamma glutamyltransferase
GLP-1	glucagon-like peptide-1
GLP-1 RA	glucagon-like peptide-1 receptor agonist
HbA_{1c}	glycosylated haemoglobin A1c
hCG	human chorionic gonadotrophin
HCV-RNA	hepatitis C virus Ribonucleic acid
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
HOMA-IR	homeostatic model assessment - insulin resistance
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IEC	independent ethics committee

IL-1R	interleukin-1 receptor
IMP	investigational medicinal product
INR	international normalized ratio
IRB	institutional review board
IWRS	interactive web response system
LDL	low-density lipoprotein
LLOQ	lower limit of quantification
LSLV	last subject last visit
MCP-1	monocyte chemoattractant protein 1
MedDRA	Medical Dictionary for Regulatory Activities
MELD	model for end-stage liver disease
MI	myocardial infarction
miR-122	microRNA 122
NAFLD	non- alcoholic fatty liver disease
NAS	NAFLD activity score
NASH	non- alcoholic steatohepatitis
NFS	NAFLD fibrosis score
NOAEL	no observable adverse effect level
PG	plasma glucose
PRO	patient reported outcome
SAE	serious adverse event
SAF	steatosis-activity-fibrosis

SAP	statistical analysis plan
SAS	safety analysis set
s.c.	subcutaneous(ly)
SF-36	short form 36
SGLT-2	sodium–glucose cotransporter 2
SMPG	self-measured plasma glucose
SUSAR	suspected unexpected serious adverse reaction
T2D	type 2 diabetes
TSH (applicable for Sweden)	thyroid-stimulating hormone
TMM	trial materials manual
UNL	upper normal limit
UTN	universal trial number
VLDL	very low density lipoprotein

1 Summary

Objectives and endpoints:

Primary objective

To compare the effect of semaglutide subcutaneous (s.c.) once daily versus placebo on histological resolution of non-alcoholic steatohepatitis (NASH).

Primary endpoint

- NASH resolution without worsening of fibrosis after 72 weeks (yes/no)

Key secondary objectives

- To investigate the dose-response relationship of three dose levels of semaglutide s.c. once daily (0.1 mg/day, 0.2 mg/day and 0.4 mg/day) on histological resolution of NASH.
- To compare the effects of semaglutide s.c. once daily to placebo on liver-related histological parameters and biomarkers of NASH disease.

Key secondary endpoints

- At least one stage of liver fibrosis improvement with no worsening of NASH after 72 weeks (yes/no) (worsening defined as an increase of at least one stage of either lobular inflammation or hepatocyte ballooning according to NASH clinical research network (CRN) criteria).

Change from baseline to week 72 in:

- Non-alcoholic fatty liver disease (NAFLD) activity score (NAS) (0-8)
- Stage of fibrosis according to the Kleiner fibrosis classification (0-4)
- Activity component of steatosis-activity-fibrosis (SAF) score (0-4)
- Fasting plasma glucose (FPG)
- Glycosylated haemoglobin A1c (HbA_{1c})
- Serum enhanced liver fibrosis (ELF)

Trial design:

This is a 72-week, randomised, double-blind, placebo-controlled, six-armed, parallel group, multi-centre, multi-national trial comparing once daily administration of semaglutide s.c. in three different doses (0.1 mg, 0.2 mg and 0.4 mg) with placebo in subjects with NASH. Subjects will be randomised in a 3:3:3:1:1:1 manner to receive daily dosing of semaglutide s.c. 0.1 mg, 0.2 mg, 0.4 mg or corresponding injection volumes of placebo once daily. To avoid bias in the assessment of the different semaglutide doses, the trial will be double-blinded within dose levels. The dose levels

will not be blinded between each other because of different dose escalations and different target doses and volumes required.

The total trial duration for the individual subject will be up to 85 weeks (maximum).

Randomisation will be stratified in five strata based on region (Japanese or non-Japanese) and, within the non-Japanese group, based on diabetes status at screening (with or without type 2 diabetes) and fibrosis stage for baseline liver biopsy (F1/F2 or F3).

Trial population:

A total of 288 subjects are planned to be randomised. Based on an assumption of a 65% screening failure rate, 823 subjects are planned to be screened.

Key inclusion criteria

- 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 except for protocol described pre-screening activities which require a separate informed consent.
  Applicable for Sweden: 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.

- Male or female, aged 18-75 years (both inclusive) (for Japan: male or female aged 20-75 years (both inclusive)) at the time of signing informed consent.
- Histologic evidence of NASH based on central pathologist evaluation of a liver biopsy obtained up to 21 weeks before screening.
- A histological NAS $\geq$ 4 with a score of 1 or more in each sub-component of the score based on central pathologist evaluation.
- NASH fibrosis stage 1, 2 or 3 according to the NASH CRN fibrosis staging system based on central pathologist evaluation.

Key exclusion criteria

- Known or suspected abuse of alcohol (> 20 g/day for women or > 30 g/day for men), alcohol dependence* or narcotics. (* = assessed by the Alcohol Use Disorders Identification Test (AUDIT questionnaire)).
- Diagnosis of type 1 diabetes according to medical records.
- HbA_{1c} > 10% at screening.
- History or presence of pancreatitis (acute or chronic).
- Calcitonin $\geq$ 50 ng/L at screening.

- Family or personal history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma. Family is defined as a first degree relative.
- Body Mass Index (BMI) ≤ 25.0 kg/m^2 at the screening visit (visit 1).
- Female who is pregnant, breast-feeding or intends to become pregnant or is of childbearing potential and not using an adequate contraceptive method (adequate contraceptive measures as required by local regulation or practice).

Assessments:

Efficacy

- Liver biopsy
- Liver enzymes (alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyltransferase (GGT))
- Fibroscan® measurements (liver stiffness and liver steatosis (with controlled attenuation parameter (CAP)))
- HbA_{1c}
- Body measurements (body weight in kg)
- Lipids (Total cholesterol, free fatty acids, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, very low density lipoprotein (VLDL) cholesterol)

Safety

- Adverse events
- Pulse
- Biochemistry and haematology
- Antibodies against semaglutide

Trial products:

The following trial products will be supplied by Novo Nordisk A/S:

- Semaglutide 1.0 mg/ml, solution for injection, 3.0 ml cartridge, for NovoPen® 4
- Semaglutide placebo, solution for injection, 3.0 ml cartridge, for NovoPen® 4

[redacted]

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2 Flow chart

Trial Periods	Screening	Randomisation	Dose escalation/Maintenance period															EOT	FU	Trial product discontinuation 72 weeks FU[1]
Visit number	V1	V2[16]	P3	V4	P5	V6	P7	V8	P9	V10	P11	V12	V13	V14	V15	V16	V17	V18	V19	V19A
Weeks in relation to visit 2	-6	0	2	4	6	8	10	12	14	16	18	20	28	36	44	52	62	72	79	72
Visit window, days	±7		±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±7	±7	±7	±7	±7	±7	-7	±7
SUBJECTS																				
Informed consent	x																			
In/exclusion criteria	x	x																		
AUDIT questionnaire	x																			
Medical history/ Concomitant illness	x																			
Concomitant medication	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Demography	x																			
Tobacco use	x																			
Hypoglycaemia unawareness	x[13]																			
Childbearing potential	x[14]																			
Fundoscopy/fundus photography	x[15]																			
Criteria for premature discontinuation of trial product			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			

Trial Periods	Screening	Randomisation	Dose escalation/Maintenance period															EOT	FU	Trial product discontinuation 72 weeks FU[1]
Visit number	V1	V2[16]	P3	V4	P5	V6	P7	V8	P9	V10	P11	V12	V13	V14	V15	V16	V17	V18	V19	V19A
Weeks in relation to visit 2	-6	0	2	4	6	8	10	12	14	16	18	20	28	36	44	52	62	72	79	72
Visit window, days	±7		±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±7	±7	±7	±7	±7	±7	-7	±7
EFFICACY																				
Height	x																			
Body weight	x	x		x				x				x	x	x	x	x	x	x		x
Waist circumference		x		x				x				x	x	x	x	x	x	x		x
SF-36 questionnaire		x											x			x		x		x
Vital signs		x		x		x		x		x		x	x	x	x	x	x	x		x
Biochemistry	x	x		x				x				x	x	x	x	x	x	x		x
Fasting plasma glucose		x		x				x				x	x	x	x	x	x	x		x
HbA_{1c}	x	x		x				x				x	x	x	x	x	x	x		x
Fasting insulin and glucagon		x		x				x				x	x	x	x	x	x	x		x
Lipids		x		x				x					x			x		x		x
Liver biopsy	x[2]																	x[4]		x
Fibroscan®[3]		x											x			x		x[5]		x
Exploratory biomarkers[6]		x											x			x		x		x
SAFETY																				
ECG		x											x					x		x

Trial Periods	Screening	Randomisation	Dose escalation/Maintenance period															EOT	FU	Trial product discontinuation 72 weeks FU[1]
Visit number	V1	V2[16]	P3	V4	P5	V6	P7	V8	P9	V10	P11	V12	V13	V14	V15	V16	V17	V18	V19	V19A
Weeks in relation to visit 2	-6	0	2	4	6	8	10	12	14	16	18	20	28	36	44	52	62	72	79	72
Visit window, days	±7		±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±7	±7	±7	±7	±7	±7	-7	±7
Physical examination	x																	x		x
Haematology		x		x				x					x	x		x		x		x
INR	x	x		x				x				x	x	x	x	x	x	x		x
Hepatitis B and C	x																			
HIV antigen/antibody screening test	x																			
TSH **(Sweden only)**	x																			
Calcitonin	x	x		x						x		x	x	x	x	x	x	x		x
Pregnancy test[11]	x	x		x		x[12]		x		x		x	x	x	x	x	x	x	x[12]	
Anti-semaglutide antibodies[7]		x		x		x		x					x	x		x		x[8]	x	
Adverse events		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Hypoglycaemic episodes			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Technical complaints			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
OTHER ASSESSMENTS																				
Semaglutide plasma concentration				x		x		x		x		x	x	x		x		x[8]	x	
Biosamples for future		x											x			x		x		x

Trial Periods	Screening	Randomisation	Dose escalation/Maintenance period															EOT	FU	Trial product discontinuation 72 weeks FU[1]
Visit number	V1	V2[16]	P3	V4	P5	V6	P7	V8	P9	V10	P11	V12	V13	V14	V15	V16	V17	V18	V19	V19A
Weeks in relation to visit 2	-6	0	2	4	6	8	10	12	14	16	18	20	28	36	44	52	62	72	79	72
Visit window, days	±7		±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±7	±7	±7	±7	±7	±7	-7	±7
analysis																				
Nutritional and physical activity counselling		x		x		x		x		x		x	x	x	x	x	x	x	x	x
TRIAL MATERIAL																				
Dispensing visit		x[9]		x		x		x		x		x	x	x	x	x	x			
Drug accountability		x		x		x		x		x		x	x	x	x	x	x	x		
IWRS session	x	x		x		x		x		x		x	x	x	x	x	x	x		
REMINDERS																				
Hand out ID card	x																			
Hand out and instruct in BG-meter use[10]		x																		
Training in trial product and pen handling		x		x										x						
Handout and instruct in subject diary		x		x		x		x		x		x	x	x	x	x	x	x		
Collect subject diary and record in eCRF				x		x		x		x		x	x	x	x	x	x	x	x	
Attend visit fasting		x		x				x		x		x	x	x	x	x	x	x	x	x

Abbreviations: P = Phone visit, V = Clinic visit, ECG = Electrocardiogram, FU = follow-up, IWRS = interactive web response system, SF-36 = Short Form 36, HbA1c = glycosylated haemoglobin, BG-meter = blood glucose meter, EOT = End of treatment

1) **Subjects prematurely discontinuing trial product should attend an end of treatment visit (V18) as soon as possible and a follow-up visit 7 weeks thereafter (visit 19). In addition they should follow the trial visit schedule as planned and attend the trial product discontinuation 72 weeks FU visit 72 weeks after randomisation. However the following should not be done after visit 19 for subjects prematurely discontinuing trial product: Semaglutide plasma concentration, anti-semaglutide antibody assessment, hypo reporting and handing out subject diaries.**
2) **A liver biopsy obtained 21 weeks or less before screening (visit 1) can be used. For subjects with no historical liver biopsy within 21 weeks prior to screening, a liver biopsy must be performed during the screening period.**
3) **In selected countries only at sites with Fibroscan® equipment available.**
4) **For subjects prematurely discontinuing trial product treatment, no biopsy at end of treatment visit (V18). Biopsy will be at visit 19A (trial product discontinuation 72 weeks FU).**
5) **For subjects prematurely discontinuing trial product treatment, no Fibroscan® assessment at end of treatment visit (V18). Fibroscan® will be at visit 19A (trial product discontinuation 72 weeks FU).**
6) **Exploratory biomarkers are: CK-18 fragments, ELF, miR-122, IL-1R antagonist, MCP-1, FGF-21.**
7) **Blood samples for measurement of anti-semaglutide antibodies must be drawn prior to trial product dose.**
8) **For subjects prematurely discontinuing trial product treatment a follow-up antibody sample and semaglutide plasma concentration sample must in addition to at the end of treatment vist (V18) be taken 7 weeks thereafter (visit 19).**
9) **Hand out directions for use**
10) **Only applicable for subjects with type 2 diabetes**
11) **For women of childbearing potential: urine pregnancy test should be performed at any time during the trial if a menstrual period is missed, or as required by local law**
12) **At these visits, urine pregnancy test will be performed**
13) **Only applicable for subjects with type 2 diabetes**
14) **Only applicable for female subjects**
15) **Only applicable for patients with type 2 diabetes: Dilated fundoscopy/fundus photography performed within 90 days prior to visit 2 is acceptable if results are available for evaluation at visit 2 and there has been no deterioration in visual function since last assessment. Dilated fundoscopy/fundus photography can be performed between visit 1 and visit 2.**
16) **All visit 2 assessments must be carried out prior to first trial product dose.**

3 Background information and rationale for the trial

The trial will be conducted in compliance with this protocol, ICH GCP[1] and applicable regulatory requirements, and in accordance with the Declaration of Helsinki[2].

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

3.1 Background information

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[3]. It is estimated that 70-90% of patients with obesity have some degree of steatosis, with the prevalence increasing with the severity of obesity. To that end, NAFLD is the most common chronic liver disorder in Western countries and in the USA 30% of the adult population suffers from NAFLD[4] [5]. Obesity is associated with an increased risk of NAFLD, the risk increasing with increasing BMI[6]. Furthermore the risk rises to as much as 70-75% in patients with type 2 diabetes (T2D)[7]. NASH represents a more advanced form of NAFLD and is reported in 3-5% of the Western population[8]. The prevalence of NASH is ~12% and ~22% in patients with obesity and T2D, respectively[9]. The incidence and prevalence of NASH is rising and it is estimated that 20-30% of patients with simple steatosis develop NASH[10]. Persistent inflammation can lead to the formation of fibrous scar tissue in the liver, which eventually causes cirrhosis and in some cases hepatocellular carcinoma[11].

An estimated 10% of patients with NASH develop cirrhosis[12]. Obesity-induced NASH leading to liver cirrhosis is the third most common cause of liver transplantation in the USA today and expected to be the primary cause of liver transplantation in 2030[13] [14] [15]. The pathophysiology of NASH is not well understood, but weight gain, insulin resistance, T2D and hypertension are all recognised as key factors[16].

In most patients NASH is asymptomatic, but non-specific symptoms such as right upper quadrant discomfort or fatigue can occur. Often, NASH is first suspected on the basis of elevated liver enzymes found at routine medical health checks or incidentally by imaging or bariatric surgery. Liver enzymes (e.g. alanine aminotransferase) are elevated in 50-80% of cases and typically around 1.5 times the upper limit of the normal[17].NASH is a histological diagnosis based on liver biopsy together with clinical exclusion of consumption of >20 g ethanol/day for women and >30g ethanol/day for men[18]. Histologically, NASH is defined by the presence of steatosis, lobular inflammation, portal inflammation, cellular ballooning and varying degrees of fibrosis. The degree of fibrosis is described by the Kleiner fibrosis staging system, ranging from F0 (absence of fibrosis), F1 (portal/perisinusoidal fibrosis), F2 (perisinusoidal and portal/periportal fibrosis), F3 (septal or bridging fibrosis) through F4 (cirrhosis)[19]. Several non-invasive biomarkers are available

for the assessment NASH and liver fibrosis, however, there are currently no non-invasive methods for diagnosis or assessment of disease prognosis approved for regulatory pivotal trials[20].

Currently, no drugs are approved for the treatment of NASH. First-line treatment is lifestyle intervention to achieve weight loss and treatment of comorbidities (e.g. hyperlipidaemia, hypertension and diabetes). In the case of progression to cirrhosis and liver failure, liver transplantation is the only treatment option. The current sparse epidemiological information on progression rates and predictive factors has limited the ability to calculate risk and possible benefit of treatments[21].

3.1.1 Glucagon-like peptide-1

Glucagon-like peptide-1 (GLP-1) is an incretin hormone secreted from the L-cells in the small intestine. GLP-1 has a glucose-dependent stimulatory effect on insulin and inhibitory effect on glucagon secretion from the pancreatic islets (i.e. when plasma glucose levels are above normal)[22] [23]. Furthermore, GLP-1 is a physiological regulator of appetite and food intake and GLP-1 receptors are present in several areas of the brain involved in appetite regulation. Physiologically, GLP-1 has a pronounced inhibitory effect on gastric emptying; however this effect seems to diminish upon chronic exposure[24] [25] [26]. Endogenous GLP-1 has a very short elimination half-life of <1.5 minutes after intravenous administration due to rapid degradation by ubiquitous dipeptidyl peptidase (DPP 4)[27]. Development of a GLP-1 receptor agonist (GLP-1 RA) with longer half-life has been necessary to enable effective treatment option for T2D and obesity.

Both human and animal studies have shown a beneficial effect of GLP-1 RA including liraglutide on liver lipid metabolism and progression of fatty liver to NASH [28] [29] [30] [31]. 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[29] [32]. Semaglutide effectively lowers body weight and have been shown to indirectly increase insulin sensitivity[31] [33] [34]. Additionally, semaglutide also increase insulin and lower glucagon levels, all of which may be beneficial in patients with NASH. Other mechanisms of actions based on the GLP-1 biology are anti-inflammation and lipid lowering effects[29].

In the liraglutide phase 3 programme for treatment of T2D, 50% of the more than 4000 subjectss had elevated ALT at baseline. Compared to placebo, liraglutide dose-dependently reduced ALT in these patients suggesting an improvement of hepatic steatosis[35].

The investigator sponsored study Liraglutide Efficacy and Action in NASH (LEAN), enrolled 52 overweight subjects with and without T2D, with biopsy-confirmed NASH to receive once daily liraglutide s.c or placebo. 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 [95% CI 1·0–17·7]; p=0·019) compared to placebo.

Furthermore, significantly fewer patients treated with liraglutide had worsening of fibrosis compared to placebo[34].

Semaglutide

Semaglutide is a potent human GLP-1 RA with a half-life of approximately 160 hours, suitable for both once daily (subcutaneous (s.c.) and oral) and once weekly s.c. administration. It is structurally similar to liraglutide (Victoza® and Saxenda®), a once daily GLP-1 RA developed by Novo Nordisk and approved in several countries for the treatment of T2D and weight management, respectively.

For the semaglutide molecule the principal mechanism of protraction is albumin binding facilitated by a large fatty acid derived chemical moiety attached to the lysine in position 26. The specific modifications in the molecule are: 1) a modification in position 8 (alanine to 2-aminoisobutyric acid) of the peptide backbone in order to further increase stability against DPP-4, and a change in position 34 from a lysine to an arginine in order to only have one (1) lysine in the sequence; 2) a large hydrophilic linker between the lysine in position 26 and the gamma glutamate whereto the fatty acid is attached; 3) a C18 fatty di-acid with a terminal acidic group. The latter two (2) contribute to increased albumin binding which results in decreased renal clearance. In addition to slowed degradation in plasma and decreased renal clearance, delayed absorption from subcutis possibly also contributes to a prolonged half-life t½ of 155-183 hours.

In vitro receptor studies have shown that semaglutide is a potent and selective GLP-1 analogue, and animal studies using non-diabetic rats, non-diabetic pigs and diabetic mice have shown lowering of BG and inhibition of food intake. A clinically relevant effect on glucose metabolism and body weight has also been observed in humans.

Nonclinical data

The nonclinical programme for semaglutide was designed according to the ICH M3[36] guideline to support the clinical development. The standard nonclinical data package required to support phase 3 clinical trials has been completed. In addition, 2-year carcinogenicity studies and a pre- and postnatal development toxicity study have been completed.

Semaglutide is generally well tolerated with expected GLP-1 effects on food intake and body weight being dose limiting in mice, rats and cynomolgus monkeys. Two potential safety issues have been identified.

Thyroid C-cell tumours in rodents

Treatment-related non-genotoxic proliferative changes in the thyroid C-cells of mice and rats were observed in 2-year carcinogenicity studies with semaglutide. Early C-cell changes were also identified in repeated dose toxicity studies with semaglutide in mice. However, this was not the case

in other species including a 52-week repeat dose study in non-human primates at exposure levels up to 36-fold above the expected clinical exposure. The observed pattern of effects in mice and rats (thyroid C-cell proliferation preceded by increase in serum calcitonin) and lack of these effects in the non-human primate and in man suggest that the mechanism by which semaglutide acts on the thyroid C-cells in rodents is the same as has been demonstrated for other GLP-1 RAs, including liraglutide. The relevance for human subjects is unknown. Recently published data have shown that the GLP-1 receptor 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[37].

Teratogenicity in rats

Semaglutide has been concluded teratogenic in rats, with exposure at no observable adverse effect level (NOAEL) below expected human exposure. This effect is regarded to be caused by impairment of nutrient supply to the embryo across the inverted yolk sac with placental function which is specific to rats.

Non-human primates and humans do not depend on a yolk sac with placental function to supply nutrients to the embryo early in pregnancy. The effect on rat embryo-foetal development is therefore not likely to be relevant to humans as described below. Preliminary and main embryofoetal development and pre- and postnatal development studies with doses corresponding to 12-15 fold expected clinical exposure in cynomolgus monkeys have been finalised. In the main embryofoetal development study sporadic abnormalities were reported across all dose groups and in the pre- and postnatal development study a dose-dependent increase in early pregnancy losses was observed. The findings observed across the three studies in cynomolgus monkeys are not indicative of a teratogenic potential of semaglutide in this species. The increase in early pregnancy losses is indicative of embryo-toxicity, which may be related to the maternal effect of semaglutide (marked body weight loss). A developmental toxicity NOAEL was determined at an exposure 1- to 2 fold the expected clinical exposure (1 mg/week). A risk for the developing human embryo or foetus cannot be definitely ruled out, but the absence of findings indicative of teratogenicity in the embryo-foetal development and pre- and postnatal development studies in cynomolgus monkey decreases the level of concern.

A comprehensive review of results from the nonclinical studies can be found in the current edition of semaglutide s.c. (NN9535), T2D, Investigator's Brochure (IB)[38] or any updates hereof.

Clinical data

Semaglutide s.c. is currently being investigated in the T2D development programme (please refer to the semaglutide s.c. IB for T2D or any updates hereof [38]) and in the obesity development programme. Novo Nordisk is also developing semaglutide for oral administration, and phase 3 trials with this formulation are ongoing.

As of 22 December 2015 (the cut-off date of the latest version of the semaglutide s.c. IB for T2D[38]), 13 clinical pharmacology trials and 1 phase 2 trial have been completed with semaglutide once-weekly s.c. In the completed once-weekly semaglutide s.c. trials, 802 subjects have been exposed to semaglutide: 411 healthy subjects (both single and multiple dosing), 313 subjects with type 2 diabetes (up to 12 weeks of treatment), 48 subjects with varying degrees of renal impairment (4 subjects had type 2 diabetes) (single dosing) and 30 subjects with obesity but otherwise healthy.

As of 22 December 2015, 8 therapeutic confirmatory trials with nearly 8000 subjects enrolled are ongoing including a 104-week trial comparing the long-term safety (including cardiovascular risk) and efficacy of semaglutide once-weekly s.c.

Doses up to 1.6 mg with weekly dosing have been tested and doses up to 0.4 mg with daily dosing are being tested in the NN9536-4153 trial for the weight management indication.

A recent finalised trial (not described in the current version of the semaglutide s.c. IB for T2D[38]), investigated subjects with hepatic impairment. Following administration of a single dose of semaglutide 0.5 mg, semaglutide pharmacokinetics were compared between subjects with mild, moderate and severe hepatic impairment and subjects with normal hepatic function. The primary endpoint, total exposure in terms of area under curve (AUC), met the criterion for 'no effect' for all 3 hepatic impairment groups versus the group with normal hepatic function. Hence, exposure of semaglutide was not affected by hepatic impairment, and semaglutide pharmacokinetic properties for subjects with hepatic impairment were similar to those with normal function. No new safety or tolerability issues were observed for semaglutide following single dose administration to this subject group.

Efficacy

As of 22 December 2015, efficacy of semaglutide in subjects with T2D has been investigated in one phase 2 dose range finding trial (NN9535-1821). The trial was a 12-week, randomised, double-blind, placebo- and active-controlled trial in which 411 adults with T2D received once-weekly s.c. injection of 1 of 5 semaglutide dose levels (0.1-1.6 mg), once-daily injection of open label liraglutide (1.2 mg or 1.8 mg) or once-weekly placebo.

12 weeks of treatment, equivalent to 5-7 weeks in steady state on maintenance dose, provided statistically significant and clinically relevant improvement in glycaemic control for dose levels of 0.2 mg and above. Mean changes in glycosylated haemoglobin (HbA_{1c}) from baseline was up to -1.19% (placebo adjusted estimated treatment difference). Dose-dependent improvements in fasting plasma glucose (FPG) and postprandial PG were also observed. The improvement in glycaemic control was accompanied by weight loss for semaglutide doses of 0.8 mg and above (estimated treatment difference compared to placebo up to a mean value of -3.64 kg).

Safety

From the clinical trials completed so far the following safety observations have been made. In consistency with the findings obtained from evaluating other GLP-1 RAs, common adverse events (AEs) included nausea and vomiting; most of them were mild to moderate in severity.

Hypoglycaemia has occurred in subjects receiving semaglutide and these events have mainly been minor. As with other GLP-1 RAs, an increase in heart rate has been observed in subjects exposed to semaglutide. The implications of this increase are unknown. As with all protein based pharmaceuticals, subjects treated with semaglutide may develop immunogenic and allergic reactions. Few allergic reactions have been reported in connection with semaglutide. These have mainly been mild and transient however, more generalised reactions may occur, including urticaria, rash, pruritus and rare cases of angioedema have been observed. Injection site reactions have been infrequently reported. These have mainly been mild and transient in nature.

Please see the current edition of semaglutide s.c. (NN9535), T2D, Investigator's Brochure (IB)[38] or any updates hereof for further details.

For an assessment of benefits and risks of the trial, see Section 18.1.

3.2 Rationale for the trial

Currently, first-line treatment of NASH is lifestyle interventions to provide weight loss and to treat comorbidities (e.g. hyperlipidaemia, hypertension and diabetes) as no specific pharmaceutical therapies are approved and, thus, there is a substantial unmet medical need for effective treatment of NASH.

The results from the LEAN trial[34] showed beneficial treatment effects of liraglutide in overweight subjects with biopsy-confirmed NASH. Data from semaglutide trials, a human GLP-1 analogue structurally similar to liraglutide with similar mechanism of action, has suggested a more pronounced effect on glycaemic control and body weight loss compared to liraglutide. Therefore semaglutide is considered to have an even better potential as treatment for NASH.

The purpose of the present trial is to investigate the potential of semaglutide s.c. once daily at three dose levels to resolve NASH compared to placebo. Furthermore, the trial is designed to explore the dose response relationship for semaglutide in NASH in order to inform dose selection for phase 3. Furthermore, safety and tolerability including the formation of anti-semaglutide antibodies will be investigated.

4 Objectives and endpoints

4.1 Objectives

Primary objective

To compare the effect of semaglutide s.c. once daily versus placebo on histological resolution of NASH.

Secondary efficacy objectives

To investigate the dose-response relationship of three dose levels of semaglutide s.c. once daily (0.1 mg/day, 0.2 mg/day and 0.4 mg/day) on histological resolution of NASH.

To compare the effects of semaglutide s.c. once daily to placebo on liver-related histological parameters and biomarkers of NASH disease.

To investigate the effects of semaglutide s.c. once daily versus placebo in subjects with NASH on:

- Weight-related parameters
- Glucose metabolism related parameters
- Cardiovascular risk factors
- Patient reported outcomes

Secondary safety objectives

To evaluate the safety and tolerability of three dose levels of semaglutide s.c. once daily in subjects with NASH.

4.2 Endpoints

4.2.1 Primary endpoint

- NASH resolution* without worsening of fibrosis** after 72 weeks (yes/no)

*) Resolution of NASH defined by the NASH Clinical research network (CRN) as “no more than mild residual inflammatory cells (0 – 1) and no ballooning (0)” based on comprehensive interpretation by two independent pathologists (central reading) blinded to treatment allocation.

**) worsening defined by an increase of at least one stage of the Kleiner fibrosis classification

4.2.2 Secondary endpoints

4.2.2.1 Supportive secondary efficacy endpoints

Liver-related histological parameters

- At least one stage of liver fibrosis improvement with no worsening of NASH after 72 weeks (yes/no) (worsening defined as an increase of at least one stage of either lobular inflammation or hepatocyte ballooning according to NASH CRN criteria [19] [39]).*

Change from baseline to week 72 in:

- NAFLD activity score (NAS)*
- Stage of fibrosis according to the Kleiner fibrosis classification*
- Activity component of steatosis-activity-fibrosis (SAF) score*

Biomarkers of NASH disease

Change from baseline to week 72 in:

Algorithms:

- Fibrosis-4 score (Fib-4 score)
- NAFLD Fibrosis Score (NFS)

Blood samples:

- Liver enzymes
    - ALT, AST and GGT
- Liver synthesis function
    - Albumin, INR
- Exploratory biomarkers
    - Serum enhanced liver fibrosis (ELF)*
    - CK-18 fragments
    - miR-122
    - IL-1R antagonist
    - MCP-1
    - FGF-21

Imaging:

- Liver stiffness and liver steatosis (with controlled attenuation parameter) measurement by Fibroscan®

Weight related parameters

- Weight loss of ≥ 5% of baseline body weight at 72 weeks (yes/no)
- Weight loss of ≥ 10% of baseline body weight at 72 weeks (yes/no)

Change from baseline to 72 weeks in:

- Body weight (% and kg)
- Waist circumference
- Body mass index (BMI)

Glucose metabolism related parameters

Change from baseline to 72 weeks in:

- Glycosylated haemoglobin type A1c (HbA_{1c})*
- Fasting plasma glucose (FPG)*
- Fasting glucagon
- Homeostatic model assessment of insulin resistance (HOMA-IR)

Cardiovascular risk factors

Change from baseline to 72 weeks in:

- Systolic and diastolic blood pressure
- Lipids (total cholesterol, low density lipoprotein cholesterol (LDL cholesterol), high density lipoprotein cholesterol (HDL cholesterol), very low density lipoprotein cholesterol (VLDL cholesterol), triglycerides, free fatty acids)
- High sensitivity C reactive protein (hsCRP)

Patient reported outcomes

Change from baseline to 72 weeks in:

- Short form 36 (SF-36): Physical and mental component summary scores and scores on the individual sub-domains: Physical functioning, role functioning, bodily pain, general health, vitality, social functioning, role emotional and mental health.

4.2.2.2 Supportive secondary safety endpoints

- Number of treatment-emergent adverse events during the trial
- Number of treatment-emergent hypoglycaemic episodes during the trial
- Number of treatment-emergent severe or BG confirmed symptomatic hypoglycaemic episodes during the trial
- Number of treatment-emergent severe hypoglycaemic episodes during the trial
- Number of subjects discontinuing treatment due to gastrointestinal adverse events

Occurrence of anti-semaglutide antibodies during and after 72 weeks treatment (yes/no):

- Anti-semaglutide binding antibodies
- Anti-semaglutide binding antibodies with *in vitro* neutralising effect
- Anti-semaglutide binding antibodies cross reacting with native GLP-1
- Cross-reacting anti-semaglutide binding antibodies with *in vitro* neutralising effect to native GLP-1

Anti-semaglutide antibody binding level during and after 72 weeks treatment

Change from baseline to 72 weeks in:

- Pulse
- ECG
- Physical examination
- Haematology (haemoglobin, haematocrit, thrombocytes, erythrocytes, leucocytes, differential count)
- Biochemistry (creatinine, estimated glomerular filtration rate (eGFR), creatine phosphokinase, urea, bilirubin (total), alkaline phosphatase, ferritin, sodium, potassium, calcium (total), amylase, lipase)
- Hormones (calcitonin)

Key supportive secondary endpoints prospectively selected for disclosure (e.g. clinicaltrials.gov and EudraCT) are marked with an asterisk (*).

5 Trial design

5.1 Type of trial

This is a 72-week, randomised, double-blind, placebo-controlled, six-armed, parallel group, multi-centre, multi-national trial comparing once daily administration of semaglutide s.c. in three different doses (0.1 mg, 0.2 mg and 0.4 mg) with placebo in subjects with NASH.

A planned total of 288 subjects will be randomised. Based on an assumption of a 65% screening failure rate, 823 subjects will be screened. Subjects will be randomised in a 3:3:3:1:1:1 manner to receive daily dosing of semaglutide s.c. 0.1 mg, 0.2 mg, 0.4 mg or corresponding injection volumes of placebo once daily (for details see Figure 5–1). To avoid bias in the assessment of the different semaglutide doses, the trial will be double-blinded within dose levels. The dose levels will not be blinded between each other because of different dose escalations and different target doses and volumes required. It is expected that 15% will withdraw from the trial or prematurely discontinue treatment with trial product.

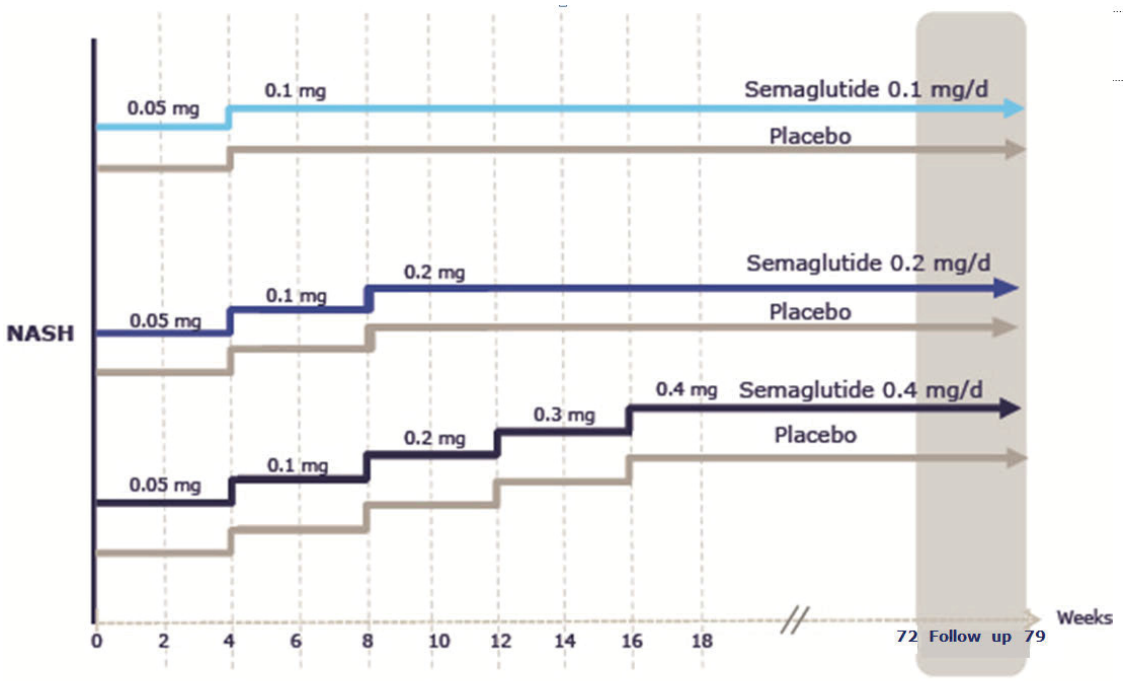


Figure 5–1 Trial design

Subjects in all treatment groups including placebo will receive nutritional and physical activity counselling by a member of the study team according to local site practice.

The randomisation of subjects to treatment will be stratified in five groups as described in section 5.2 and section 11).

The diagnosis of NASH as well as the histology based scores will be subject to central pathologist evaluation.

Subjects who prematurely discontinue the trial product treatment should continue with the originally scheduled site visits/contacts including a liver biopsy and final assessments 72 weeks after randomisation (visit 19A). However the following should not be done after visit 19 for subjects prematurely discontinuing trial product: Semaglutide plasma concentration, anti-semaglutide antibody assessment, hypo reporting and handing out subject diaries.

Subjects who prematurely discontinue trial product treatment will continue to receive nutritional and physical exercise counselling throughout their trial participation.

The total trial duration for the individual subject will be up to 85 weeks (maximum).

5.2 Rationale for trial design

Trial duration of 72 weeks is considered adequate in terms of assessing the primary endpoint. Furthermore, a 72-week trial period is considered to be sufficient to characterise the semaglutide safety and tolerability profile in patients with NASH.

Randomisation will be stratified in five strata based on region (Japanese or non-Japanese) and, within the non-Japanese group, based on diabetes status at screening (with or without type 2 diabetes) and fibrosis stage for baseline liver biopsy (F1/F2 or F3). This is to ensure an even distribution of the treatment arms within the specified strata. Balance of treatment arms with respect to region can help an evaluation of consistency of treatment effect between the entire population and Japanese subjects. Diabetes status and fibrosis stage for baseline liver biopsy are considered important prognostic covariates and including them in the stratification may enhance the credibility of the results of the trial as well as improve the precision of the estimated treatment effect. Stratification based on diabetes status and fibrosis stage is not feasible within the Japanese group due to small sample sizes.

As gastrointestinal AE rates are anticipated to increase with higher doses and with large excursions in the semaglutide plasma concentration, semaglutide is dosed once daily to ensure less variability in concentrations. Dose escalation every fourth week is chosen to reach steady state at each dose level before increasing the dose. This could potentially reduce gastrointestinal AEs.

The trial design and protocol has been developed with harmonised advice from the regulatory authorities of the USA and Germany, and based on the recommendation of the Liver Forum[40] [41].

5.3 Treatment of subjects

The dosing of semaglutide or placebo will be once daily with increase to the next dose step every four weeks until the randomised dose level is reached. During the dose escalation period subjects will be allowed to stay up to one extra week on each dose level, if the dose is not tolerable due to gastrointestinal events or for other reasons as judged by the investigator.

Table 5–1 Duration of dose escalation period

Target dose	Scheduled time to target dose	Flexibility allowed if not tolerated	Maximum time to target dose
Semaglutide 0.4 mg/day	16 weeks	4 weeks	20 weeks
Semaglutide 0.2 mg/day	8 weeks	2 weeks	10 weeks
Semaglutide 0.1 mg/day	4 weeks	1 week	5 weeks

Once the randomised target dose is reached the subject should not change the dose. In case the dose escalation regimen or the target dose cannot be tolerated the subject must be discontinued from treatment.

The following investigational medicinal products (IMP) will be supplied by Novo Nordisk A/S, Denmark:

- Semaglutide 1.0 mg/ml, solution for injection, 3.0 ml cartridge, for NovoPen® 4
- Semaglutide placebo, solution for injection, 3.0 ml cartridge, for NovoPen® 4

Auxiliaries to IMP will be supplied by Novo Nordisk e.g. needles.

The NovoPen® 4 device that will be used in this trial will display a value and not mg.

The conversion table below shows the connection between each volume matched dose level and the value shown in the display on the NovoPen® 4. Subjects must be instructed to administer the value shown in the display.

Table 5–2 Dose conversion table

Value shown in display	Semaglutide (mg)	µL
5	0.05 mg	50 µL
10	0.10 mg	100 µL
20	0.20 mg	200 µL
30	0.30 mg	300 µL
40	0.40 mg	400 µL

Injections may be administered in the thigh, abdomen or upper arm, at any time of day irrespective of meals. The injections should be administered at approximately the same time of day during the trial.

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 subjects participate in any organised weight reduction programme throughout the trial.

For subjects treated with vitamin E or pioglitazone according to exclusion criterion 8, these medications must be kept at a stable dose throughout the trial.

5.3.1 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 $HbA_{1c} \leq 8.0$ % at screening:

Subjects with $HbA_{1c} \leq 8.0$ % at screening (visit 1) should have the total daily insulin dose reduced by 30 % at start of trial product treatment to limit the potential risk of hypoglycaemia induced by the combination of insulin and semaglutide.

5.3.2 Treatment of subjects with poorly controlled glycaemia

Subjects with type 2 diabetes and with persistent and unacceptable hyperglycaemia should be offered treatment intensification. If any HbA_{1c} value reported by central laboratory exceeds 9% from at least 4 weeks after end of dose escalation, the subject should be offered treatment intensification at the discretion of the investigator. However, the following treatment types must not be used: GLP-1 RAs (other than trial product) and SGLT-2 inhibitors. Subjects that are started on treatment intensification medication should continue to follow the protocol specified visit schedule and stay on trial product treatment unless the investigator judges that this will jeopardise the safety of the subject.

All treatment intensification medication given should be documented in medical records and reported in the eCRF. Treatment intensification medication will not be provided nor reimbursed by Novo Nordisk.

5.3.3 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 at the discretion of the investigator. However the following treatments must not be used: GLP-1 RAs (other than trial product) and SGLT-2 inhibitors.

The antidiabetic medication prescribed by the investigator will not be provided nor reimbursed by Novo Nordisk.

5.3.4 Missed dose

If a subject forgets to inject a trial product dose, the dose can be administered as soon as the subject remembers. However, if it is more than 12 hours since the subject should have administered the dose, the subject should skip the missed dose and take the next dose as usual on the following day.

If a subject has missed several consecutive doses of trial product, trial product can be continued. Please refer to guidance document describing recommendations on how to re-initiate trial product.

5.3.5 Nutritional and physical activity counselling

All subjects will receive nutritional and physical activity counselling (see section 8.6.3).

5.4 Treatment after discontinuation of trial product

When discontinuing trial products, either at the scheduled end of treatment visit or if trial product is discontinued prematurely, the investigator should discuss other potential treatment options with the subject. For subjects with type 2 diabetes investigator should also discuss potential treatment options for type 2 diabetes.

5.5 Rationale for treatment

Subjects are enrolled for a treatment period of 72 weeks in order to be able to evaluate the full effect of treatment on the primary and secondary endpoints as well as to be able to make a reasonable safety assessment. This is based on the knowledge from the LEAN study (investigator sponsored study) where a statistically significant greater number of patients had resolution of NASH after 48 weeks of treatment with liraglutide 1.8 mg compared with placebo in patients with biopsy confirmed NASH. 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 [95% CI 1·0–17·7]; p=0·019) compared to placebo[34]. Thus, given the relatively long time required to reach the target dose of the highest semaglutide doses, and in order to see the full effect of the different doses, trial duration of 72 weeks was chosen.

The comparator in the trial is placebo. Placebo is used in order to evaluate the absolute safety and efficacy of once-daily semaglutide. Currently, there are no approved therapies for NASH.

The semaglutide dose levels of 0.1 mg/day to 0.4 mg/day have been chosen to get a wide range of exposure. This will allow for dose-response modelling which in combination with safety information related to the individual doses, will form the basis for selecting the optimal semaglutide dose for patients with NASH.

6 Trial population

6.1 Number of subjects

Number of subjects planned to be screened: 823.

Number of subjects planned to be randomised: 288 (65% screen failure rate).

Number of subjects expected to complete the trial on or off trial product: 259 (10% trial withdrawal rate).

Number of subjects expected to complete the trial on trial product: 245 (15% total trial product discontinuation rate).

The aim is that between 30 and 70% of subjects should have NASH and type 2 diabetes.

To ensure that a sufficient number of subjects with F2 and F3 are included in the trial the aim is to randomise a maximum of approximately 30% subjects with F1.

6.2 Inclusion criteria

For an eligible subject, all inclusion criteria must be answered "yes".

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 except for protocol described pre-screening activities which require a separate informed consent.
   Applicable for Sweden: 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) (for Japan: male or female aged 20-75 years (both inclusive)) at the time of signing informed consent.

3. Stable body weight (defined as less than 5% self-reported change in body weight in the period from 28 days prior to screening or if recent biopsy is used from 28 days prior to baseline liver biopsy until time of screening).

4. Accept to have one liver biopsy performed during the screening period (if no biopsy within 21 weeks before screening is available) and one at 72 weeks after randomisation.

5. Histologic evidence of NASH based on central pathologist evaluation of a liver biopsy obtained up to 21 weeks before screening.

6. A histological NAS $\geq$ 4 with a score of 1 or more in each sub-component of the score based on central pathologist evaluation.

7. NASH fibrosis stage 1, 2 or 3 according to the NASH CRN fibrosis staging system based on central pathologist evaluation.

6.3 Exclusion criteria

For an eligible subject, all exclusion criteria must be answered "no".

Liver-related:

1. Documented causes of chronic liver disease other than NASH.

2. Positive HBsAg, positive anti-HIV, positive HCV-RNA.

3. AST greater than 5 times upper normal limit (UNL) at screening.

4. ALT greater than 5 times UNL at screening.

5. Elevated total bilirubin (> 1.5 mg/dL) at screening. Total bilirubin level >1.5 mg/dL is allowed if conjugated bilirubin is < 1.5 × UNL.

6. International normalized ratio (INR) of prothrombin time > 1.3 at screening.

7. Known or suspected abuse of alcohol (> 20 g/day for women or > 30 g/day for men), alcohol dependence* or narcotics. (* = assessed by the Alcohol Use Disorders Identification Test (AUDIT questionnaire)).

8. Treatment with vitamin E or pioglitazone which has not been at a stable dose in the period from 90 days prior to screening or if recent biopsy is used from 90 days prior to baseline liver biopsy until time of screening.

9. Treatment or anticipated initiation (for more than 14 consecutive days) of medications known to have an effect on steatosis (e.g. treatment with Corticosteroids (topical and inhaled are allowed), Methotrexate, Tamoxifen, Valproic acid, Amiodarone or Tetracycline) in the period from 28 days prior to screening or if recent biopsy is used from 28 days prior to baseline liver biopsy until time of screening.

Glycaemia related:

10. HbA_{1c} > 10% at screening.

11. Treatment with GLP-1 RAs or SGLT-2 inhibitors in the period from 90 days prior to screening or if recent biopsy is used from 90 days prior to baseline liver biopsy until time of screening.

12. Treatment with other glucose lowering agent(s) (apart from GLP-1 RAs or SGLT-2 inhibitors) not stable in the period from 28 days prior to screening or if recent biopsy is used from 28 days prior to baseline liver biopsy until time of screening. Changes without clinical relevance in the opinion of the investigator are allowed.

13. Diagnosis of type 1 diabetes according to medical records.

    Obesity related:

14. Body Mass Index (BMI) ≤ 25.0 kg/m^2 at the screening visit (visit 1).

15. Treatment with orlistat, zonisamide, topiramate, phentermine, lorcaserin, bupropion and naltrexone alone or in combination or any other medication that could promote weight loss in the opinion of the investigator in the period from 28 days prior to screening or if recent biopsy is used from 28 days prior to baseline liver biopsy until time of screening.

16. Participation in an organised weight reduction program (e.g. WeightWatchers®) in the period from 28 days prior to screening or if recent biopsy is used from 28 days prior to baseline liver biopsy until time of screening.

17. Previous surgical treatment for obesity. However (1) liposuction and/or abdominoplasty if performed > 6 months before baseline liver biopsy is allowed or 2) lap banding where the band has been removed > 6 months before baseline liver biopsy is allowed 3) intragastric balloon where the balloon has been removed > 6 months before baseline liver biopsy is allowed.

    General safety:

18. For patients with type 2 diabetes only: Proliferative retinopathy or maculopathy requiring acute treatment verified by fundus photography or dilated fundoscopy performed within the past 90 days prior to randomisation.

19. History or presence of pancreatitis (acute or chronic).

20. Calcitonin ≥ 50 ng/L at screening.

21. Family or personal history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma. Family is defined as a first degree relative.

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

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

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

25. Language barrier, mental incapacity, unwillingness or inability to adequately understand or comply with study procedures.

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

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

28. Participation in any clinical trial of an approved or non-approved investigational medicinal product within 90 days before screening.

29. Female who is pregnant, breast-feeding or intends to become pregnant or is of childbearing potential and not using an adequate contraceptive method (adequate contraceptive measures as required by local regulation or practice).

For EU countries: The following contraceptive measures are considered adequate:

- Combined estrogen and progestogen containing hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation :
  - oral
  - injectable
  - implantable
- Placement of an
  - intrauterine device (IUD)
  - intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Barrier methods of contraception (condom or occlusive cap with spermicidal foam/gel/film/cream/suppository) **(not applicable for Belgium, Denmark, Finland, Greece, Spain, Sweden)**

- Vasectomised partner (where partner is sole partner of subject) **(not applicable for Denmark)**
- True sexual abstinence **(not applicable for Denmark)**. Sexual abstinence is defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

30. Renal impairment measured as estimated Glomerular Filtration Rate (eGFR) value of eGFR < 30 ml/min/1.73 m^2 as defined by Kidney Disease: Improving Global Outcomes (KDIGO).[42]

31. **Applicable for Sweden**: TSH > 6 mIU/L or < 0.4 mIU/L at screening.

6.4 Criteria for premature discontinuation of trial product

Efforts must be made so that subjects attend and complete all scheduled visit procedures. However the following should not be done after visit 19 for subjects prematurely discontinuing trial product: Semaglutide plasma concentration, anti-semaglutide antibody assessment, hypo reporting and handing out subject diaries. Subjects should stay in the trial irrespective of lack of adherence to randomised treatment, lack of adherence to visit schedule or missing assessments. Only subjects who decline any further contact with the site in relation to the trial will be considered as withdrawn from the trial (see section 6.5).

The subject may be prematurely discontinued from trial product at the discretion of the investigator due to a safety concern.

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

1. Included in the trial in violation of the inclusion and/or exclusion criteria
2. Pregnancy
3. Intention of becoming pregnant
4. Simultaneous participation in another clinical trial of an approved or non-approved investigational medicinal product.
5. In case of code break
6. If the target treatment dose of the randomised trial product is not tolerated by the subject
7. Diagnosis of acute pancreatitis
8. Diagnosis of medullary thyroid carcinoma

9. Surgical treatment for obesity

10. Treatment with other GLP-1 receptor agonists or SGLT-2 inhibitors

11. Persistent abnormal liver blood parameters indicating drug induced liver injury (DILI) (see details in section 8.7.2)

See section 8.1.6 for procedures to be performed for subjects discontinuing trial product prematurely.

6.5 Withdrawal from trial

The subject may withdraw consent at will at any time. The subject's request to withdraw from the trial must always be respected.

Please see section 8.1.7 for procedures to be performed for subjects withdrawing consent.

6.6 Subject replacement

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

6.7 Rationale for trial population

Patients with NASH have an increased risk of all cause and liver related mortality. As there is currently no established, safe and effective pharmacological treatment for NASH there is a significant unmet medical need.

As the prevalence of NASH is high in patients with T2D (approximately 25% of patients with T2D have NASH) and considering the glycaemic properties of semaglutide it is appropriate not to exclude patients with T2D in the trial. Hence both patients with and without T2D can be included as it is the aim to include a broad NASH population.

The trial population will consist of patients with NASH and a fibrosis stage of F 1-F3. Patients with F0 will be excluded as they do not have fibrosis. Furthermore, subjects with fibrosis stage 4 (cirrhosis) will be excluded from the trial as an important endpoint addressing worsening in fibrosis cannot be addressed in this population (the Kleiner classification has a maximum score of 4).

7 Milestones

Planned duration of recruitment period: 103 weeks

End of trial is defined as LSLV

Recruitment:
The screening and randomisation rate will be followed closely via the interactive web response system (IWRS) in order to estimate when to stop screening. All investigators will be notified immediately when the recruitment period ends, after which no further subjects may be screened and the IWRS will be closed for further screening. All subjects screened during the recruitment period and found eligible for randomisation can be randomised within the timelines specified in the flowchart (see section 2).

Trial registration:

Information of the trial will be disclosed at clinicaltrials.gov and novonordisk-trials.com. According to the Novo Nordisk Code of Conduct for Clinical Trial Disclosure[43], it will also be disclosed according to other applicable requirements such as those of the International Committee of Medical Journal Editors (ICMJE)[44], the Food and Drug Administration Amendment Act (FDAAA)[45], European Commission Requirements[46] [47] 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.

8 Methods and assessments

The following sections describe the assessments and procedures that must be performed during this trial. The overview of when they must be performed is included in the flow chart (section 2).

8.1 Visit procedures

8.1.1 Screening, re-screening and screen failures

Informed consent must be obtained before any trial related activity, see section 18.2. Separate informed consent forms for long-term storage of human samples and genotyping are available and informed consent must be obtained before activities related to any of these are undertaken.

Additionally a separate informed consent form for optional pre-screening is available. This must be signed before any optional pre-screening activities are performed (see section 8.1.2).

At screening (visit 1), subjects will be provided with a card stating that they are participating in a trial and giving contact address(es) and telephone number(s) of relevant trial site staff. Subjects should be instructed to return the card to the investigator at the last trial visit or to destroy the card after the last visit.

Each subject will be assigned a unique 6-digit subject number which will remain the same throughout the trial.

The investigator must keep a subject screening log, a subject identification code list and a subject enrolment log. Only subjects who have signed the informed consent form should be included on the logs. The subject screening log and subject enrolment log may be combined in one log and may be generated from the IWRS (see section 10).

Screening failures

For screening failures the screening failure form in the electronic case report form (eCRF) must be completed with the reason for not continuing in the trial. Serious and non-serious adverse events from screening failures must be transcribed by the investigator into the eCRF. Follow-up on serious adverse events (SAEs) must be carried out according to section 12.
A screening failure session must be made in the IWRS. The case book in the eCRF must be signed.

Re-screening

Re-screening of screening failures is allowed only once within the limits of the recruitment period. However, re-screening is NOT allowed if the subject has failed one of the inclusion/exclusion criteria related to laboratory parameters (pathology and/or blood parameters). In the event of re-screening, a new informed consent must be obtained and a new subject number must be allocated.

All assessments and laboratory samples must be repeated.
For subjects meeting exclusion criterion number 6, re-test of INR is allowed once within the limits of the screening period for that subject. To be eligible for INR re-test the subject must have a screening albumin within central laboratory reference range. Re-test of INR does not require a new informed consent or new subject number.

8.1.2 Optional pre-screening (not applicable for Sweden)

The Investigator may, after obtaining separate informed consent, perform pre-screening of potential trial candidates. Pre-screening assessments include blood parameters and imaging (except for imaging methods with radiation involved).The purpose of such assessments is to assess trial eligibility potential.

Pre-screening assessments are not defined as trial-related procedures. Results of pre-screening assessments will not be collected in the trial database and will not be monitored. Concerns related to any pre-screening assessment must not be reported as an adverse event.

Pre-screening assessments (blood parameters and imaging) performed after signature of the separate informed consent can be reimbursed by Novo Nordisk A/S.

8.1.3 AUDIT questionnaire

The AUDIT questionnaire is used to assess the frequency of alcohol consumption and screen out alcohol-related problems, and dependence symptoms.

8.1.4 Fasting visits

Subjects must attend most clinic visits in a fasting state (see section 2).

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 blood sampling has been performed. 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. Fasting procedures include body weight, Fibroscan® measurements and blood sampling (FPG, fasting insulin, fasting glucagon, calcitonin and lipids (Total cholesterol, free fatty acids, HDL cholesterol, LDL cholesterol, triglycerides, VLDL cholesterol)).

Prior to Fibroscan® measurements, only two hours of fasting is required.

At visit 19, the subject must be fasting for two hours prior to the anti-semaglutide antibody sampling (see section 8.5.3.7).

8.1.5 Missed visits

If an entire visit is missed and it is not possible to re-schedule the visit within the time window, every effort should be made to re-schedule the visit at the earliest possible date before the next visit.

8.1.6 Premature discontinuation of trial product

If a subject prematurely discontinues trial product treatment, the investigator must undertake procedures similar to those for visit 18 (end of treatment) as soon as possible and the follow up visit (visit 19) must be performed 7 weeks later. **Females only:** All female subjects using an adequate contraceptive method must be reminded to continue this for 7 weeks after discontinuation of trial product treatment.

Following visit 19, subjects should continue with the originally scheduled site visits/contacts up to and including visit 19A. Visit 19A should take place 72 weeks (± 7 days) after their randomisation date (for details refer to section 2). However the following should not be done after visit 19 for subjects prematurely discontinuing trial product: Semaglutide plasma concentration, anti-semaglutide antibody assessment, hypo reporting and handing out subject diaries.

If a subject is not willing to attend one or more of the above mentioned visits, it should be documented in the subject's medical record that the subject has refused to attend the visit and why.

For subjects discontinued from trial product, final drug accountability must be performed and a treatment discontinuation session must be made in the IWRS. The primary reason for premature discontinuation of trial product must be specified in subject's medical records and the eCRF.

8.1.7 Withdrawn subjects

If a subject withdraws consent, the investigator must aim to undertake procedures similar to those for visit 18 (end of treatment) as soon as possible. If the subject agrees, the follow up visit (visit 19) must be performed 7 weeks later.

The end-of-trial form must be completed, and final drug accountability must be performed even if the subject is not able to come to the trial site. A treatment discontinuation session must be made in the IWRS. The case book must be signed.

Although a subject is not obliged to give his/her reason(s) for withdrawing consent, 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 withdrawing consent must be specified in the end-of-trial form in the eCRF.

8.1.8 Subject training

Subject diaries

The subject must be provided with diaries at the specified visits (section 2). The investigator should instruct the subjects in filling in the diary according to the provided diary instructions (see section 8.4.7 and 8.6.2). The diaries dispensed to subjects should be collected at the specified visits (section 2).

Trial product

Trial product must be dispensed to subjects at the specified visits (see section 2). Trial product will be dispensed to the subject by the site. At the visits specified in section 2 and as needed, the subjects will be instructed in the handling of trial product and trained in the use of the pen-injector and in the administration of s.c. injection of trial product.

Subjects must be instructed to administer the value shown in the display, see Table 5–2.

Hypoglycaemic episodes recognition

The investigator or delegate will train the subjects in symptom recognition and handling of hypoglycaemia.

Suspected pregnancy

Female subjects must be instructed to contact site if a menstrual period is missed so they can come in for urine pregnancy test.

8.2 Subject related information/assessments

8.2.1 Demography

Demography will be recorded at screening and consists of:

- Date of birth (according to local regulation)
- Sex
- Ethnicity (according to local regulation)
- Race (according to local regulation)

8.2.2 Concomitant illness and medical history

A **concomitant illness** is any illness that is present at the start of the trial (i.e. at visit 1) or found as a result of a screening procedure or other trial procedures performed before exposure to trial product.

Any change to a concomitant illness should be recorded during the trial. A clinically significant worsening of a concomitant illness must be reported as an AE.

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.

It must be possible to verify the subject's medical history in source documents such as subject's medical record. If a subject is not from the investigator´s own practice; the investigator must make reasonable effort to obtain a copy of the subject's medical record from any relevant party e.g. primary physician. The investigator must document any attempt to obtain external medical information by noting the date(s) when information was requested and who has been contacted.

8.2.3 Concomitant medication

A **concomitant medication** is any medication, other than the trial product(s), which is taken during the trial, including the screening and follow-up periods.

Details of any concomitant medication must be recorded at the first visit. Changes in concomitant medication must be recorded at each visit as they occur.

The information collected for each concomitant medication includes trade name or generic name, indication, start date and stop date or continuation. For vitamin E and pioglitazone the daily dose must be recorded as well.

If a change is due to an AE, then this must be reported according to section 12. If the change influences the subject's eligibility to continue in the trial, the monitor must be informed.

8.2.4 Hypoglycaemia unawareness

For subjects with type 2 diabetes information on hypoglycaemia unawareness will be recorded at screening according to Clarke's questionnaire, question 8[48]. The investigator must ask the subject in the following way: "To what extent can you tell by your symptoms that your blood glucose is low?" The subject can answer never, rarely, sometimes, often or always.

Subjects answering 'never, rarely or sometimes' are considered as having impaired awareness of hypoglycaemia.

8.2.5 Childbearing potential

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

Pregnancy testing must be performed on female subjects of childbearing potential as described in section 8.5.3.6. Female subjects of childbearing potential must be instructed to use adequate contraceptive methods throughout the trial and until 7 weeks after end of treatment.

Female of non-childbearing potential is defined as:

- Female who has undergone a hysterectomy, bilateral oophorectomy or bilateral tubal ligation
- Postmenopausal defined as no menses for 12 months without an alternative medical cause
- Other medical reasons preventing childbearing potential

8.2.6 Tobacco use

Details of tobacco use must be recorded at the first visit. Smoking is defined as smoking at least one cigarette or equivalent daily.

Smoking status:

- Never smoked
- Previous smoker
- Current smoker

8.2.7 Fundoscopy/Fundus photography

For subjects with type 2 diabetes dilated fundoscopy/fundus photography will be performed as specified in section 2. Fundoscopy requires pharmacological dilation of both pupils. Results of the dilated fundoscopy/fundus photography will be evaluated by the investigator and the investigator evaluation must be documented either on the dilated fundoscopy/fundus photography result report or in the subject's medical record.

The investigator or medically qualified delegate must sign, date and interpret the dilated fundoscopy/fundus photography by using the following categories:

- Normal
- Abnormal
  - Was the result clinically significant? (Yes/No)

If a dilated fundoscopy/fundus photography has been performed within 90 days prior to randomisation, the procedure does not need to be repeated, unless there has been worsening of visual function since the last examination. The results must be available prior to randomisation.

If the dilated fundoscopy/fundus photography is performed before the subject has signed the informed consent form, it must be documented in the medical records that the reason for performing the procedure was not related to this trial.

8.3 Efficacy assessments

8.3.1 Liver biopsy

Liver biopsies must be performed according to site standard procedures.

To be randomised, subjects must have histologic evidence of NASH based on central pathologist evaluation of a liver biopsy. Histologic evidence of NASH can be based on a liver biopsy obtained up to 21 weeks prior to screening. For subjects with no historical liver biopsy within 21 weeks prior to screening, a liver biopsy must be performed during the screening period. The histologic evidence of NASH by central pathologist evaluation of the liver biopsy must be available prior to randomisation of the subject.

In case the liver biopsy obtained during the screening period or up to 21 weeks prior to screening cannot be used for confirmation of NASH diagnosis 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 should have a liver biopsy performed at end of treatment (if the 72 weeks treatment period is completed) or at 72 weeks after randomisation (if trial product has been prematurely discontinued). 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.

Tissue samples will be returned to the relevant sites no later than at finalisation of the clinical trial report (CTR).

8.3.1.1 Central pathologist evaluation

The histologic evidence of NASH and histology based scores will be centrally assessed by two independent pathologists with expertise and experience in NASH.

The central pathologist evaluation will include the following:

- Presence or absence of NASH
- NAFLD Activity Score (NAS) components (steatosis, lobular inflammation and hepatocyte ballooning)
- Stage of fibrosis (according to Kleiner fibrosis classification)

The pathologists will be blinded to the subject and treatment and to each other's assessment of the tissue until both have reached a final conclusion. Both pathologists have to agree on the outcome of the assessment. In case of misalignment of the conclusions, a consensus needs to be reached by discussion or joint assessment of the two pathologists. If not possible a third independent, qualified pathologist will make the final decision.

8.3.2 Fibroscan® measurements

At sites where Fibroscan® equipment is not available, no assessment should be done.

Liver stiffness

At sites with Fibroscan® equipment available, measurements of liver stiffness must be performed at the specified visits (section 2). Fibroscan measurements can be performed up to 2 weeks prior to each visit. A result measured in kPa must be available. The same equipment should preferably be used for all measurements throughout the trial.

All randomised subjects should have a liver stiffness measurement performed 72 weeks after randomisation regardless of whether trial product has been discontinued prematurely or not.

The liver stiffness measurements must be performed in fasting state (see section 8.1.4) and according to site standard procedures. The result of the measurement must be documented and investigator evaluation of the result must be documented either on the actual report or in the subject´s medical record.

Liver steatosis

At sites with Fibroscan® equipment available with Controlled Attenuation Parameter (CAP) option available, measurements of liver steatosis must be performed at the specified visits (section 2). Fibroscan measurements can be performed up to 2 weeks prior to each visit. A result measured in

dB/m must be available. The same equipment should preferably be used for all measurements throughout the trial.

All randomised subjects should have a liver steatosis measurement performed 72 weeks after randomisation regardless of whether trial product has been discontinued prematurely or not.

The liver steatosis measurements must be performed in fasting state (see section 8.1.4) and according to site standard procedures. The result of the measurement must be documented and investigator evaluation of the result must be documented either on the actual report or in the subject´s medical record.

8.3.3 Body measurements

8.3.3.1 Body weight

Body weight must be measured in a fasting state (except at visit 1), see flowchart (section 2) and will only be measured at visits where subjects are fasting due to blood sampling.

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

8.3.3.2 Height

Height is measured at screening (visit 1) without shoes in centimetres or inches (one decimal).

8.3.3.3 Body mass index

Body mass index will be calculated by the eCRF from visit 1 height data and must be in accordance with exclusion criterion 14.

8.3.3.4 Waist circumference

The waist circumference is defined as the abdominal circumference located midway between the lower rib margin and the iliac crest and will be measured at the specified visits (section 2).

One waist measurement must be performed and is measured in the horizontal plane with one decimal using a non-stretchable measuring tape. The same measuring tape should preferably be used throughout the trial.

The subject should be measured in a standing position with an empty bladder and wearing light clothing. The subject should be standing, feet together with arms at the side and waist accessible. 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.

8.3.3.5 Vital signs

Systolic and diastolic blood pressure

One measurement of blood pressure must be performed at the visits specified in section 2.

The method for measuring systolic and diastolic blood pressure needs to follow the standard clinical practice at site, but as a minimum, the following guideline must be adhered to:

- Avoid caffeine, smoking and exercise at least 30 minutes prior to measuring the blood pressure
- Blood pressure should be measured in a sitting position, with the legs uncrossed, the back and arms supported
- The subject should be sitting for five minutes before the measurement is taken
  The same arm and an appropriate cuff size should be used for blood pressure measurement at all visits

Pulse

Pulse (beat/min) will be recorded in a sitting position after resting for five minutes at the specified visits (section 2).

8.3.4 SF-36 questionnaires

The Short Form 36 (SF-36) should be completed by subjects at the visits specified in section 2.

The questionnaires must be completed by the subject and should preferably be completed after conclusion of all fasting-related activities, but before any other visit-related activities. Subjects must be given the opportunity to complete the questionnaires by themselves without interruption.

SF-36 measures the individual's overall health-related quality of life (HRQoL) on 8 domains: physical functioning, role functioning, bodily pain, general health, vitality, social functioning, role emotional and mental health.

Review of the questionnaires must be documented either on the documents and/or in the subject's medical record. If clarification of entries or discrepancies in the patient reported outcomes questionnaires is needed, the subject must be questioned and a conclusion made in the subject's medical record. Care must be taken not to bias the subject.

It is the responsibility of the investigator or delegated staff to review the questionnaires to report possible AEs immediately following completion.

All results from the SF-36 questionnaires must be transferred into the eCRF.

8.4 Safety assessments

8.4.1 Physical examination

Physical examination will be performed at the specified visits (section 2) according to local procedure. Physical examination must be recorded in the subject´s medical record and should include:

- General appearance
- Thyroid gland
- Respiratory system
- Cardiovascular system
- Gastrointestinal system including mouth
- Musculoskeletal system
- Central and peripheral nervous system
- Skin
- Lymph node palpation
- Head, ears, eyes, nose, throat and neck

Any abnormal, clinically significant findings at visit 1 must be recorded as a concomitant illness (see section 8.2.2).

8.4.2 Electrocardiogram

A 12-lead ECG will be performed at the visits specified in the flow chart (section 2). The investigator or delegate must sign, date and interpret the ECG by using the following categories:

- Normal
- Abnormal
    - Was the result clinically significant? (Yes/No)

All ECGs will in addition undergo central evaluation. Sites will be informed of the central ECG evaluation in case this evaluation reveals an abnormal ECG reading. If the abnormality, in the opinion of the investigator, represents an unreported AE, such finding must be reported by the investigator (see section 12.2).

If the central ECG evaluation of a post-baseline ECG is suggestive of new MI, a confirmatory ECG should be performed. All findings suggestive of new MI detected by the central ECG reading will be adjudicated by the event adjudication committee (EAC) (see section 12.7.2).

Additional unscheduled ECG recordings can be performed at the investigator's discretion at other visits than the planned ECG visits. If unscheduled ECGs are recorded and submitted for central assessment the reason should be documented and an AE reported (if applicable).

8.4.3 Adverse events

Adverse events (AEs) must be reported at each visit in accordance with the procedures outlined in section 12.

8.4.4 Medication error

If a medication error is observed during the trial, the following information is required and a specific event form must be completed in the eCRF in addition to the AE form:

- Trial product(s) involved
- Classification of medication error
- Whether the subject experienced any hypoglycaemic episodes and/or adverse event(s) as a result of the medication error
- Suspected primary reason for the medication error

For definition of medication errors, see section 12.1.4.

8.4.5 Adverse events requiring additional data collection

For the following AEs additional data collection is required and specific event forms must be completed in the eCRF in addition to the AE form:

- Acute coronary syndrome (myocardial infarction, silent myocardial infarction or unstable angina pectoris)
- Cerebrovascular event (stroke or transient ischaemic attack)
- Heart failure requiring hospitalisation or urgent unscheduled visit
- Acute pancreatitis
- Acute gallbladder disease
- Neoplasm
- Hepatic event

See appendix B for details about the additional information to report.

In case any of these events fulfil the criteria for a serious adverse event, please report accordingly, see section 12.2. For events requiring adjudication, please see Table 12–1.

8.4.6 Self-measured plasma glucose

At the randomisation visit (visit 2) subjects with type 2 diabetes will be provided with a blood glucose meter (BG-meter) including auxiliaries as well as instructions for use. The subjects will be instructed in how to use the device and the instruction will be repeated at regular intervals as needed. Subjects must be instructed to measure their blood glucose in connection with symptoms of hypoglycaemia.

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

Only the blood glucose meter provided by Novo Nordisk should be used for the measurements required in the protocol.

Subjects without type 2 diabetes at the randomisation visit will not be provided with BG-meters and hypoglycaemic episodes will only be identified by subjects via symptoms of hypoglycaemia.

In case a subject is diagnosed with type 2 diabetes during trial participation, the subject must be provided with a BG-meter and must be instructed in how to use the device and to measure their blood glucose in connection with symptoms of hypoglycaemia in the remaining trial period.

Subjects with type 2 diabetes should be instructed in how to record the results of the SMPG values in the diaries. The record of each SMPG value should include date, time and value. All data from the diary must be transcribed into the eCRF during or following the contact. If obtained via phone and a discrepancy is later detected, the values in the eCRF must be corrected.

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

8.4.7 Hypoglycaemic episodes

All subjects will at randomisation be instructed in symptom recognition and handling of hypoglycaemia.

All subjects will be provided with diaries for capturing information related to hypoglycaemic episodes throughout the trial from visit 2 to visit 19 (7 weeks after end of treatment visit (visit 18)).

For subjects with type 2 diabetes plasma glucose should always be measured and recorded when a hypoglycaemic episode is suspected.

All plasma glucose 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 in the diary according to the instructions below throughout the trial from visit 2 to visit 19 (7 weeks after end of treatment visit (visit 18)).

Upon onset of a hypoglycaemic episode the subject is recommended to measure plasma glucose every 15 minutes until the SMPG value is >3.9 mmol/L (70 mg/dL) and/or symptoms have been resolved in accordance to current guidelines[49].

An SMPG value ≤ 3.9 mmol/L (70 mg/dL) or hypoglycaemic symptoms must trigger a hypoglycaemic episode form to be completed by the subject. Repeated SMPG measurements and/or symptoms, occurring within a period of 60 min after onset on a hypoglycaemic episode, 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 and should be reported on one hypoglycaemic episode form. SMPG measurements ≤ 3.9 mmol/L (70 mg/dL) or hypoglycaemic symptoms after the 60 min period shall trigger the reporting of a new hypoglycaemia episode and prompt the subject to fill out a new hypoglycaemic episode form until a succeeding measurement is > 3.9 mmol/L (70 mg/dL) and/or symptoms have been resolved.

In case of several low SMPG values within the 60 minutes interval, 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 SMPG value and/or symptom.

For all subjects the records on hypoglycaemic episodes should include the following information (in subject diaries):

- Start date and time of the hypoglycaemic episode.
- Stop date and time of the hypoglycaemic episode (stop time is the first time the plasma glucose value is > 3.9 mmol/L (70 mg/dL) (only applicable for subjects with type 2 diabetes) and/or symptoms have been resolved).
- The plasma glucose level before treating the episode (if available) and any follow up measurements (only applicable for subjects with type 2 diabetes).
  The lowest value measured during the hypoglycaemic episode will be reported as the plasma glucose value for the episode, the remaining values will be kept as source data in the diary.
- Whether the episode was symptomatic (Yes/No).
  A hypoglycaemic episode starting without symptoms should be updated to symptomatic if the subject experiences symptoms later during the episode.
- Whether the subject was able to treat him/herself.

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

- Date, time and dose of last trial product administration prior to the episode.
- Date and time of last main meal (not including snacks) prior to the episode.
- Whether the episode occurred in relation to physical activity.
- Change in any concomitant illness.
- Any sign of fever and/or other acute disease.
- Whether the subject was asleep when the episode occurred.
  - If yes, whether the symptoms of the episode woke up the subject

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. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration[49].

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

If the question "Was the subject able to treat him/herself?" is answered "No", the following information should be recorded by the subject:

- Who assisted in the treatment of the hypoglycaemic episode (i.e. medical person or non-medical person, please specify)?
- Where the treatment was administered (in clinic/emergency room/hospital or other. If the subject was treated in clinic/emergency room/hospital, whether they were transported in an ambulance or not, please specify)
- Type of treatment provided by another person (i.e. oral carbohydrates, glucagon, intravenous (IV) glucose or other, please specify)
- Were symptoms alleviated after administration of treatment?
- Factors contributing to the episode (i.e. physical activity, missed meal, diet change, medication error (i.e. overdose, mix-up between products, incorrect use of device), miscalculation of dose of antidiabetic medication, other factors not listed or unknown)
- Did the subject experience seizure?
- Was the subject unconscious/comatose?
- Did the subject experience any of the following symptoms[50] (layman term used in the diary is specified in brackets if different from the protocol term)?
  - Autonomic: sweating, trembling, hunger or palpitations (rapid or irregular heart beat)
  - Neuroglycopenic: confusion, drowsiness, speech difficulty, visual disturbances, odd behaviour, impaired balance or incoordination (reduced ability to coordinate movement)
  - General malaise: headache or malaise (feeling discomfort/unease)

- Other symptoms

If the hypoglycaemic episode fulfils the criteria for an SAE then an AE form and a safety information form must also be filled in, see section 12.

8.4.8 Hyperglycaemic episodes

Self-measured plasma glucose values or central laboratory FPG values > 16.7 mmol/L (300 mg/dL) must be reported as adverse events (see section 12.2). Subjects should be instructed to contact site staff in case of hyperglycaemia. **Applicable for subjects with type 2 diabetes only**: Whenever a hyperglycaemic episode is suspected, plasma glucose should be measured with the BG-meter handed out.

8.5 Laboratory assessments

The laboratory analyses will be performed by a central laboratory except for laboratory analyses for pre-screening, analysis of anti-semaglutide antibodies and semaglutide plasma concentration analysis and some exploratory biomarkers which will be performed at specialised laboratories. The central laboratory may utilise subcontractors for their analyses.

Descriptions of laboratory supplies, procedures for obtaining samples, handling, storage and shipments of samples, will be given in the trial-specific laboratory manual provided by the central laboratory.

Only laboratory samples specified in the protocol must be sent to the central laboratory for analysis; if additional laboratory sampling is needed, e.g. to follow up on AEs, this must be done at a local laboratory.

The laboratory provides results to the trial sites in the units preferred by the trial sites while the results that are transferred to the trial database will always be in SI units.

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 and report these according to section 8.2.2 and section 12.

Laboratory samples may be drawn on another day than the day of the actual visit, as long as it is within the visit window outlined in the flow chart (see section 2).

Laboratory results will be made available to the investigator on an on-going basis except for the anti-semaglutide antibody results, the results of the semaglutide plasma concentration analysis and the exploratory biomarker results. Anti-semaglutide antibody results and the results of the

semaglutide plasma concentration analysis 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 will not be provided to the investigator, as these results will not be used for any clinical evaluation during the trial.

Laboratory samples, including specific safety assessments, will be destroyed no later than at finalisation of the clinical trial report (CTR).

Antibody samples and biosamples for future analysis will be stored as described in section 24.2.

8.5.1 Review of laboratory reports

Review of laboratory reports must be documented either on the documents and/or in the subject's medical record.

For laboratory report values outside the reference range, the investigator must specify whether the value is clinically significant or not. The evaluation of screening results must be documented prior to visit 2 (randomisation), for the subsequent visits preferably on the day of evaluation.

It is the responsibility of the investigator or delegated staff to review the laboratory reports and to report possible AEs immediately following completion of the review.

8.5.2 Laboratory assessments for efficacy

8.5.2.1 Biochemistry

- ALT
- AST
- GGT
- hsCRP
- Lipids (Total cholesterol, free fatty acids, HDL cholesterol, LDL cholesterol, triglycerides, VLDL cholesterol)
- Fib-4 and NFS (refer to section 17.4.1.1)

8.5.2.2 Glucose metabolism

- FPG
- HbA_{1c}
- Fasting insulin
- Fasting glucagon
- HOMA-IR (refer to section 17.4.1.1)

FPG is measured to evaluate metabolic control. The subjects must attend these visits fasting (for definition of fasting, see section 8.1.4). An FPG result ≤3.9 mmol/L (70 mg/dL) should not be reported as a hypoglycaemic episode but as a clinical laboratory adverse event (CLAE) at the discretion of the investigator (see section 12.1.1).

8.5.2.3 Exploratory biomarkers

- CK-18 fragments
- ELF (refer to section 17.4.1.1)
- miR-122
- IL-1R antagonist
- MCP-1
- FGF-21

8.5.2.4 Biosamples for future analysis:

Biosamples for future analysis must be drawn/collected and shipped to the central lab at the visits specified in section 2. The details and instructions around these samples are described in the trial-specific central laboratory manual. Please refer to section 24.2 for more information about the planned use of the samples.

8.5.3 Laboratory assessments for safety

Blood samples for haematology and biochemistry must be collected at the specified visits (section 2).

8.5.3.1 Biochemistry

- Bilirubin, total
- Bilirubin, conjugated
- Calcium
- Creatine phosphokinase
- Creatinine
- eGFR (per CKD-EPI formula)[51]
- Lipase
- Potassium
- Sodium
- Alkaline phosphatase
- Amylase
- Albumin
- Ferritin
- Urea

- MELD score[52]

8.5.3.2 Hormones

- Calcitonin (see Appendix A)
- **For Sweden**: Thyroid-stimulating hormone (TSH)

8.5.3.3 Haematology

- Erythrocytes
- Haematocrit
- Haemoglobin
- Leucocytes
- Thrombocytes
- Differential count:
  - Eosinophils
  - Basophils
  - Lymphocytes
  - Monocytes
  - Neutrophils

8.5.3.4 Coagulation marker

- International Normalised Ratio (INR) of prothrombin time

8.5.3.5 HIV and hepatitis

- Hepatitis B
- Hepatitis C
- HIV antigen/antibody screening test

8.5.3.6 Pregnancy test

Females of childbearing potential will have a human chorionic gonadotropin (hCG) serum pregnancy test performed at the specified visits in the flow chart (see section 2).

Urine pregnancy tests (dipstick) will be performed for females of childbearing potential at the visits specified in the flowchart (section 2). If a female subject misses a menstrual period, she should contact site to come in for a urine pregnancy test (dipstick). Urine pregnancy tests will be supplied by the central laboratory. The test will be performed at the site.

Pregnancy testing is not required for women who are of non-childbearing potential as defined in section 8.2.5.

For Austria: Urine pregnancy test must be done once a month for women of childbearing potential.

8.5.3.7 Anti-semaglutide antibodies

Blood samples will be drawn during the trial and analysed at a specialised laboratory for determination of serum antibodies against semaglutide, including cross reactivity to endogenous GLP-1 (see flow chart, section 2).

Subjects must be instructed to withhold their trial product dose in the morning until blood sampling has been performed at the visit.

Samples taken at the follow-up visit (visit 19) must be taken fasting (as a minimum by only having consumed water for at least 2 hours). Samples taken at the follow-up visit which are positive for anti-semaglutide antibodies will be further characterised for *in vitro* neutralising effect towards semaglutide. In addition, samples taken at the follow-up visit which are positive for cross-reactivity against endogenous GLP-1 will be analysed for *in vitro* neutralising effect towards endogenous GLP-1.

8.6 Other assessments

8.6.1 Semaglutide plasma concentration

For all subjects a single blood sample for measurement of plasma semaglutide concentration will be drawn at selected visits (see section 2).

Subjects must be instructed to withhold their trial product dose in the morning until blood sampling is performed on the visit. In addition subjects must be instructed to complete their diary (see section 8.6.2) and bring it to the visits.

8.6.2 Subject diaries

Review of subject diaries must be documented either on the documents and/or in the subject's medical record. If clarification of entries or discrepancies in the diary is needed, the subject must be questioned and a conclusion made in the subject's medical record. Care must be taken not to bias the subject.

The following information will be captured in subject diaries:

- Information regarding first trial product dose (date, time, dose, injection site)
- Information regarding trial product doses (prior to each visit with blood sampling for measurement of semaglutide plasma concentration after randomisation until the end of treatment visit)
- Information regarding hypoglycaemic episodes

Trial product dosing information

The subject must record the date, time, dose and injection site of the last trial product injection prior to the clinic visit. Furthermore, the subject must fill in if any trial product doses were not taken in the previous two weeks. This information will be collected at all visits with blood sampling for measurement of semaglutide plasma concentration until the end of treatment visit. The information will be transcribed to the eCRF by the investigator or delegate together with the exact date and time for blood sampling, when applicable.

Hypoglycaemic episodes

For information to be captured regarding hypoglycaemic episodes, please refer to section 8.4.7.

8.6.3 Nutritional and physical activity counselling

Subjects will receive nutritional and physical activity counselling in accordance with site practice at the visits specified in section 2.

8.7 Specific safety requirements

8.7.1 Suspicion of acute pancreatitis

Assessments in case of suspicion of acute pancreatitis

The diagnosis of acute pancreatitis requires two of the following three features:

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

Abdominal pain

Most patients with acute pancreatitis experience abdominal pain that is located generally in the epigastrium and radiates to the back. The onset of the pain may be swift reaching maximum intensity within 30 minutes, it is frequently unbearable and characteristically persists for more than 24 hours without relief. The pain is often associated with nausea and vomiting. Physical examination usually reveals severe upper abdominal tenderness at times associated with guarding.

Lipase and amylase

In general, both amylase and lipase are elevated during the course of acute pancreatitis. The serum lipase may remain elevated slightly longer than amylase. The level of the serum amylase and/or

lipase does not correlate with the severity of acute pancreatitis. In general, serum lipase is thought to be more sensitive and specific than serum amylase in the diagnosis of acute pancreatitis.

In case of suspicion of acute pancreatitis, the trial product should promptly be interrupted (NO treatment discontinuation call should be made in IWRS before diagnosis of acute pancreatitis is confirmed). Appropriate additional examinations must be performed, including local measurement of amylase and lipase.

If acute pancreatitis is ruled out, trial product should be re-initiated.

If acute pancreatitis is confirmed, appropriate treatment and careful monitoring of the subject should be initiated. The subject must be discontinued from trial product (treatment discontinuati on call), but should remain in the trial (see section 6.4). The event should be reported as an AE requiring additional data collection (see section 8.4.5 and Appendix B) and will undergo assessment by the EAC (see section 12.1.5).

8.7.2 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 > 7x UNL
- ALT or AST > 2x baseline value
- Total bilirubin > 2.0 mg/dL
- INR > 1.6

For definition of baseline values, see section 17.

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 (Hy's Law) (see section 12.1.2).
- 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 in subjects where the baseline values were ≥ 2x UNL but < 5x UNL.
- ALT or AST increase to > 2x baseline value AND the increase is accompanied by a concomitant total bilirubin increase to > 2x baseline value OR concomitant INR increase by > 0.2 from baseline.

- 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 section 8.4.5, section12 and Appendix B.

For all such events repeat testing must occur within 48 to 72 hours and work up for competing etiologies must be performed[53] 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 only if an alternative etiology is definitively identified and liver blood parameters have returned to pre-event levels.

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 prematurely discontinued (see section 6.4).

8.7.3 Training in the delivery device (NovoPen® 4)

Trial product must be dispensed to subjects at the specified visits (see section 2). At the visits specified in section 2 and as needed, the subjects will be instructed in the handling of trial product and trained in the use of NovoPen® 4 and in the administration of s.c. injection of trial product.

The subjects must be trained in how to handle the delivery device (NovoPen® 4) and in use of the pen-injector when handed out the first time. Training must be repeated during the trial at regular intervals and as needed in order to ensure correct use of the device.

The following should be emphasised:

- Always use a new needle for each injection as this will prevent contamination and blocked needles
- Priming the pen to ensure product flow

- The needle should be kept in the skin while counting slowly to 6 after the dose counter has returned to zero after injection. If the needle is removed too early then the full dose may not have been delivered.

8.8 Subject 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. If the subject continues to be non-compliant the investigator may discontinue the subject from trial product (see section 6.4).

Treatment compliance: will be assessed by monitoring of drug accountability. Prior to visits where drug accountability is performed the subject will be asked to return all used, partly used and unused trial products. The investigator must assess the amount of trial products returned compared to what was dispensed at the last dispensing visit and, in case of discrepancies, question the subject.

9 Trial supplies

Trial supplies comprise trial products and auxiliary supplies. Additional details regarding trial supplies can be found in the trial materials manual (TMM).

Trial products must not be dispensed to any person not included in the trial.

Trial product must not be used, if it does not appear clear and colourless.

9.1 Trial products

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

Table 9–1 Trial products

Trial product	Strength	Dosage form	Route of administration	Container/delivery device
Semaglutide 1.0 mg/mL (Investigational medicinal product (IMP))	1.0 mg/mL	Solution for injection	Subcutaneous (s.c.) injection	3 mL Cartridge for NovoPen® 4
Semaglutide placebo (Investigational medicinal product (IMP))	N/A			

Semaglutide 1.0 mg/mL and semaglutide placebo are visually identical.

9.2 Labelling

The trial products will be labelled in accordance with Annex 13[54], local regulations and trial requirements.

Each trial site will be supplied with sufficient trial products for the trial on an on-going basis controlled by the IWRS.

Each dispensing unit (DU) is uniquely numbered with a Dispensing Unit Number (DUN).

NovoPen® 4 is a CE-marked, US FDA and Japan MHLW (Ministry of Health, Labour and Welfare) approved pen injector device for subcutaneous administration of insulin. This trial is investigating

an indication outside the approved intended use or indication for use and the NovoPen® 4 will therefore be labelled "exclusively for clinical investigations" worded in accordance with national legislation. A description of the device is included in the Investigator's Brochure.

The investigator must document that direction for use (DFU) is given to the subject orally and in writing at the first dispensing visit (visit 2). At the later dispensing visits the investigator or delegate should ensure that subjects comply with injection procedures and re-dispense DFU, if needed.

9.3 Storage

Table 9–2 Storage conditions

Trial product	Storage conditions (not-in-use)	In-use conditions	In-use time[a]
Semaglutide 1.0 mg/mL	Store in a refrigerator between 2°C - 8°C (36°F – 46°F) Do not freeze Protect from light	Store below 30°C (86°F) Do not refrigerate Do not freeze Protect from light	Use within 28 days
Semaglutide placebo			

[a] In-use time starts when the product is taken out of the refrigerator at subjects home

The investigator must ensure that trial product is kept under proper storage conditions and record and evaluate the temperature. The investigator must inform Novo Nordisk **immediately** if any trial product has been stored outside specified conditions (e.g. outside temperature range). Additional details regarding handling of temperature deviations can be found in the trial materials manual (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 must take appropriate action to ensure correct storage.

9.4 Drug accountability and destruction

Drug accountability of all trial products received at site is the responsibility of the investigator.

Returned trial product (used/partly used and/or unused), expired or damaged trial product can be stored at room temperature and must be stored separately from non-allocated trial product.

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

The trial products will be dispensed to each subject as required according to treatment group. The IWRS will allocate trial product to the subject at randomisation and each dispensing visit. The correct dispensing unit number(s) (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.

Subjects must be instructed to return all used, partly used and unused trial product including empty packaging material at each dispensing visit and at end of treatment visit.

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

9.5 Auxiliary supplies

The following auxiliary supplies will be provided by Novo Nordisk in accordance with the TMM:

- Needles for NovoPen® 4 pen injector (maximum length to be used is 8 mm)
- Direction for use for NovoPen® 4 pen injector
- Blood glucose meters (including lancets, plasma-calibrated test strips and control solutions). User manual will be provided along with the blood glucose meter.

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

10 Interactive voice/web response system

A trial-specific IWRS will be set up which can be accessed at any time via the internet or telephone. Access to the IWRS must be restricted to and controlled by authorised persons.

In this trial, the IWRS is used for:

- Screening
- Screening failure
- Randomisation
- Medication arrival
- Dispensing
- Treatment discontinuation
- Completion
- Code break
- Drug accountability
- Data change

IWRS user manuals will be provided to each trial site. DUNs will be allocated using the IWRS. It is important to dispense the exact allocated DUNs to a subject.

11 Randomisation procedure and breaking of blinded codes

The trial is a double-blinded trial. A randomisation session will be carried out for all subjects using the IWRS.

At the randomisation visit (visit 2), eligible subjects will be randomised in a 3:3:3:1:1:1 manner to receive daily dose of:

- semaglutide 0.1, 0.2 or 0.4 mg (dose escalation every fourth week) or
- placebo (matching each of the active treatment arms with corresponding injection volumes)

Randomisation will be controlled by the IWRS and stratified in five strata defined by region, diabetes status and fibrosis stage for baseline liver biopsy according to the criteria below:

- Japanese
- Non-Japanese, with type 2 diabetes, fibrosis stage 1/2
- Non-Japanese, with type 2 diabetes, fibrosis stage 3
- Non-Japanese, without type 2 diabetes, fibrosis stage 1/2
- Non-Japanese, without type 2 diabetes, fibrosis stage 3

This is to ensure an even distribution of the treatment arms within the five strata.

11.1 Breaking of blinded codes

The IWRS will notify Novo Nordisk (monitor and the Global Safety department) immediately after the code is broken.

The code for a particular subject may be broken in a medical emergency if knowing the actual treatment would influence the treatment of the subject. Whenever a code is broken the person breaking the code must print the Code Break Confirmation Notification generated by the IWRS, record the reason, and sign and date the document.

When the code 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 code break the IWRS helpdesk should be contacted. Contact details are listed in Attachment I.
If the code has been broken, the subject must discontinue treatment with trial product and a treatment discontinuation session must be completed in IWRS.

12 Adverse events, technical complaints and pregnancies

12.1 Definitions

12.1.1 Adverse event

An adverse event (AE) is any untoward medical occurrence in a subject administered a medicinal product, and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a product, whether or not considered related to the product.

An AE includes:

- A clinically significant worsening of a concomitant illness.
- A clinical laboratory adverse event (CLAE): a clinical laboratory abnormality which is clinically significant, i.e. an abnormality that suggests a disease and/or organ toxicity and is of a severity that requires active management. Active management includes active treatment or further investigations, for example change of medicine dose or more frequent follow-up due to the abnormality.

The following should **not** be reported as AEs:

- Pre-existing conditions, including those found as a result of screening or other trial procedures performed before exposure to trial product (pre-existing conditions should be reported as medical history or 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.
- Non-serious hypoglycaemia is an AE, but is reported on a hypoglycaemic episode form instead of on an AE form, see section 8.4.7.

The following three definitions are used when assessing an AE:

- **Severity**
  - **Mild –** no or transient symptoms, no interference with the subject's daily activities.
  - **Moderate** – marked symptoms, moderate interference with the subject's daily activities.
  - **Severe** – considerable interference with the subject's daily activities; unacceptable.
- **Causality**
  Relationship between an AE and the relevant trial product*(s)*:
  - **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.

- **Final outcome**
  - **Recovered/resolved** - The subject has fully recovered, or by medical or surgical treatment the condition has returned to the level observed at the first trial-related activity after the subject signed the informed consent.
  - **Recovering/resolving** - The condition is improving and the subject is expected to recover from the event. This term is only applicable if the subject has completed the trial or has died from another AE.
  - **Recovered/resolved with sequelae** - The subject has recovered from the condition, but with lasting effect due to a disease, injury, treatment or procedure. If a sequela meets an SAE criterion, the AE must be reported as an SAE.
  - **Not recovered/not resolved** - The condition of the subject has not improved and the symptoms are unchanged, or the outcome is not known.
  - **Fatal** - This term is only applicable if the subject died from a condition related to the reported AE. Outcomes of other reported AEs in a subject before he/she died should be assessed as "recovered/resolved", "recovering/resolving", "recovered/resolved with sequelae" or "not recovered/not resolved". An AE with fatal outcome must be reported as an SAE.
  - **Unknown** - This term is only applicable if the subject is lost to follow-up.

12.1.2 Serious adverse event

A serious adverse event (SAE) is an experience that at any dose results in any of the following:

- Death.
- A life-threatening[a] experience.
- In-patient hospitalisation[b] or prolongation of existing hospitalisation.
- A persistent or significant disability or incapacity[c].
- A congenital anomaly or birth defect.
- Important medical events that may not result in death, be life threatening[a] or require hospitalisation[b] may be considered an SAE when - based on appropriate medical judgement - they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition of SAE[d].

a. The term "life threatening" in the definition of SAE 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 was more severe.

b. The term "hospitalisation" is used when a subject:

- Is admitted to a hospital or in-patient, irrespective of the duration of physical stay, or
- Stays at the hospital for treatment or observation for more than 24 hours

Medical judgement must always be exercised, and when in doubt, the hospital contact should be regarded as a hospitalisation. 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.

[c.] A substantial disruption of a subject's ability to conduct normal life functions (e.g. following the event or clinical investigation the subject has significant, persistent or permanent change, impairment, damage or disruption in his/her body function or structure, physical activity and/or quality of life).

[d.] For example intensive treatment in an emergency room or at home of allergic bronchospasm, blood dyscrasia or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

The following adverse events must always be reported as an SAE using the important medical event criterion if no other seriousness criteria are applicable:

- suspicion of transmission of infectious agents via the trial product
- risk of liver injury defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 x UNL and total bilirubin >2 x UNL, where no alternative aetiology exists (Hy's law).

12.1.3 Non-serious adverse event

A non-serious AE is any AE which does not fulfil the definition of an SAE.

12.1.4 Medication errors

A medication error concerning trial products is defined as:

- Administration of wrong drug or use of wrong device.
  Note: Use of wrong DUN is not considered a medication error.
- Wrong route of administration, such as intramuscular instead of subcutaneous.
- Administration of an overdose with the intention to cause harm (e.g. suicide attempt), misuse or abuse of trial product.
- Accidental administration of a lower or 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.

Medication errors must be reported on an AE form and a specific event form, see section 8.4.4.

12.1.5 Adverse events requiring additional data collection

AEs requiring additional data collection are AEs where the additional data will benefit the evaluation of the product safety. Some events in this trial will be adjudicated by an independent external committee as described in section 12.7.2.

Table 12–1 lists AEs that require completion of specific event forms in the eCRFs and/or are subject to event adjudication.

For further information regarding definitions and which data to collect for the events that require additional data collection, please see Appendix B.

Table 12–1 Adverse events requiring completion of specific eCRF event forms and/or are subject to event adjudication

Event	Specific event form	Event adjudication
Fatal event	No	Yes
Acute coronary syndrome (myocardial infarction, silent myocardial infarction or unstable angina pectoris)	Yes	Yes
Cerebrovascular event (stroke or transient ischaemic attack)	Yes	Yes
Heart failure (requiring hospitalisation or urgent unscheduled visit)	Yes	Yes
Acute pancreatitis	Yes	Yes
Acute gallbladder disease	Yes	No
Neoplasm	Yes	No
Hepatic event	Yes	No

For details about specific event forms, see appendix B.

Identification and reporting of events relevant for adjudication is the responsibility of the investigator including but not limited to the following:

- Identification of adverse events relevant for adjudication according to the protocol.
- Completing the "Adjudication" form in the Novo Nordisk eCRF system within the required timelines.
- Providing alternative aetiology for events initially not reported as an event relevant to adjudication, identified via for example the Novo Nordisk Event Adjudication Group, a centralised ECG reading or the event adjudication committee.
- Uploading redacted copies of source data as specified on the adjudication form directly into the source document collection database, provided by the event adjudication supplier. This

responsibility also covers uploading of clinical data for events identified in the preferred term (PT) search and evaluated to be relevant to adjudication by the event adjudication supplier or the committee chair or appointed delegate. In case copies of source data cannot be retrieved or are pending for a long time, the investigator should prepare and provide a narrative describing the event based on the information which the investigator has access to.

12.1.6 Technical complaints

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:

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

12.2 Reporting of adverse events

All events meeting the definition of an AE must be collected and reported. This includes events from the first trial-related activity after the subject has signed the informed consent until the end of the post-treatment follow-up period (visit 19) or visit 19A for subjects discontinuing trial product prematurely. The events must be recorded in the applicable eCRF forms in a timely manner, see timelines below and Figure 12–1.

During each contact with the trial site staff, the subject must be asked about AEs and technical complaints, for example by asking: “Have you experienced any problems since the last contact?”

All AEs, either observed by the investigator or subject, must be reported by the investigator and evaluated.

All AEs must be recorded by the investigator on an AE form. The investigator should report the diagnosis, if available. If no diagnosis is available, the investigator should record each sign and symptom as individual AEs using separate AE forms.

For SAEs, a safety information form must be completed in addition to the AE form. If several symptoms or diagnoses occur as part of the same clinical picture, one safety information form can be used to describe all the SAEs.

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.

Timelines for initial reporting of AEs:

The investigator must complete the following forms in the CRF/eCRF within the specified timelines:

- **SAEs:** The AE form **within 24 hours** and the safety information form **within 5 calendar** days of the investigator's first knowledge of the SAE.

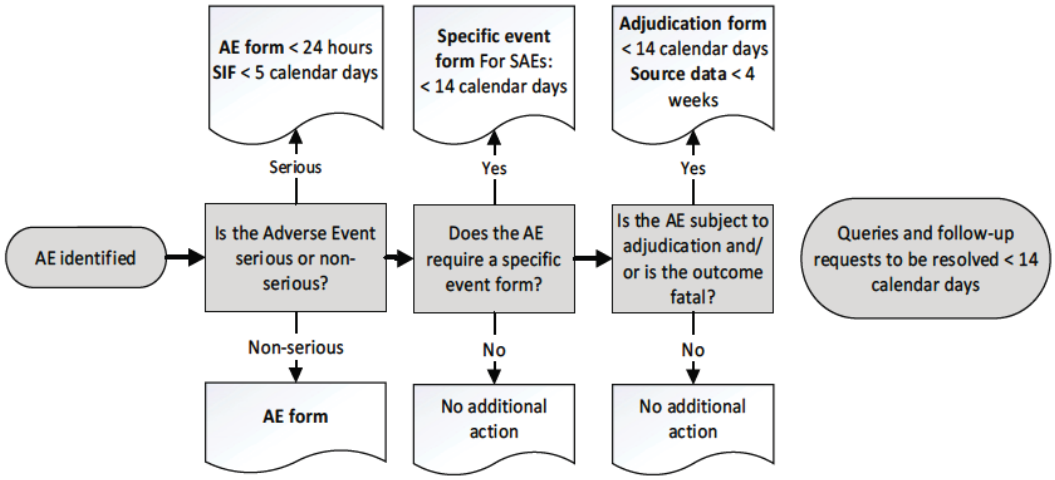
Both forms must be signed within 7 calendar days from the date the information was entered in the eCRF.

For SAEs requiring reporting on a specific event form: In addition to the above the specific event form within 14 calendar days from the investigator's first knowledge of the AE.

Events for Adjudication: The adjudication form should be completed within 14 calendar days of the investigator's first knowledge of the AE and all relevant predefined documents provided within 4 weeks, see Section 12.7.2.

If the eCRF is unavailable, the concerned AE information must be reported on a paper AE form and sent to Novo Nordisk by fax, e-mail or courier within the same timelines as stated above. When the eCRF becomes available again, the investigator must enter the information on the form into the eCRF.

Contact details (fax, telephone, e-mail and address) are provided in the investigator trial master file.



Timelines are for the completion of forms from the time of investigator's awareness
AEs requiring specific event forms are descibed in Section 12.1.4 and 12.1.5
AEs for adjudication are described in Section 12.1.5
AE: Adverse event **SIF:** Safety information form

Figure 12–1 Reporting of AEs

Novo Nordisk assessment of AE expectedness:

Novo Nordisk assessment of expectedness is performed according to the following reference documents: Semaglutide Investigator´s Brochure, s.c., T2D[38], current version and any updates thereto.

Reporting of trial product-related SUSARs by Novo Nordisk:

Novo Nordisk will notify the investigator of trial product-related suspected unexpected serious adverse reactions (SUSARs) in accordance with local requirements and ICH GCP[1]. In addition, the investigator will be informed of any trial-related SAEs that may warrant a change in any trial procedure.

In accordance with regulatory requirements, Novo Nordisk will inform the regulatory authorities, including EMA, of trial product-related SUSARs. In addition, Novo Nordisk will inform the IRBs/IECs of trial product-related SUSARs in accordance with local requirement and ICH GCP[1], unless locally this is an obligation of the investigator.

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.

12.3 Follow-up of adverse events

The investigator must record follow-up information by updating the forms in the eCRF.

Follow-up information must be reported to Novo Nordisk according to the following:

- **SAEs:** All SAEs must be followed until the outcome of the event is "recovered/resolved", "recovered/resolved with sequelae" or "fatal", and until all queries have been resolved. Cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE) may be closed with the outcome "recovering/resolving" or "not recovered/not resolved". Cases can be closed with the outcome of "recovering/resolving" when the subject has completed the follow-up period and is expected by the investigator to recover.

  The SAE follow-up information should only include new (e.g. corrections or additional) information and must be reported **within 24 hours** of the investigator's first knowledge of the information. This is also the case for previously non-serious AEs which subsequently become SAEs.

- **Non-serious AEs:** Non-serious AEs must be followed until the outcome of the event is "recovering/resolving", "recovered/resolved" or "recovered/resolved with sequelae" or until the end of the follow-up period stated in the protocol, whichever comes first, and until all queries related to these AEs have been resolved. Cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE) may be closed with the outcome "recovering/resolving" or "not recovered/not resolved". Cases can be closed with the outcome of "recovering/resolving" when the subject has completed the follow-up period and is expected by the investigator to recover.

The investigator must ensure that the recording of the worst case severity and seriousness of an event is kept throughout the trial. A worsening of an unresolved AE must be reported as follow up with re-assessment of severity and/or seriousness of the event.

Queries or follow-up requests from Novo Nordisk must be responded to **within 14 calendar days** from the date of receipt of the request, unless otherwise specified in the follow-up request.

SAEs after end of trial: If the investigator becomes aware of an SAE with a suspected causal relationship to the investigational medicinal product occurring to a subject after the subject has

ended the trial, the investigator should report this SAE within the same timelines as for SAEs during the trial.

12.4 Technical complaints and technical complaint samples

12.4.1 Reporting of technical complaints

All technical complaints on any of the following products:

- Semaglutide 1.0 mg/mL or semaglutide placebo, 3 mL cartridge
- NovoPen® 4
- Novo Nordisk needles

which occur from the time of first usage of the product until the time of the last usage of the product, must be collected and reported to Customer Complaint Center, Novo Nordisk.

Contact details (fax, e-mail and address) are provided in Attachment I to the protocol.

The investigator must assess whether the technical complaint is related to any AEs and/or SAEs.

Technical complaints must be reported on a separate technical complaint form:
- One technical complaint form must be completed for each affected DUN
- If DUN is not available, a technical complaint form for each batch, code or lot number must be completed

The investigator must complete the technical complaint form in the eCRF within the following timelines of the trial site obtaining knowledge of the technical complaint:
- Technical complaint assessed as related to an SAE **within 24 hours**
- All other technical complaints **within 5 calendar days**

If the eCRF 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 eCRF becomes available again, the investigator must enter the information on the technical complaint form in the eCRF.

12.4.2 Collection, storage and shipment of technical complaint samples

The investigator must collect the technical complaint sample and notify the monitor **within 5 calendar days** of obtaining the sample at trial site. The monitor must coordinate the shipment to Customer Complaint Center, Novo Nordisk (the address is provided in Attachment I) and ensure that the sample is sent as soon as possible. A copy of the technical complaint form must be included

in the shipment of the sample. If several samples are returned in one shipment, the individual sample and the corresponding technical complaint form must be clearly separated.

The investigator must ensure that the technical complaint sample contains the batch, code or lot number and, if available, the DUN. All parts of the DUN should be returned.

If the technical complaint sample is unobtainable, the investigator must specify on the technical complaint form why it is unobtainable.

Storage of the technical complaint sample must be done in accordance with the conditions prescribed for the product.

12.5 Pregnancies

12.5.1 Pregnancies in female subjects

Female subjects must be instructed to notify the investigator immediately if they become pregnant during the trial. The investigator must report any pregnancy in subjects who have received trial product(s).

The investigator must follow the pregnancy until the pregnancy outcome and the newborn infant is one month of age.

The investigator must report information about the pregnancy, pregnancy outcome, and health of the newborn infant(s), as well as AEs in connection with the pregnancy, and AEs in the foetus and newborn infant.

The following must be collected and reported by the investigator to Novo Nordisk - electronically (e.g. in PDF format), or by fax or courier:

1. **Reporting of pregnancy information**
   Information about the pregnancy and pregnancy outcome/health of the newborn infant(s) has to be reported on Maternal Form 1A and 1B, respectively.

   When the pregnancy outcome is abnormal (i.e. congenital anomalies, foetal death including spontaneous abortion and/or any anomalies of the foetus observed at gross examination or during autopsy), and/or when a congenital anomaly is diagnosed within the first month, further information has to be reported for the female subject on Maternal Form 2. In addition, information from the male partner has to be reported on the Paternal Form, after an informed consent has been obtained from the male partner.

   Initial reporting and follow-up information must be reported **within 14 calendar days** of the investigator's first knowledge of initial or follow-up information.

2. Reporting of AE information

The investigator has to report AEs in connection with the pregnancy as well as in the foetus and newborn infant(s). The SAEs that must be reported include abnormal outcome, such as foetal death (including spontaneous abortion), and congenital anomalies (including those observed at gross examination or during autopsy of the foetus), as well as other pregnancy complications fulfilling the criteria of an SAE.

Forms and timelines for reporting AEs:

Non-serious AEs:

- AE form[a] **within 14 calendar days** of the investigator's first knowledge of the initial or follow-up information to the non-serious AE.

SAEs:

- AE form[a] **within 24 hours** of the investigator's first knowledge of the SAE.
- Safety information form **within 5 calendar days** of the investigator's first knowledge of the SAE.
- **SAE follow-up information** to the AE form and/or safety information form **within 24 hours** of the investigator's first knowledge of the follow-up information.

[a] It must be clearly stated in the AE diagnosis field on the AE form if the event occurred in the subject, foetus or newborn infant. If the AE occurred in the foetus or newborn infant, the AE can only be reported on paper AE and safety information form.

Any queries or follow-up requests from Novo Nordisk to non-serious AEs, SAEs and pregnancy forms must be responded to by the investigator **within 14 calendar days** from the date of receipt of the request, unless otherwise specified in the follow-up request.

12.6 Precautions and/or overdose

Limited data are available with regard to overdose and semaglutide. Expected adverse events in connection to an overdose of subcutaneous semaglutide are gastrointestinal AEs and hypoglycaemia (if combined with SU and insulin). Events of nausea, vomiting and headache have been reported in connection with accidental administration of up to 4 mg semaglutide. No symptoms of hypoglycaemia have been reported in connection with overdose of semaglutide. In the event of overdosage, appropriate supportive treatment should be initiated according to the subject's clinical signs and symptoms.

12.7 Committees related to safety

12.7.1 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.

12.7.2 Event adjudication committee

An independent external event adjudication committee is established to perform validation of selected AEs according to pre-defined diagnostic criteria. The validation is based on review of pre-defined clinical source data related to the specific AE. The pre-defined clinical source data consist of copies of source documents collected and delivered by the investigational sites.

The EAC is composed of permanent members covering required medical specialities. The EAC members must disclose any potential conflicts of interest and must be independent of Novo Nordisk.

The events are reviewed by the event adjudication committee in a blinded manner. The EAC will have no authorisation to impact on trial conduct, trial protocol or amendments.

The EAC works in accordance with written guidelines included in the EAC Charter describing in details the composition, tasks, responsibilities and work processes of the committee.

The AEs for adjudication are listed in Table 12–1. In addition, cardiovascular events are being adjudicated according to FDA requirements[1 55].

There are different processes for capturing events for adjudication:

1. Direct reporting by investigator:

All AEs need to be assessed by the investigator if any AE category is applicable. If the AE category selected is in scope for adjudication, the adjudication form in the eCRF will be populated for sites to complete. For AEs with fatal outcome the Fatal Adjudication form will appear in the eCRF when a fatal outcome is selected for an AE.

2. Screening:

All AEs will be screened by Novo Nordisk for potential missed events for adjudication and if needed, the investigator will be asked to provide additional information such as an alternative aetiology, underlying cause(s) and/or clinical details.

All ECGs will be centrally read. If the central reading conclusion is suggestive of new MI, the ECG adjudication form will be populated for sites to complete for all post -baseline ECGs.

3. EAC identified events:

The EAC can decide to have an AE adjudicated even if not initially reported as an event for adjudication by the investigator.

Event adjudication will be performed for AEs in randomised subjects including AEs with an onset date during the screening period. Event adjudication will not be performed for AEs in screening failures.

AEs for adjudication must be reported according to section 12.2. In addition the specific adjudication form should be completed within 14 calendar days of the investigator's first knowledge of the AE, and all relevant predefined documents provided within 4 weeks according to instructions in the event adjudication site manual.

The EAC will review copies in English (translated if necessary) of medical documentation received in the adjudication packages (e.g. x-ray, ECGs, ultrasound images, discharge summaries, pathology reports and death certificates). The investigator must provide medical documentation as soon as possible, when they receive the request from Novo Nordisk or the event adjudication vendor.

The assessment made by the event adjudication committee will be included in the clinical trial report as well as the assessments made by the investigator. However, the adjudication made by the event adjudication committee, given its independent analysis of each event, will be attributed with greater importance of the two. The outcome of adjudication will be kept in the clinical trial database.

13 Case report forms

For this trial a combination of electronic case report forms (eCRFs) and paper CRFs will be used.

Novo Nordisk will provide a system for the electronic case report forms (eCRF). This system and support services to the system will be provided by an external supplier.

Ensure that all relevant questions are answered, and that no empty data field exists. If a test or an assessment has not been done and will not be available, or if the question is irrelevant (e.g. is not applicable), indicate this according to the data entry instructions.

The following will be provided as paper CRFs:

- Pregnancy forms

The following will be provided as paper CRFs to be used when access to the eCRF is revoked or if the eCRF is 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)

On the paper CRF forms print legibly, using a ballpoint pen. Ensure that all questions are answered, and that no empty data blocks exist. Ensure that no information is recorded outside the data blocks. If a test/assessment has not been done and will not be available, indicate this by writing “ND” (not done) in the appropriate answer field in the CRF. If the question is irrelevant (e.g. is not applicable) indicate this by writing “NA” (not applicable) in the appropriate answer field. Further guidance can be obtained from the instructions in the CRF.

The investigator must ensure that all information is consistent with the source documentation. By electronically signing the case book in the eCRF, the investigator confirms that the information in the eCRF and related forms is complete and correct.

13.1 Corrections to case report forms

Corrections to the eCRF data may be made by the investigator or the investigator’s delegated staff. An audit trail will be maintained in the eCRF 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 the investigator has signed the case book, the case book must be signed and dated again by the investigator.

13.2 Case report form flow

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

Site specific eCRF data (in an electronic readable format) will be provided to the trial site before access to the eCRF is revoked. This data must be retained at the trial site.

14 Monitoring procedures

During the course of the trial, the monitor will visit the trial site to ensure that the protocol is adhered to, that all issues have been recorded, to perform source data verification and to monitor drug accountability. The first monitoring visit will be performed as soon as possible after FSFV at the trial site and no later than 4 weeks after. The monitoring visit intervals will depend on the outcome of the remote monitoring of the eCRFs, the trial site's recruitment rate and the compliance of the trial site to the protocol and GCP, but will not exceed 8 weeks during recruitment and 12 weeks after end of recruitment until LSLV at the trial site for sites with subjects between visit 1 and visit 19/19A.

The monitor must be given direct access to all source 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).

All data must be verifiable in source documentation other than the eCRF.

For all data recorded the source document must be defined in a source document agreement at each trial site. There must only be one source defined at any time for any data element.

Source data generated by the trial site can be corrected by another person than the person entering the source data if accepted by local regulations; any correction must be explained, signed and dated by the person making the correction.

The original of the completed diaries and PROs must not be removed from the trial site.

The monitor will ensure that the eCRFs are completed and that paper CRFs are collected.

`The following data will be source data verified for screening failures:

- Date for obtaining informed consent.
- Reason for screening failure
- Serious adverse events (if any)

Monitors will review the subject's medical records and other source data (e.g. the diaries and PROs) to ensure consistency and/or identify omissions compared to the eCRF. If discrepancies are found, the investigator must be questioned about these.

A follow-up letter (paper or electronic) will be sent to the investigator following each monitoring visit. They should address any action to be taken.

15 Data management

Data management is the responsibility of Novo Nordisk. Data management may be delegated under an agreement of transfer of responsibilities to a contract research organisation (CRO).

Appropriate measures, including encryption of data files containing person identifiable data, will be used to ensure confidentiality of subject data, when they are transmitted over open networks.

Data from central laboratories will be transferred electronically. In cases where data is transferred via non-secure electronic networks, data will be encrypted during transfer.

The subject and any biological material obtained from the subject will be identified by subject number and trial ID. Appropriate measures such as encryption or leaving out certain identifiers will be enforced to protect the identity of subjects in all presentations and publications as required by local, regional and national requirements.

16 Computerised systems

Novo Nordisk will capture and process clinical data using computerised systems that are described in Novo Nordisk Standard Operating Procedures and IT architecture documentation. The use and control of these systems are documented.

Investigators working on the trial may use their own electronic systems to capture source data.

17 Statistical considerations

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

The estimand addressing the primary objective is defined as the de-facto (effectiveness) treatment effect on NASH resolution without worsening in fibrosis for all randomised subjects after 72 weeks. All post-baseline scheduled visit data will be included in the statistical analysis, including data collected after discontinuation of trial product. The chosen estimand assesses the difference in resolution of NASH in a future population that results from initiating treatment with semaglutide as compared to placebo. Generalisation of this estimand depends among other things on the extent to which treatment adherence in this trial reflects clinical practice.

If not otherwise specified, the three different placebo arms will be pooled into one placebo arm in the statistical analyses. The pooling is based on the assumption that there is no substantial effect of different placebo volumes on the efficacy and safety endpoints. The validity of this assumption will be checked for the primary endpoint and treatment-emergent adverse events by evaluating descriptive statistics where each placebo arm is presented separately. In addition, the assumption will be evaluated based on estimates from a supportive analysis of the primary endpoint (see section 17.3).

The statistical analyses will in general consist of the following three pairwise treatment comparisons:

- semaglutide 0.4 mg versus placebo
- semaglutide 0.2 mg versus placebo
- semaglutide 0.1 mg 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. The problem of multiple testing will be taken into account with respect to the primary endpoint (see section 17.3) but not for any of the secondary endpoints.

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 (see the definition of the sets in section 17.2).

The baseline measurement is defined as the latest available measurement at or prior to the randomisation visit. An exception is made for identifying abnormal laboratory findings (including ALT, AST, GGT, bilirubin and INR) in which case the baseline value is defined as the mean of the available measurements at the screening and randomisation visits.

Laboratory values below the lower limit of quantification (LLOQ) will be set to ½LLOQ.

17.1 Sample size calculation

The sample size calculation is based on an aim to detect a difference in the probability of achieving NASH resolution (without worsening in fibrosis) between the highest semaglutide dose and the pooled placebo arm at 5% significance level, using Pearson chi-square test with normal approximation. The power is set to 90%.

It is expected that some subjects will respond to standard care. In the LEAN trial, 2 (9%) of 22 placebo subjects had improvement in liver histology. In the FLINT[56] and PIVENS[57] trials, clearance of NASH was a secondary endpoint and the corresponding numbers were 13 (13%) of 98 subjects and 17 (21%) of 83 subjects, respectively. However, these figures also included patients that had worsening of fibrosis. In the more recent trials, CENTAUR[58] and GOLDEN-505[59], the numbers were 9 (7%) of 126 subjects and 11 (14%) of 77 subjects, respectively, for an endpoint that was defined in the same way as the primary endpoint in the present trial. As a conservative assumption, it is anticipated that up to 17% of the placebo completers will achieve resolution of NASH with no worsening of fibrosis.

It is uncertain how many subjects on semaglutide should be expected to achieve resolution of NASH. In the LEAN trial, an improvement was found in 9 (39%) of 23 subjects who received liraglutide 1.8 mg. Results from semaglutide trials in subjects with T2D and/or obesity suggest a greater effect of semaglutide on glycaemic control and body weight loss compared to liraglutide. In communication with medical advisers, a treatment difference of 20-30 percentage points was deemed to be a realistic target as well as clinically relevant. Therefore, it is assumed that 45% of the subjects who complete treatment with semaglutide 0.4 mg achieve resolution of NASH.

Based on the previous NASH trials, 15% of the randomised subjects are anticipated to prematurely discontinue trial product before week 72. These will be included in the main analysis either by using the observed outcome at week 72 (if the outcome is known) or by using imputation (if the outcome is not known). In either case, it is assumed that none of these subjects will achieve resolution of NASH.

Based on the assumptions above, the required number of randomised subjects per arm for the 3 semaglutide arms and the pooled placebo arm is found to be 70. Since the number in the pooled placebo arm needs to be divisible by 3, the number of subjects in each arm is adjusted to 72. Hence, the total number of subjects to be randomised is 288.

In order to investigate the influence of the values of the model parameters such as treatment difference and rate of premature discontinuation of trial product on the calculation, sample sizes have been calculated for different alternative scenarios. The results can be seen in Table 17–1.

Table 17–1 Sample size calculations for different scenarios - number of subjects per arm

Probability of achieving resolution of NASH			
Semaglutide completers	Placebo completers	Rate of premature discontinuation	N per arm
50%	17%	10%	49
		15%	53
		20%	58
45%	17%	10%	65
		15%	70
		20%	77
40%	17%	10%	92
		15%	99
		30%	108

17.2 Definition of analysis sets

The following analysis sets are defined in accordance with the ICH-E9 guidance[60]:

- 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".

Before data are locked for statistical analysis, a review of all data will take place. Any decision to exclude a subject or single observations from the statistic al analysis is the joint responsibility of the trial statistician, the international trial manager and the medical specialist. Exclusion of data from analyses will be used restrictively and normally no data should be excluded from the FAS. If any data is excluded, the decision will be justified and documented. The subjects and observations excluded from analysis sets, and the reason for their exclusion, will be described in the clinical trial report.

Observation periods

Data will be evaluated based on different observation periods which will be derived individually for each subject. The following two observation periods are defined:

- In-trial: This period starts on the date of the randomisation visit and ends on the date of the last trial-related procedure/assessment whether or not the subject has stopped taking trial product.

- 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 (V19), or c) end of the in-trial period. For evaluation of all other data, the period ends at the date of the last dose of trial product +1 day in order to ensure specificity to reversible effects of treatment.

The statistical analyses of the efficacy endpoints will primarily be based on the in-trial period. The on-treatment period is used for some supportive efficacy analyses and all statistical analyses of safety endpoints. Summary statistics will in general be presented for both observation periods.

Data collected after the observation period in question will be excluded from any summary or analysis based on that observation period.

Missing data

With respect to the primary analysis of the primary endpoint, missing week 72 data will be imputed as no resolution of NASH. Sensitivity analyses will be performed using imputation methods based on treatment adherence and unconditional reference, respectively (see section 17.3). For the secondary endpoints, the handling of missing data depends on the type of endpoint and analysis (see section 17.4).

In the analyses based on the in-trial period, the proportion of missing data is expected to be maximum 10%. These data would be missing due to subjects withdrawing from trial or being lost to follow-up. In the analyses based on the on-treatment period, the proportion of missing data is expected to be higher (15%) since data collected after discontinuation of trial product will be excluded. The most common reasons for premature discontinuation of trial product are anticipated to be AEs, ineffective therapy, and noneligibility (subjects randomised although not fulfilling inclusion/exclusion criteria). AEs leading to treatment discontinuation are expected to be equally common across treatment arms except possibly for a higher incidence of AEs due to gastrointestinal side effects in the semaglutide arms. On the other hand, more subjects in the placebo arms may be expected to drop out due to an experienced lack of effect with respect to body weight loss. Overall, the proportion of missing data is expected to be similar across treatment arms.

17.3 Primary endpoint

The primary endpoint is the binary outcome NASH resolution without worsening in fibrosis after 72 weeks (yes/no).The primary analysis will be based on the Cochran-Mantel-Haenszel (CMH) test[61] which will be performed separately for the comparisons between each of the semaglutide arms and placebo. The test will adjust for baseline diabetes status (with or without T2D) and baseline fibrosis stage (F1, F2 or F3). The response data will consist of the outcomes of the week 72 biopsy including assessments taken after premature discontinuation of trial product. Missing response data

will be imputed as no resolution of NASH. This approach does not rely on an assumption of missing at random and should be considered conservative for estimating the treatment effect.

The result of each comparison will be presented as the p-value for testing the null hypothesis of no treatment difference versus a two-sided alternative. The asymptotic p-value obtained from a chi-square distribution will be used unless it is not considered a valid approximation based on the Mantel-Fleiss criterion[62], in which case the exact p-value will be calculated. Besides the p-value, the common odds ratio will be estimated together with a 95% confidence interval using the Mantel-Haenszel estimator associated with the CMH test.

Hierarchical testing procedure

In order to confirm the effect of semaglutide without risk of inflation of the type 1 error, the comparisons will be evaluated hierarchically according to descending semaglutide dose using a family-wise error rate of 5%. The testing procedure will start with the comparison of semaglutide 0.4 mg versus placebo and then continue by in turn comparing semaglutide 0.2 mg versus placebo and semaglutide 0.1 mg versus placebo. Each test will use a local two-sided significance level of 5%. If one of the tests fails to reject the null hypothesis, the testing procedure will stop and no further conclusions will be made.

Sensitivity analyses

To investigate the sensitivity of the results of the primary analysis with regard to the handling of missing data, the following four sensitivity analyses will be performed:

- Analysis using imputation based on treatment adherence: An analysis based on the same type of non-parametric method as for the primary analysis but with missing data handled by a multiple imputation (MI) method which assumes that the unobserved outcomes are well described by the observed outcomes from subjects who at week 72 are similar in terms of treatment adherence. This will be done as follows:

1. Missing data are imputed by sampling with replacement from the empirical distribution of observed outcomes separately within the 8 groups of subjects defined by randomised treatment arm and whether subjects complete the 72-week treatment or not. If a group completely lacks observed outcomes, missing data within this group will be imputed as no resolution of NASH. Multiple (1000) replicates of a complete data set are generated in this way.

2. For each complete data set, the log odds ratios are estimated using the same method as in the primary analysis.

3. The estimates and standard errors for the 1000 complete data sets are pooled using Rubin's rule[63]:

$$m_{MI} = \frac{1}{N}\sum_{i=1}^{N} m_i\,, \qquad SE_{MI} = \sqrt{\frac{1}{N}\sum_{i=1}^{N} SE_i^2 + \left(1+\frac{1}{N}\right)\left(\frac{1}{N-1}\right)\sum_{i=1}^{N}(m_i - m_{MI})^2},$$

where m_i and SE_i are the estimated log odds ratios and standard errors for the $N = 1000$ data sets, and m_{MI} and SE_{MI} are the pooled estimates. From m_{MI} and SE_{MI}, the 95% confidence intervals for the odds ratios and associated p-values are calculated.

This analysis differs from the primary analysis in that it assumes that subjects with missing week 72 data have the same chances of NASH resolution as subjects with week 72 data in the same treatment group, accounting for whether they completed or discontinued the randomised treatment. This is a less conservative assumption than the one used in the primary analysis since it includes the possibility that subjects with missing week 72 data may have NASH resolution. The analysis intends to address missing data relative to what the measurements would have been had the measurements been taken.

- 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 of the subjects in the placebo arm 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. 1000 replicates of a complete data set will be generated that will then be analysed in the same way as in the MI analysis based on treatment adherence. This analysis differs from the primary analysis in that it assumes that subjects with missing week 72 data have the same chances of NASH resolution as subjects with week 72 data in the placebo group. If there are more missing week 72 data in the semaglutide group than in the placebo group, this analysis is less conservative than the primary analysis and probably gives better estimate of the treatment effect. Compared to the first sensitivity analysis, this analysis is more conservative since it assumes that subjects with missing week 72 data in the semaglutide group have the same chance of NASH resolution as subjects in the placebo group.
- Complete case in-trial analysis: The same as the primary analysis but where subjects with missing week 72 data are excluded from the analysis.
- Complete case on-treatment analysis: The same as the primary analysis but where subjects with missing week 72 data or for whom the data were collected after the on-treatment period are excluded from the analysis.

The two complete case analyses are included as benchmarks. They are not based on the randomisation principle and do not estimate any causal effect of semaglutide treatment. The results are expected to be biased in favour of semaglutide and must be interpreted with extreme caution.

The adjustment for covariates in the primary analysis does not exactly match the stratification used for the randomisation. The rationale is that it will not be possible to adjust for region (Japanese or non-Japanese) and, at the same time, adjust for diabetes status and baseline fibrosis stage within the Japanese group due to small sample sizes. Adjustment for region is not expected to influence the overall results but is included in the stratification to facilitate an evaluation of consistency of treatment effect between the entire population and Japanese subjects. Region has therefore been excluded from the primary analysis. However, a CMH test stratified according to the five strata used for the randomisation will be performed as a sensitivity analysis.

Adjustment for baseline body weight as a continuous covariate may potentially give more precise estimates of the treatment effects. To investigate the influence of such an adjustment, a sensitivity analysis will be performed using a logistic regression model which includes treatment, baseline diabetes status, baseline fibrosis stage and diabetes-by-fibrosis interaction as factors and baseline body weight as a covariate.

The use of vitamin E may affect the chance of NASH resolution. Therefore, a sensitivity analysis will be performed using a logistic regression model which includes vitamin E use at baseline (yes/no) as factor together with randomised treatment, baseline diabetes status, baseline fibrosis stage and diabetes-by-fibrosis interaction. Furthermore, a subgroup analysis will be performed using the same logistic regression model but with the addition of a term for the interaction betw een randomised treatment and vitamin E use.

Supportive analysis

As part of an evaluation of the appropriateness of pooling the three placebo arms, a supportive analysis will be performed using the same CMH test as in the primary analysis but without pooling the placebo arms. Each semaglutide arm will instead be compared with the placebo arm which received the same injection volume.

Exploratory analysis

The dose-response relationship with respect to the primary endpoint will be further explored by fitting a modified logistic regression model with baseline diabetes status, baseline fibrosis stage and diabetes-by-fibrosis interaction as factors and the log-transformed dose level and baseline body weight as covariates. The model may be expressed as

$$\boldsymbol{p_i = c_1 + \frac{(c_2 - c_1)}{1 + e^{-\beta \cdot X_i}}}$$

where $\boldsymbol{p_i}$ is the probability of NASH resolution for subject i, $\boldsymbol{c_1}$ and $\boldsymbol{c_2}$ are the asymptotic probabilities of NASH resolution at zero and infinite dose levels, respectively, and $\boldsymbol{\beta \cdot X_i}$ is the linear prediction function of factors and covariates. The response in the placebo arm will be included in

the analysis to help estimate c_1. If the model does not describe the dose-response relationship well or if there are convergence problems, a different approximation may be investigated.

17.4 Secondary endpoints

17.4.1 Supportive secondary endpoints

17.4.1.1 Efficacy endpoints

Liver-related histological parameters

The following secondary histological endpoint will be analysed:

- At least one stage of liver fibrosis improvement with no worsening of NASH after 72 weeks (yes/no)

The analysis of this binary endpoint will be based on a logistic regression model which includes treatment, baseline diabetes status, baseline fibrosis stage and diabetes-by-fibrosis interaction as factors and baseline body weight as a covariate. The analysis will include all assessments taken during the in-trial period. Missing week 72 data will be imputed as no improvement in fibrosis.

In addition, separate analyses will be performed for the change from baseline to week 72 in the following histological feature scores:

- Total NAS (0-8) and each of the components:
    - Steatosis (0-3)
    - Lobular inflammation (0-3)
    - Hepatocyte ballooning (0-2)
- Stage of fibrosis according to the Kleiner fibrosis classification (0-4)
- Activity component of SAF score (0-4)

The activity component of the SAF score is defined as the unweighted sum of hepatocyte ballooning and lobular inflammation. The definition of the lobular inflammation score is modified in this calculation so that the scores 2 and 3 on the original scale are merged to a score 2. The possible range of the sum is thus 0 to 4. For all scores, a higher value indicates a more severe state of disease.

The histological feature scores will be analysed by an ordered logistic regression model (also known as a proportional odds model) with the score at week 72 as response; treatment, baseline

diabetes status, baseline fibrosis stage, diabetes-by-fibrosis interaction and corresponding baseline score as factors; and baseline body weight as a covariate. The analyses will be based on the in-trial period and missing week 72 data will be imputed as no change from baseline in agreement with the analyses of the binary histological endpoints. The results will be presented as an estimate of the cumulative odds ratio for each treatment comparison together with the associated 95% confidence intervals and p-values.

Biomarkers of NASH disease

Analyses will be performed for the change from baseline to week 72 in the following biomarkers for NASH disease:

- Algorithms
  - Fibrosis-4 score
  - NAFLD Fibrosis Score
- Blood samples
  - Liver enzymes
    - ALT
    - AST
    - GGT
  - Liver synthesis function
    - Albumin
    - INR
  - Exploratory biomarkers
    - ELF
    - CK-18 fragments
    - miR-122
    - IL-1R antagonist
    - MCP-1
    - FGF-21
- Imaging
  - Liver stiffness
  - CAP (liver steatosis)

The Fib-4 score will be derived according to the formula[64]:

$$\text{Fib-4} = \frac{\text{Age (years)} \times \text{AST (U/L)}}{\text{Thrombocyte count } (10^9/\text{L}) \times \sqrt{\text{ALT (U/L)}}}$$

The derivation will be performed at each visit where ALT, AST and thrombocyte count have been assessed. If any of the three laboratory parameters is missing at a specific visit, the Fib-4 score will be considered missing as well.

The NAFLD Fibrosis Score will be derived according to the linear regression formula[65]:

$$\begin{aligned}\text{NFS} = -1.675 + 0.037 \times \text{Age (years)} + 0.094 \times \text{BMI (kg/m}^2\text{)} + 1.13 \\ \times \text{Hyperglycaemia (yes/no)} + 0.99 \times \text{AST/ALT} - 0.013 \\ \times \text{Thrombocyte count (10}^9\text{/L)} - 0.66 \times \text{Albumin (g/dL)}\end{aligned}$$

Hyperglycaemia (yes/no) is a binary variable defined as 1 if FPG ≥ 6.1 mmol/L (110 mg/dL) at the corresponding visit of assessment or the subject has been diagnosed with T2D at screening; otherwise, the variable is defined as 0. NFS will be derived at each visit where body weight, FPG, ALT, AST, thrombocyte count and albumin have been assessed.

The ELF discriminant score will be derived as a log-linear combination of the markers hyaluronic acid (HA), amino-terminal propeptide of type III collagen (PIIINP) and tissue inhibitor of metalloproteinase 1 (TIMP1) according to the formula[66]:

$$\begin{aligned}\text{ELF} = -7.412 + 0.681 \times \ln(\text{HA (ng/mL)}) + 0.775 \\ \times \ln(\text{P3NP (ng/mL)}) + 0.494 \times \ln(\text{TIMP1 (ng/mL)})\end{aligned}$$

Analyses of liver stiffness and CAP (liver steatosis) will only be applicable to sites where these assessments were possible. Subjects at sites which did not have capability to assess liver stiffness or CAP (liver steatosis) will be excluded from the corresponding analysis.

All biomarkers except for NFS, ELF and CAP (liver steatosis) will be logarithmically transformed before the statistical analysis. The treatment differences will subsequently be back-transformed to the original scale and expressed as treatment ratios.

The main analysis of each of the biomarkers will be analysis of covariance (ANCOVA) with missing data handled by unconditional reference-based imputation. This will be done as follows:

1. An ANCOVA model with baseline diabetes status, baseline fibrosis stage and diabetes-by-fibrosis interaction as factors and baseline body weight and baseline value of the corresponding biomarker as covariates is fitted to the change from baseline to 72 weeks for the placebo group only.

2. 1000 sets of values of the model parameters are drawn from the posterior distribution. For each replicated set of parameter values, the model is used to generate a complete data set by imputing missing values at 72 weeks for subjects in all treatment groups based on their baseline diabetes

status, baseline fibrosis stage, baseline body weight and baseline value of the corresponding biomarker.

3. For each complete data set, the change from baseline to 72 weeks is analysed using an ANCOVA model with treatment, baseline diabetes status, baseline fibrosis stage and diabetes-by-fibrosis interaction as factors and baseline body weight and baseline value of the corresponding biomarker as covariates.

4. The estimated treatment differences and standard errors for the 1000 complete data sets are pooled using Rubin's rule. From the pooled estimates and standard errors, the 95% confidence intervals for the treatment differences and associated p-values are calculated.

A supportive on-treatment analysis using a mixed model for repeated measurements (MMRM) will be performed for each of the biomarkers. In this model, all scheduled post-baseline measurements taken during the individual subject's on-treatment period will enter as response; treatment, baseline diabetes status, baseline fibrosis stage and diabetes-by-fibrosis interaction will be included as factors; and baseline body weight and baseline value of the corresponding biomarker will be included as covariates. All factors and covariates will be nested within visit and an unstructured covariance matrix for measurements within subject will be employed. There will be no explicit imputation of missing values. As for the main analysis, the estimated treatment differences at week 72 with associated 95% confidence intervals and p-values will be presented.

Whereas the main analysis attempts to estimate the de-facto treatment effect (in agreement with the chosen estimand for the primary objective), the supportive analysis aims to estimate the de-jure effect that would have been observed if all subjects had remained on treatment and completed all visits. The latter analysis relies on the assumption that data are missing at random, which means that given the observed data, the events that lead to data being missing are independent of the unobserved data.

Additional exploratory analyses will be conducted to evaluate the performance of the biomarkers as predictors of NASH (yes/no), fibrosis (stage ≥2, ≥3 and 4, respectively) and/or steatosis (score ≥1, ≥2 and 3, respectively) as applicable using the liver biopsy as the gold-standard reference. Separate analyses will be performed at baseline and week 72 for each predictor. A measurement will be classified as "positive" if the value of the predictor exceeds a chosen cut-point. The performance will be illustrated by the receiver operating characteristic (ROC) curve which describes the relationship of the true positive rate (sensitivity) versus the false positive rate (1 - specificity) as one moves the cut-point. The area under the ROC curve will be used to summarise the overall performance of a predictor and the optimal cut-point will be determined by finding the maximum of Youden's index (sensitivity + specificity - 1). In addition, new algorithms may be explored by constructing a logistic regression model which includes a large set of potential predictors and then selecting the most useful ones using stepwise backward elimination.

Weight-related parameters

The secondary endpoints related to weight are defined as change from baseline to 72 weeks in:

- Body weight (% and kg)
- Waist circumference
- BMI

These endpoints will be analysed separately using the same type of ANCOVA with MI as for the biomarkers with treatment, baseline diabetes status, baseline fibrosis stage and diabetes-by-fibrosis interaction as factors and corresponding baseline value as a single covariate. Supportive on-treatment analyses will be performed based on MMRM in the same way as for the biomarkers with factors and covariates specified as in the ANCOVA model.

In addition to the continuous endpoints, the following binary endpoints related to weight will be analysed separately:

- Weight loss of ≥ 5% of baseline body weight at 72 weeks (yes/no)
- Weight loss of ≥ 10% of baseline body weight at 72 weeks (yes/no)

The binary endpoints will be compared between treatment arms using an MI approach similar to the continuous endpoints but based on logistic regression. The 1000 data sets with imputed values for percent change in body weight will be reused to derive an equal number of complete data sets for the binary outcomes. For each data set, the binary outcomes will be analysed using a logistic regression model which includes treatment, diabetes status, baseline fibrosis stage and diabetes-by-fibrosis interaction as factors and baseline body weight as a covariate. The estimated log odds ratios and standard errors for the 1000 complete data sets are then pooled using Rubin's rule. From the pooled estimates and standard errors, the 95% confidence intervals for the odds ratios and associated p-values are calculated.

Glucose metabolism related parameters

The secondary endpoints related to glucose metabolism are defined as change from baseline to 72 weeks in:

- HbA_{1c}
- FPG
- Fasting glucagon
- HOMA-IR, derived through the approximation formula[67]:

$$\text{HOMA-IR} = \text{FPG (mmol/L)} \times \text{Fasting insulin (mmol/L)} / 22.5$$

These endpoints will be analysed using the same type of ANCOVA with MI as for the biomarkers. For each endpoint, the ANCOVA will be performed separately for subjects with and without type 2 diabetes at screening. The model will include treatment and baseline fibrosis stage as factors and

corresponding baseline value as covariate. Supportive on-treatment analyses will be performed based on MMRM in the same way as for the biomarkers with factors and covariates specified as in the ANCOVA model. Fasting glucagon and HOMA-IR will be logarithmically transformed before analysis.

Cardiovascular risk factors

The secondary endpoints related to cardiovascular risk factors are defined as change from baseline to 72 weeks in:

- Systolic and diastolic blood pressure
- Lipids (total cholesterol, LDL cholesterol, HDL cholesterol, VLDL cholesterol, triglycerides, free fatty acids)
- hsCRP

These endpoints will be analysed separately using the same type of ANCOVA with MI as for the biomarkers with treatment, baseline diabetes status, baseline fibrosis stage and diabetes-by-fibrosis interaction as factors and corresponding baseline value as a single covariate. Supportive on-treatment analyses will be performed based on MMRM in the same way as for the biomarkers with factors and covariates specified as in the ANCOVA model. The lipids and hsCRP will be logarithmically transformed before analysis.

Patient reported outcomes

The results from SF-36 questionnaire will be analysed as the change from baseline to 72 weeks in overall mental and physical scores, respectively, as well as the change in each of the 8 domains:

- Physical functioning
- Role functioning
- Bodily pain
- General health
- Vitality
- Social functioning
- Role emotional
- Mental health

The change in score will be analysed as a continuous endpoint using the same type of ANCOVA with MI as for the biomarkers with treatment, baseline diabetes status, baseline fibrosis stage and diabetes-by-fibrosis interaction as factors and corresponding baseline score as a single covariate. Supportive on-treatment analyses will be performed based on MMRM in the same way as for the biomarkers with factors and covariates specified as in the ANCOVA model.

17.4.1.2 Safety endpoints

The following secondary endpoints are used to support the safety objectives:

- Number of treatment-emergent adverse events during the trial
- Number of treatment-emergent hypoglycaemic episodes during the trial
- Number of treatment-emergent severe or BG confirmed symptomatic hypoglycaemic episodes during the trial
- Number of treatment-emergent severe hypoglycaemic episodes during the trial
- Number of subjects discontinuing treatment due to gastrointestinal adverse events
- Change from baseline to 72 weeks in:
    - Pulse
    - ECG
    - Physical examination
    - Haematology (haemoglobin, haematocrit, thrombocytes, erythrocytes, leucocytes, differential count)
    - Biochemistry (creatinine, eGFR, creatine phosphokinase, urea, bilirubin (total), alkaline phosphatase, ferritin, sodium, potassium, calcium (total), amylase, lipase)
    - Hormones (calcitonin)
- Occurrence of anti-semaglutide antibodies during and after 72 weeks treatment (yes/no):
    - Anti-semaglutide binding antibodies
    - Anti-semaglutide binding antibodies with *in vitro* neutralising effect
    - Anti-semaglutide binding antibodies cross reacting with native GLP-1
    - Cross-reacting anti-semaglutide binding antibodies with *in vitro* neutralising effect to native GLP-1
- Anti-semaglutide antibody binding level during and after 72 weeks treatment

Adverse events

AEs will be coded using the most recent version of the Medical Dictionary for regulatory Activities (MedDRA) coding. A treatment emergent adverse event (TEAE) is defined as an event that has onset date during the on-treatment period (see section 17.2).

AE data will be displayed in terms of the number of subjects with at least one event, the percentage of subjects with at least one event, the number of events and the event rate per 100 patient years of exposure. The main AE summaries will only contain TEAEs. Non-treatment emergent AEs will be included in listings and overview summaries.

Hypoglycaemic episodes

Hypoglycaemic episodes will be classified and then summarised descriptively in terms of the number of subjects with at least one event, the percentage of subjects with at least one event, the

number of events and the event rate per 100 patient years of exposure. The summaries will be made separately for subjects with and without type 2 diabetes at randomisation.

For subjects with type 2 diabetes at randomisation, the severe or BG confirmed symptomatic hypoglycaemic episodes will be analysed using a negative binomial regression model with the number of treatment emergent episodes as response, the logarithmic function as link function and the logarithm of the time period during which episodes are considered treatment emergent as offset. The model will include treatment and baseline fibrosis stage as factors and baseline HbA_{1c} as a covariate. The results will be described by the rate ratio for the comparison of each semaglutide dose versus placebo with the associated 95% confidence interval and two-sided p-value.

Classification of Hypoglycaemia:

Treatment emergent: hypoglycaemic episodes will be defined as treatment emergent if the onset of the episode occurs during the on-treatment period (see section 17.2).

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 (see Figure 17–1) and the ADA classification of hypoglycaemia (see Figure 17–2). For subjects without type 2 diabetes, the episodes will only be classified as either severe or probable symptomatic according to the ADA classification.

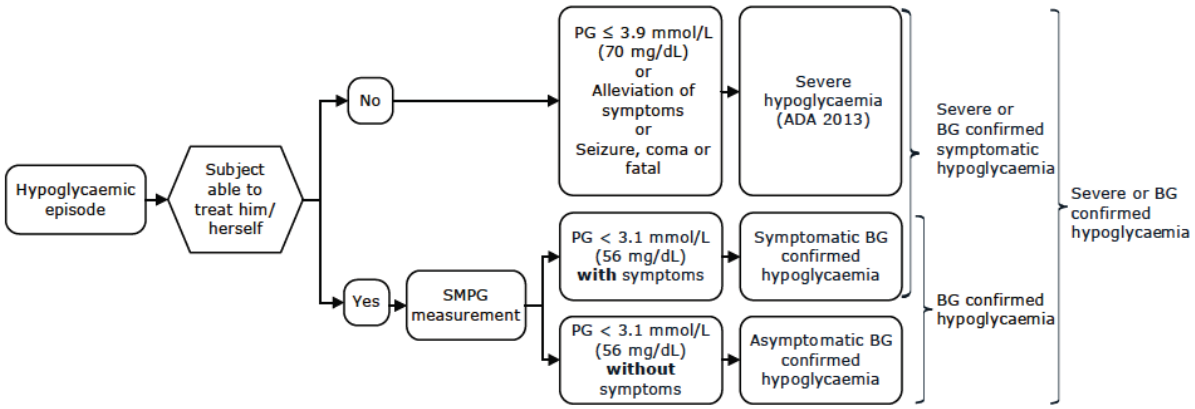
Novo Nordisk classification of hypoglycaemia

In normal physiology, symptoms of hypoglycaemia occur below a plasma glucose level of 3.1 mmol/L (56 mg/dL)[68]. Therefore, Novo Nordisk has included hypoglycaemia with plasma glucose levels below this cut-off point in the definition of blood glucose (BG) confirmed hypoglycaemia.

Novo Nordisk uses the following classification (see Figure 17–1) in addition to the ADA classification:

- Severe hypoglycaemia according to the ADA classification[49].
- Symptomatic BG confirmed hypoglycaemia: An episode that is BG confirmed by plasma glucose value <3.1 mmol/L (56 mg/dL) **with** symptoms consistent with hypoglycaemia.
- Asymptomatic BG confirmed hypoglycaemia: An episode that is BG confirmed by plasma glucose value <3.1 mmol/L (56 mg/dL) **without** symptoms consistent with hypoglycaemia.
- Severe or BG confirmed symptomatic hypoglycaemia: An episode that is severe according to the ADA classification[49] or BG confirmed by a plasma glucose value <3.1 mmol/L (56 mg/dL) **with** symptoms consistent with hypoglycaemia.
- BG confirmed hypoglycaemia: An episode that is BG confirmed by a plasma glucose value <3.1 mmol/L (56 mg/dL) **with** or **without** symptoms consistent with hypoglycaemia.

- Severe or BG confirmed hypoglycaemia: An episode that is severe according to the ADA classification[49] or BG confirmed by a plasma glucose value <3.1 mmol/L (56 mg/dL) **with** or **without** symptoms consistent with hypoglycaemia.



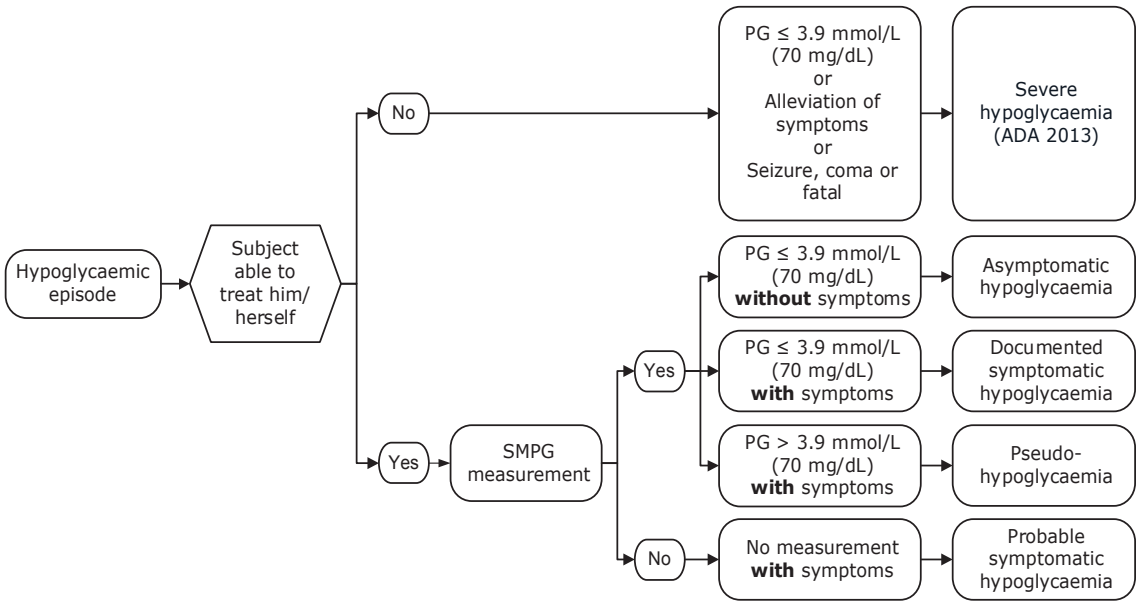
Note: Glucose measurements are performed with capillary blood calibrated to plasma equivalent glucose values

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

Figure 17–1 Novo Nordisk classification of hypoglycaemia

ADA classification[49] of hypoglycaemia

- Severe hypoglycaemia: An episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.
- Asymptomatic hypoglycaemia: An episode not accompanied by typical symptoms of hypoglycaemia, but with a measured plasma glucose concentration ≤ 3.9 mmol/L (70 mg/dL).
- Documented symptomatic hypoglycaemia: An episode during which typical symptoms of hypoglycaemia are accompanied by a measured plasma glucose 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 plasma glucose 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 plasma glucose determination but that was presumably caused by a plasma glucose concentration ≤ 3.9 mmol/L (70 mg/dL).



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

PG: plasma glucose SMPG: Self-measured plasma glucose

Figure 17–2 ADA classification of hypoglycaemia

Pulse

Pulse will be summarised by descriptive statistics and analysed using the same type of MMRM as for the on-treatment analyses of the biomarkers with treatment, baseline diabetes status, baseline fibrosis stage and diabetes-by-fibrosis interaction as factors and baseline pulse as a covariate.

ECG

ECG will be described by summarising the number and percentage of subjects with normal and abnormal readings (separated into clinically significant and not clinically significant). The summaries will be presented by visit and as shift tables from baseline to week 72.

Physical examination

The results of the physical examination will be summarised descriptively in the same way as ECG.

Laboratory assessments

The haematology and biochemistry parameters will be summarised and evaluated by descriptive statistics.

Amylase and lipase will be analysed separately using the same type of MMRM as for the on-treatment analyses of the biomarkers with treatment, baseline diabetes status, baseline fibrosis stage and diabetes-by-fibrosis interaction as factors and the baseline value of the corresponding laboratory parameter as a covariate. A logarithmic transformation will be applied for both amylase and lipase

Calcitonin will be summarised in tables including number and percentage of observations > and ≤ LLOQ, quartiles, minimum and maximum. Persistent and incidental abnormal elevation of calcitonin will further be displayed in terms of the number and percentage of subjects and the event rate per 100 patient years of exposure.

Antibodies

The occurrence of anti-semaglutide antibodies will be described by summarising the number and percentage of subjects with antibodies in the different treatment arms. The antibody binding level will be presented in listings.

In addition, a comparison of the change in HbA_{1c} and body weight between antibody-positive and antibody-negative subjects will be performed using descriptive statistics and graphs. The impact of anti-semaglutide antibodies on safety will be similarly assessed by descriptive statistics.

17.4.1.3 Pharmacokinetic endpoints

The plasma concentrations of semaglutide will be summarised by descriptive statistics. In addition, the data will be used for population pharmacokinetic (PK) modelling, see section 17.6.

17.5 Interim analysis

No interim analyses or other analyses of unblinded data will be performed before the database is locked.

17.6 Pharmacokinetic and/or pharmacodynamic modelling

Exploratory population PK and PK/PD modelling will be used to evaluate the semaglutide dose-exposure, the effects of pre-specified covariates on the exposure and the semaglutide exposure-response on selected efficacy and safety parameters. It will follow a modelling analysis plan that is to be finalised before database lock, describing criteria for inclusion of data, pre-specification of covariates and criteria for presentation of results.

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

17.7 Health economics and/or patient reported outcomes

The PRO questionnaire SF-36 will be used to evaluate the effects on quality of life, see section 17.4.1.1 for the details of the statistical analysis. The results will be included in the CTR.

18 Ethics

18.1 Benefit-risk assessment of the trial

Risks and precautions for semaglutide

The sections below describe potential risks associated with semaglutide treatment, based on findings with other GLP-1 RAs and observations in nonclinical and clinical trials with semaglutide administered s.c. once weekly. For each of these risks, mitigating actions have been implemented to minimise the risks for subjects enrolled in this trial.

The nonclinical safety programme of semaglutide has revealed no identified safety issues for humans based on conventional studies of safety pharmacology, repeat -dose toxicity or genotoxicity.

Identified risks

Diabetic retinopathy

A transient worsening of diabetic retinopathy is a recognised complication in selected patients with diabetes after initiation of intensive antidiabetic treatment[69-71]. Risk factors for these events include long-standing poor glycaemic control and presence of proliferative retinopathy, and initial large improvements in blood glucose maybe an additional aggravating factor. Several studies have, however, documented long-term beneficial effects of intensive glycaemic treatment in reducing retinopathy progression[72, 73] even in intensively treated patients who experienced early worsening[70]. In a cardiovascular outcomes trial with s.c. semaglutide, results indicate an increased risk of ev ents related to diabetic retinopathy in subjects treated with semaglutide compared to placebo. As a precaution in this trial, all subjects with type 2 diabetes are required to have a fundus photography or dilated fundoscopy performed before enrolment into the trial; moreover, subjects with proliferative retinopathy or maculopathy requiring acute treatment will be excluded. As part of good diabetes management the investigator is encouraged to ensure adequate monitoring and treatment of diabetic retinopathy in subjects enrolled into the trial[74].

Gastrointestinal adverse events

Consistent with findings from other GLP-1 RAs, the most frequently reported AEs in the clinical trials with semaglutide thus far have been gastrointestinal (GI) di sorders (nausea, vomiting, diarrhoea, dyspepsia and constipation). However, based on a completed clinical trial (NN9535-3819) where slower dose escalation substantially improved the GI tolerability profile, a 4-week dose escalation regimen has been developed and is used in the ongoing clinical phase 3 programme for semaglutide s.c. administered once weekly as well as in this trial.

Potential risks

Thyroid C-cell tumour

The human relevance of the proliferative C-cell changes found in rodents is unknown, but data suggest that rodents are more sensitive to the mode of action for induction of C-cell tumours with GLP-1 RAs. However, as a precaution subjects with a family or personal history of Multiple Endocrine Neoplasia type 2 (MEN 2), familial medullary thyroid carcinoma (MTC), personal history of non-familial medullary thyroid carcinoma, and subjects with a screening calcitonin ≥50 ng/L will be excluded from trial. During the trial calcitonin will be measured on a regular basis and guidance for investigators of further evaluation and action on elevated plasma calcitonin is provided in appendix A.

Allergic reactions and injection site reactions

As is the case with all protein based pharmaceuticals, subjects treated with semaglutide risk developing immunogenic and allergic reactions. These may include localised injection site reactions or generalised reactions including urticaria, rash or pruritus. Severe allergic reactions such as anaphylactic reactions could potentially also pose a risk for subjects treated with semaglutide.

Hypoglycaemia

Based on current knowledge about the GLP-1 RA drug class, there is a risk of hypoglycaemic episodes. Hypoglycaemic episodes have mainly been observed when a GLP-1 RA is combined with sulphonylurea (SU) or insulin in patients with T2D. The risk for development of hypoglycaemia specifically with semaglutide in combination with SU and insulin is unknown due to limited data. To reduce the risk of hypoglycemia the insulin dose will be reduced by 30% in subjects with HbA_{1c} ≤ 8.0% at screening.

Altered renal function

Based on current knowledge about the GLP-1 RA drug class, there is a risk of volume depletion, resulting from nausea, vomiting and dehydration, such as acute renal failure have been observed in subjects treated with other GLP-1 RAs. As a precaution serum creatinine is measured regularly.

Acute pancreatitis

Based on current knowledge about the GLP-1 RA drug class, there is a risk of acute pancreatitis, including severe necrotising and haemorrhagic forms. As a precaution patients with a history of acute or chronic pancreatitis will be excluded from the trial. Subjects will be monitored for elevated activity levels of amylase and lipase and be informed of the characteristic symptoms of acute pancreatitis.

Pancreatic cancer

There is currently no support from non-clinical or clinical trials or post-marketing data that GLP-1-based therapies increase the risk of pancreatic cancer. However, as the long-term effects of stimulation of β-cells and suppression of α-cells are largely unknown, pancreatic cancer is considered a potential risk by the European Medicine Agency (EMA).

Other safety considerations

Teratogenicity (nonclinical embryo-foetal toxicity)

Semaglutide has been concluded teratogenic in rats. This effect is regarded to be caused by impairment of nutrient supply to the embryo across the inverted yolk sac with placental function. As the yolk sac does not play such a role for nutrition of the embryo in humans, this effect is unlikely to be relevant for humans. However, as a precaution subjects fulfilling exclusion criterion 29 will be excluded from trial participation. Furthermore, as specified in the flowchart, female subjects included in the trial will have pregnancy testing performed frequently during the entire duration of the trial.

General risks and precautions

All subjects will be included after a thorough evaluation in regards to in- and exclusion criteria defined in order to ensure that subjects are eligible for trial treatment.

All subjects will have one or two liver biopsies performed as part of participation in the trial. Pain is the most common complication of percutaneous liver biopsy, occurring in up to 84% of patients, including those with relatively mild discomfort. The most important complication of liver biopsy is bleeding. Severe bleeding may require hospitalization blood transfusion, or even radiological intervention or surgery. Such bleeding has been estimated to occur in between 1 in 2500 to 1 in 10,000 biopsies after an intercostal percutaneous liver biopsy. Mortality after liver biopsy is usually related to hemorrhage. It is very uncommon after percutaneous biopsy, but precise figures vary widely. The most commonly quoted mortality rate is less than or equal to 1 in 10,000 liver biopsies[75]. The risk of liver biosy is minimised by excluding patients with liver cirrhosis and coagulopathy, and by requiring that liver biopsy is performed according to standard practice.

Benefits

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

In the LEAN trial significantly more patients who received liraglutide 1.8 mg/day had resolution of NASH compared with patients in the placebo group. Further, significantly fewer patients in the

liraglutide had progression of fibrosis compared to the placebo group[34]. Currently the standard of care of NASH is weight loss, and reduction of body weight was speculated to be one of the modes of action of liraglutide by the authors of the LEAN study[34]. In a phase 2 trial (NN9535-1821), semaglutide resulted in a clinical meaningful and dose-dependent weight loss. Doses ≥ 0.8 mg/week semaglutide provided a greater weight loss than liraglutide 1.8 mg/day. In clinical studies with liraglutide 3.0 mg/day, approximately 2/3 of the subjects lost more than 5% of their initial body weight and approximately 1/3 lost more than 10% of their initial body weight. Additionally, semaglutide also increase insulin, lower glucagon levels and improves insulin sensitivity and blood lipids, all of which are beneficial in patients with NASH. Finally, semaglutide may have anti-inflammatory effects.

Although subjects will have to spend time on site visits and procedures required by trial participation, it is expected that all subjects (including those subjects randomised to placebo) will benefit from participation through close contact with the trial site, with close follow-up of their NASH and general metabolic state, and a careful medical examination. Furthermore, all subjects will receive nutritional and physical activity counselling throughout the trial. All of which will probably result in a better management of their NASH.

Conclusion

The trial products may be associated with AEs, but relevant precautions have been implemented in the design and planned conduct of the trial in order to minimise the risks and inconveniences of participation in the trial. These precautions include thorough information regarding the correct administration of the trial products and gradual dose adjustment. Furthermore, subjects are informed about possible AEs and inconveniences and will be instructed to contact the investigator in case of any concerns regarding the trial participation.

When treatment with trial products ends, the subject and investigator will decide on the best available treatment.

It is concluded that the potential benefits from participating in the trial outweigh the potential risks including the risk related to the liver biopsy. The safety profile of semaglutide generated from the clinical and nonclinical development programme in T2D has not revealed any safety issues that would prohibit administration of once weekly doses of 0.5 mg or 1.0 mg semaglutide. Based on the nature and frequency of the AEs in the T2D trials, it appears to be safe to investigate daily doses of up to 0.4 mg as in the current trial. Additional safety surveillance will be instituted in all treatment arms during the dose escalation period until 4 weeks after last target dose is reached (steady state). It is concluded that the risk to the subjects in this trial is low and acceptable in view of the potential benefits a long-acting GLP-1 analogue would provide subjects with NASH.

18.2 Informed consent

In seeking and documenting informed consent, the investigator must comply with applicable regulatory requirement(s) and adhere to ICH GCP[1] and the requirements in the Declaration of Helsinki[2].

Before any trial-related activity, the investigator must give the subject verbal and written information about the trial and the procedures involved in a form that the subject can read and understand. This includes the use of an impartial witness where required.

The subjects must be fully informed of their rights and responsibilities while participating in the trial as well as possible disadvantages of being treated with the trial products.

The investigator must ensure the subject ample time to come to a decision whether or not to participate in the trial.

A voluntary, signed and personally dated informed consent must be obtained from the subject before any trial-related activity.

Separate informed consent forms for long-term storage of human biosamples and genotyping are available for this trial, and informed consent must be obtained before activities related to any of these are undertaken.

Additionally a separate informed consent form for optional pre-screening is available. This must be signed before any optional pre-screening activities are performed (see section 8.1.2).

The responsibility for seeking informed consent must remain with the investigator, but the investigator may delegate the task to a medically qualified person, in accordance with local requirements. The written informed consent must be signed and personally dated by the person who seeks the informed consent before any trial-related activity.

If information becomes available that may be relevant to the subject's willingness to continue participating in the trial, the investigator must inform the subject in a timely manner, and a revised written subject information must be provided and a new informed consent must be obtained.

18.3 Data handling

If the subject withdraws from the trial or is lost to follow up, then the subject's data will be handled as follows:

- Data already collected and any data collected at the end-of-trial visit including follow up visits will be retained by Novo Nordisk, entered into the database and used for the clinical trial report.

- Safety events will be reported to Novo Nordisk and regulatory authorities according to local/national requirements.

If data is used, it will always be in accordance with local regulations and IRBs/IECs.

18.4 Information to subjects during trial

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

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.

18.5 Premature termination of the trial and/or trial site

Novo Nordisk, the IRBs/IECs or a regulatory authority may decide to stop the trial, part of the trial or a trial site at any time, but agreement on procedures to be followed must be obtained.

If the trial is suspended or prematurely 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.

If, after the termination of the trial, the benefit-risk analysis changes, the new evaluation must be provided to the IRBs/IECs in case it has an impact on the planned follow-up of subjects who have participated in the trial. If it has an impact, the actions needed to inform and protect the subjects should be described.

19 Protocol compliance

19.1 Protocol deviations

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 eCRF or via listings from the trial database. Novo Nordisk will monitor protocol deviations on an on-going basis throughout the trial followed by appropriate actions (e.g. re-training of site staff).

Documentation on protocol deviations must be kept in the investigator trial master file and sponsor trial master file.

19.2 Prevention of missing data

The importance of subject retention will be addressed by Novo Nordisk in the training and communication with the trial sites.

The subjects will be carefully informed about the trial procedures before signing informed consent, so that they know the implications of participating in the trial.

Close surveillance of subject retention will be performed throughout the trial by Novo Nordisk with focus on reasons for premature discontinuation of trial product or withdrawal of consent to secure early mitigations in collaboration with the trial sites. The investigator will make every effort to ensure that all assessments are performed and data is collected (see section 8.1.6). If missing data does occur the reason will be collected via the protocol deviation process described in section 19.1.

20 Audits and inspections

Any aspect of the clinical trial may be subject to audits conducted by Novo Nordisk or inspections from domestic or foreign regulatory authorities or from IRBs/IECs. Audits and inspections may take place during or after the trial. The investigator and the site staff as well as Novo Nordisk staff have an obligation to cooperate and assist in audits and inspections. This includes giving auditors and inspectors direct access to all source documents and other documents at the trial site relevant to the clinical trial. This includes permission to examine, analyse, verify and reproduce any record(s) and report(s) that are relevant to the evaluation of the trial.

21 Critical documents

Before a trial site is allowed to start screening subjects, written notification from Novo Nordisk must be received and the following documents must be available to Novo Nordisk:

- Regulatory approval and/or acknowledgement of notification as required
- Approval/favourable opinion from IRBs/IECs clearly identifying the documents reviewed as follows: protocol, any protocol amendments, subject information/informed consent form, any other written information to be provided to the subject and subject recruitment materials
- List of IRB/IEC members and/or constitution (or a general assurance number/statement of compliance)
- Curricula vitae of investigator and sub-investigator(s) (current, dated and signed - must include documented GCP training or a certificate)
- Signed receipt of Investigator's Brochure
- Signed and dated Agreement on Protocol
- Signed and dated Agreement on Protocol Amendment, if applicable
- Contract, signed by the investigator and/or appropriate parties on behalf of the investigator's site and Novo Nordisk
- Source document agreement
- Central laboratory certification and normal ranges
- Insurance statement, if applicable
- Financial disclosure form from investigator and sub-investigator(s)

Only applicable for US trial sites:

- For US trial sites: verification under disclosures per Code of Federal Regulations (CFR) of Financial Conflict of Interest
- For US trial sites: FDA form 1572 must be completed and signed by the investigator at each site

FDA form 1572:

For US sites:

- Intended for US sites
- Conducted under the IND
- All US investigators, as described above, will sign FDA Form 1572

For sites outside the US:

- Intended for participating sites outside of the US
- Not conducted under the IND
- All investigators outside of the US will not sign FDA form 1572

Novo Nordisk will analyse and report data from all sites together if more than one site is involved in the trial.

By signing the protocol agreement, each investigator agrees to comply fully with ICH GCP[1] applicable regulatory requirements and the Declaration of Helsinki[2].

By signing the protocol agreement, each investigator also agrees to allow Novo Nordisk to make investigator's name and information about site name and address publically available if this is required by national or international regulations.

22 Responsibilities

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

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

The investigator will follow instructions from Novo Nordisk when processing data.

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 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).

23 Reports and publications

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 physicians 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 investigator will be appointed by Novo Nordisk to review and sign the clinical trial report (signatory investigator) on behalf of all participating investigators. The signatory investigator will be appointed based upon the criteria defined by the International Committee of Medical Journal Editors for research publications[76].

23.1 Communication of results

Novo Nordisk commits to communicating, and otherwise making available for public disclosure, results of trials regardless of outcome. Public disclosure includes publication of a paper in a 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, as reflected in the Novo Nordisk Code of Conduct for Clinical Trial Disclosure[43].

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

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.

Novo Nordisk maintains the right to be informed of plans by any investigator to publish and to review any scientific paper, presentation, communication or other information concerning the investigation described in this protocol. Any such communication must be submitted in writing to Novo Nordisk before submission for comments. Comments will be given within four weeks from receipt of the planned communication.

23.1.1 Authorship

Authorship of publications should be in accordance with the Uniform Requirements of the International Committee of Medical Journal Editors[76] (sometimes referred to as the Vancouver Criteria).

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

For a multi-centre 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. It is a Novo Nordisk policy that such individual reports do not precede the primary manuscript and should always reference the primary manuscript of the trial.

Novo Nordisk reserves the right to prior review of such publications. Further to allow for the primary manuscript to be published as the first, Novo Nordisk asks for deferment of publication of individual site results until the primary manuscript is accepted for publication. As Novo Nordisk wants to live up to the industry publication policy, submission of a primary publication will take place no later than 18 months after trial completion.

23.2 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.

24 Retention of clinical trial documentation and human biosamples

24.1 Retention of clinical trial documentation

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

The investigator must agree to archive the documentation (this includes both electronic and paper-based records) pertaining to the trial in an archive after completion or discontinuation of the trial if not otherwise notified. The investigator should not destroy any documents without prior permission from Novo Nordisk. If the investigator cannot archive the documents at the trial site, Novo Nordisk can refer the investigator to an independent archive provider that has a system in place to allow only the investigator to access the files.

The investigator must be able to access his/her trial documents without involving Novo Nordisk in any way. Site-specific CRFs and other subject data (in an electronic readable format or as paper copies or prints) will be provided to the investigator before access is revoked to the systems and/or electronic devices supplied by Novo Nordisk. These data must be retained by the trial site. If the provided 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.

Novo Nordisk will maintain Novo Nordisk documentation pertaining to the trial for at least 20 years after discontinuation of the marketing authorisation, termination of the trial or cancellation of the research project whichever is longest.

The files from the trial site/institution must be retained for 15 years after end of trial as defined in section 7), or longer if required by local regulations or Novo Nordisk. In any case trial files cannot be destroyed until the trial site/institution is notified by Novo Nordisk. The deletion process must ensure confidentiality of data and must be done in accordance with local regulatory requirements.

24.2 Retention of human biosamples

24.2.1 Antibody samples

Antibody samples may be retained for later analysis for further characterisation of antibody responses towards drug if required by health authorities or for safety reasons. The samples will not be used for other purposes.

The samples will be stored at a bio-repository after end of trial and until marketing authorisation approval or until the research project terminates, but no longer than 15 years from end of trial after which they will be destroyed.

The subject's identity will remain confidential and the antibody 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.

Only Novo Nordisk staff and bio-repository personnel will have access to the stored antibody samples.

Subjects can contact the investigator if they wish to be informed about results derived from stored antibody samples obtained from their own body.

24.2.2 Samples for future analysis

As new biomarkers related to the disease and/or safety, efficacy, or mechanism of action of semaglutide may evolve during the conduct of the trial or after end of trial, the analyses of the stored biosamples may also include biomarkers that are unknown at present or have not been included in the scientific hypotheses at initiation of the trial. Likewise if genetic high risk population or populations are described for NASH, Novo Nordisk may want to investigate if such genetic predispositions are associated with different response to semaglutide.

Subjects must sign and date a separate informed consent form before biosamples to be stored for future analysis are drawn/collected (refer to section 8.1.1).

After trial completion the biosamples will be stored at a central storage facility contracted by Novo Nordisk A/S. Only Novo Nordisk and storage facility employees will be able to access the stored biosamples. The biosamples may be transferred to other countries for analysis and will be destroyed at the latest 15 years after end of trial.

The subject may request the stored biosamples to be destroyed by withdrawing consent. The results obtained from any already performed analyses of the samples will still be used.

In the event that the collected biosamples (blood and urine) 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.

25 Institutional Review Boards/Independent Ethics Committees and regulatory authorities

IRB/IEC:

Written approval or favourable opinion must be obtained from IRB/IEC prior to commencement of the trial.

During the trial, the investigator or Novo Nordisk, as applicable, must promptly report the following to the IRB/IEC, in accordance with local requirements: updates to Investigator's Brochure, unexpected SAEs where a causal relationship cannot be ruled out, protocol amendments according to local requirements, deviations to the protocol implemented to eliminate immediate hazards to the subjects, new information that may affect adversely the safety of the subjects or the conduct of the trial (including new benefit-risk analysis in case it will have an impact on the planned follow-up of the subjects), annually written summaries of the trial status, and other documents as required by the local IRB/IEC.

The investigator must ensure submission of the clinical trial report synopsis to the IRB/IEC.

Protocol amendments must not be implemented before approval or favourable opinion according to local regulations, unless necessary to eliminate immediate hazards to the subjects.

The investigator must maintain an accurate and complete record of all submissions made to the IRB/IEC. The records must be filed in the investigator trial master file and copies must be sent to Novo Nordisk.

Regulatory Authorities:

Regulatory authorities will receive the clinical trial application, protocol amendments, reports on SAEs, and the clinical trial report according to national requirements.

26 Indemnity statement

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

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

Novo Nordisk accepts liability in accordance with:

For Netherlands only: Wetgeving betreffende geneesmiddelen; geneesmiddelenwet 1 juli 2007 (Medicines Law, 1 July 2007). De Wet Medisch-wetenschappelijk Onderzoek met mensen (WMO), 1 maart 2006 (Medical Research Involving Human Subjects Act, 1 March 2006). Besluit verplichte verzekering bij medisch-wetenschappelijk onderzoek met mensen 2015, 24 november 2014 (Decree compulsory insurance in medical research involving human subjects 2015, 24 November 2014)." The national protocol requirement is also here under compliance: http://globeshare.novonordisk.com/rd/gd/gdareas/qrd/gcc/Pages/Default.aspx

For France only: 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. "The sponsor is responsible for identification of the harmful consequences of the biomedical research for the person lending himself thereto and for indemnification of his beneficiaries, except in case of proof, incumbent on it, that the prejudice is not attributable to his fault of or the fault of any intervening party, without the sponsor's being entitled to call on acts by a third party or the voluntary withdrawal of the person who had initially consented to cooperating in the research.

For Austria only: Arzneimittelgesetz (BGBI. Nr. 185/1983) last amended with BGBI Nr. 105/2015.

For Russia only: Federal law of 12 April 2010 No. 61-FZ 'On Medicinal Drugs' Circulation and Order No. 200n dated April 01, 2016 of the Ministry of Health of the Russian Federation On Approval of Rules for Good Clinical Practice.

For Belgium only: Law concerning experiments on the human person of 07 May 2004 - Article 29:

§1. Even if without fault, the sponsor is liable for the damage which the subject and/or his rightful claimants sustain and which shows either a direct or an indirect connection with the trial.

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Appendix A

NN9931-4296

Monitoring of calcitonin

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1 Background

Treatment with GLP-1 receptor agonists has shown to be associated with thyroid C-cell changes in rodents but not in non-human primates. The human relevance of this finding is unknown. However, based on the findings in rodents, monitoring of serum calcitonin (a sensitive biomarker for C-cell activation) is currently being performed in clinical trials with semaglutide.

While there is general agreement on the clinical interpretation of substantially elevated calcitonin levels (greater than 100 ng/L) is likely indicative of C-cell neoplasia; the interpretation of values between upper normal range (5.0 and 8.4 ng/L for women and men, respectively) and 100 ng/L is less clear with regards to indication of the neoplasia.

There are several known confounding factors affecting calcitonin levels, e.g.:

- renal dysfunction
- smoking
- autoimmune thyroiditis
- several drug classes (e.g. proton pump inhibitors, beta-blockers, H_2-blockers and glucocorticoids)

Physiology of C-cell activation in various clinical conditions and in different patient populations (i.e. with various co-morbidities) is poorly understood. There may be various clinical conditions not identified so far which mildly or moderately affect calcitonin secretion by C-cells.

2 Calcitonin monitoring

A blood sample will be drawn at pre-specified trial visits for measurement of calcitonin.

In case a subject has a calcitonin value ≥ 10 ng/L, the algorithm outlined below should be followed. The algorithm applies for all calcitonin values including screening values.

Please consider reporting clinically significant abnormal values as an adverse event (see Section 12 in the protocol).

2.1 Calcitonin ≥ 100 ng/L

Action: The subject (even if a screen failure) must immediately be referred to a thyroid specialist for further evaluation and the trial product must be discontinued (see protocol section 6.5 premature discontinuation of trial product). The subject can remain in the trial; however, all suspected medications must be discontinued until diagnosis has been established.

Background: These values were found in 9 (0.15%) of a population of 5817 patients with thyroid nodular disease.[1] All of these patients were diagnosed with MTC resulting in a positive predictive value of 100 %.

Diagnostic evaluation should include:

- thyroid ultrasound
- fine needle aspiration of any nodules >1 cm
- potentially surgery with neck dissection

In case a subject is diagnosed with MTC, it is common clinical practice to explore the family history of MTC or MEN2 and perform a genetic test for RET proto-oncogene mutation.

2.2 Calcitonin ≥ 50 and < 100 ng/L

Action: The subject (even if a screen failure) must be referred to a thyroid specialist for further evaluation. The subject can remain in the trial and continue on trial product.

Background: These values were found in 8 (0.14%) of the population of 5817 patients with thyroid nodular disease[1] Two of these subjects were diagnosed with MTC and two were diagnosed with C-cell hyperplasia, resulting in a positive predictive value of a C-cell anomaly of 50%.

Diagnostic evaluation should include:

- thyroid ultrasound examination
- if available and there are no contraindication, a pentagastrin stimulation test. Subjects with positive pentagastrin stimulation tests should be considered to undergo surgery
- if pentagastrin is not available, thyroid ultrasound and fine needle aspiration biopsy may add important clinical information about the need for surgery.

2.3 Calcitonin ≥ 10 and <50 ng/L

Action: The subject can continue in the trial on trial product. Continue sampling of calcitonin according to the protocol.

If the subject is a screen failure, or if the value is from the last sample taken in the trial, the subject should be referred to a thyroid specialist for further evaluation.

Background: Calcitonin values from 20-50 ng/L were found in up to 1% of subjects of the population of 5817 patients with thyroid nodular disease.[1] The predictive value of a C-cell anomaly for this calcitonin level was 8.3%. However, the likelihood of having a medullary carcinoma >1 cm with calcitonin in this range is extremely low.

For calcitonin values 10-20 ng/L Costante et al[1] identified 216 (3.7%) patients. One patient out of the 216 had a subsequent basal (unstimulated) calcitonin of 33 ng/L, and had C-cell hyperplasia at surgery. Two other studies used a cut-off of CT > 10 ng/L to screen for C-cell disease, but they do not provide sufficient information on patients with basal CT >10 and <20 ng/L to allow conclusions[2, 3]

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Appendix B

NN9931-4296

Adverse events with additional data collection and adverse events requiring event adjudication

[redacted]

[redacted]

Adverse events with additional data collection/ Events requiring adjudication

Event	Definition	Additional data collection	Event adjudication
Fatal events	All-cause mortality: – Cardiovascular death, – Non-cardiovascular death, – Undetermined cause of death[1]	No specific event form for fatal events. A fatal event must be reported as a SAE as described in the protocol.	Yes
Acute coronary syndrome: • Myocardial Infarction • Unstable angina pectoris	All types of myocardial infarction (MI) must be reported: • Spontaneous MI (including re-infarction and MI associated with stent thrombosis) • Percutaneous coronary intervention (PCI) related MI • Coronary artery bypass graft	If an event of acute coronary syndrome (ranging from unstable angina pectoris to myocardial infarction) is observed during the trial the following additional information must be reported if available on the acute coronary syndrome form: • Duration of symptoms • Changes in ECG	Yes

Event	Definition	Additional data collection	Event adjudication
	surgery (CABG) related MI • Silent MI All events with symptoms of myocardial ischemia must be reported.	• Collection of cardiac biomarkers • Cardiac imaging • Cardiac stress testing • Angiography • Use of thrombolytic drugs	
Cerebrovascular event (stroke or transient ischemic attack)	Transient ischemic attack (TIA) is defined as a transient (<24 hours) episode of focal neurological dysfunction caused by brain, spinal cord, or retinal ischemia, without acute infarction.[1] Stroke (Ischemic, haemorrhagic, undetermined) is defined as an acute episode of neurological dysfunction caused by focal or global brain, spinal cord, or retinal vascular injury as a result of haemorrhage or infarction.[1]	If a cerebrovascular event (e.g. transient ischaemic attack, stroke, haemorrhage) is observed during the trial the following additional information must be reported if available on the cerebrovascular event form: • Type of event (e.g. transient ischaemic attack (TIA), Stroke) • Contributing condition • Neurologic signs and symptoms • History of neurologic disease • Imaging supporting the event	Yes

Event	Definition	Additional data collection	Event adjudication
		• Treatment given for the event	
Heart failure requiring hospitalisation or urgent unscheduled visit	Clinical manifestations of new episode or worsening of existing heart failure requiring hospitalisation.	If an event of heart failure requiring hospitalisation (admission to an in-patient unit or a visit to an emergency department that results in at least a 24 hour stay) is observed during the trial the following information must be reported if available on the heart failure form: • Signs and symptoms of heart failure • New York Heart Association (NYHA) Class • Supportive imaging • Supportive laboratory measurements • Initiation or intensification of treatment for this condition • History of heart failure	Yes
Acute pancreatitis	Two of following diagnostic criteria fulfilling the diagnosis of acute pancreatitis: 1. severe acute abdominal pain	If an event of pancreatitis, acute or chronic is observed during the trial, the following information must be reported if available on the pancreatitis form: • Signs, symptoms and severity of pancreatitis	Yes

Event	Definition	Additional data collection	Event adjudication
	2. amylase and/or lipase activity levels >3x upper normal range (UNR) 3. characteristic imaging finding (ultrasound, computerised axial tomography (CT), magnetic resonance imaging (MRI)) Chronic pancreatitis will be defined by characteristic imaging finding (ultrasound, CT, MRI) with abnormal pancreatic function tests or characteristic histological findings	• Specific laboratory test supporting a diagnosis of pancreatitis • Imaging performed and consistency with pancreatic disease • Treatment given for the event • Relevant risk factors associated with the event	
Acute gallbladder disease	All types of acute gallbladder or acute biliary disorders	If an event of acute gallstone disease or clinical suspicion of this is observed during the trial, this must be recorded as an AE and on a specific acute gallstone disease event form in the eCRF. The following information should be reported if available: • Signs and symptoms of acute gallstone disease • Specific laboratory test supporting a diagnosis of gallstone: o White blood cell count (WBC) o C-reactive protein (CRP) o Direct, indirect and total bilirubin	No

Event	Definition	Additional data collection	Event adjudication
		○ ALT and AST ○ Alkaline phosphatase (ALP) ○ Amylase ○ Lipase • Imaging performed and consistency with gallstone disease • Treatment given for the condition • Relevant risk factors for acute gallstone disease including ○ History of gallstones ○ Family history of gallstones ○ Relevant surgery	
Neoplasm	All types of neoplasms must be reported including: • Malign neoplasm • Pre-malignant neoplasm/carcinoma in-situ • Benign neoplasm • Neoplasm of uncertain or unknown behaviour	All events of neoplasms (including thyroid neoplasms) must be recorded as an AE and on a specific neoplasm event form in the eCRF. The following information should be obtained if available as part of standard of care: • Type of neoplasm • Symptoms leading to identification of event • Diagnostic imaging • Pathological examination results • Treatment for the event • Participation in screening programs • Risk factors associated to the event	No

Event	Definition	Additional data collection	Event adjudication
Hepatic event	• ALT or AST > 5x UNL • ALT or AST > 3x baseline value • ALT or AST > 3x UNL and total bilirubin > 2x UNL (Biochemical Hy's Law) • Total bilirubin > 1.5 mg/dL • INR > 1.3 • Model For End-Stage Liver Disease (MELD) score ≥15 • Liver transplant • Ascites requiring medical intervention • Gastroesophageal variceal bleeding • Hepatic encephalopathy • Spontaneous bacterial	If one of the hepatic events is observed during the trial the following additional information must be reported if available: • Signs and symptoms associated to the event • Risk factors • Relevant laboratory test results • Liver biopsy results • Diagnostic procedures performed including imaging • Treatment given for the event • Possible cause(s) of the event	No

Event	Definition	Additional data collection	Event adjudication
	peritonitis • Hepatic events leading to trial product discontinuation		

1. Standardized Definitions for Cardiovascular and Stroke End Point Events in Clinical Trials (DRAFT). Karen A. Hicks, H. M. James Hung, Kenneth W. Mahaffey, Roxana Mehran, Steven E. Nissen; Norman L. Strockbridge, Shari L. Targum, Robert Temple; on behalf of the Standardized Data Collection for Cardiovascular Trials Initiative. August 20, 2014. *Or any updates here*

Global and country key Novo Nordisk staff

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

Content: Global key staff and Country key staff

Protocol Amendment

no 1
to Protocol, final version 1.0
dated 20-Jun-2016

Trial ID:NN9931-4296

Investigation of efficacy and safety of three dose levels of subcutaneous semaglutide once daily versus placebo in subjects with non-alcoholic steatohepatitis

Trial phase: Phase 2

Applicable to all countries

Amendment originator:

[redacted] Senior International Trial Manager

TrialOps 2, GLP-1 Diabetes, NADs & Complications

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1 Introduction including rationale for the protocol amendment

Please see below the rationales for development of this global protocol amendment:

- Further clarification of the safety process for handling of increased levels of liver blood parameters.
- For exclusion criterion 20, specification that the criterion is only applicable for patients with type 2 diabetes has been added. Due to the assessment requirement in the criterion, fundoscopy/fundus photography has been added to the flowchart and a separate section for fundoscopy/fundus photography has been added in section 8 (8.2.7).
- Exclusion criterion for subjects with severe renal impairment (eGFR < 30 ml/min/1.73 m^2) has been added and also that eGFR will be monitored continuously throughout the trial.

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

2 Changes

2.1 List of abbreviations

eGFR	*estimated glomerular filtration rate*
DILI	*Drug induced liver injury*

2.2 Section 2 Flowchart

Fundoscopy/Fundus photography

Footnote 15: Only applicable for patients with type 2 diabetes: Dilated fundoscopy/fundus photography performed within 90 days prior to visit 2 is acceptable if results are available for evaluation at visit 2 and there has been no deterioration in visual function since last assessment. Dilated fundoscopy/fundus photography can be performed between visit 1 and visit 2.

2.3 Section 4.2.2.2 Supportive secondary safety endpoints

Change from baseline to 72 weeks in:

- Biochemistry (creatinine, *estimated Glomerular Filtration Rate (eGFR),* creatinine phosphokinase, urea, bilirubin (total), alkaline phosphatase, ferritin, sodium, potassium, calcium (total), amylase, lipase)

2.4 Section 6.3 Exclusion criteria

20. *For patients with type 2 diabetes only:* Proliferative retinopathy or maculopathy requiring acute treatment verified by fundus photography or dilated fundoscopy performed within the past 90 days prior to randomisation.

32. Renal impairment measured as estimated Glomerular Filtration Rate (eGFR) value of eGFR <30 ml/min/1.73 m^2 as defined by Kidney Disease: Improving Global Outcomes (KDIGO)(ref. 42).

2.5 Section 6.4 Criteria for premature discontinuation of trial product

11. Persistent abnormal liver blood parameters indicating drug induced liver injury (DILI) (see details in section 8.7.2)

2.6 *New section: Section 8.2.7 Fundoscopy/Fundus photography*

For subjects with type 2 diabetes dilated fundoscopy/fundus photography will be performed as specified in section 2. Results of the dilated fundoscopy/fundus photography will be evaluated by the investigator and the investigator evaluation must be documented either on the dilated fundoscopy/fundus photography result report or in the subject's medical record.

The investigator or medically qualified delegate must sign, date and interpret the dilated fundoscopy/fundus photography by using the following categories:

- *Normal*
- *Abnormal*
    - *Was the result clinically significant? (Yes/No)*

If a dilated fundoscopy/fundus photography has been performed within 90 days prior to randomisation, the procedure does not need to be repeated, unless there has been worsening of visual function since the last examination. The results must be available prior to randomisation.

If the dilated fundoscopy/fundus photography is performed before the subject has signed the informed consent form, it must be documented in the medical records that the reason for performing the procedure was not related to this trial.

2.7 Section 8.5.3.1 Biochemistry

- *eGFR (per CKD-EPI formula)(ref. 51)*

2.8 Section 8.7.2 Assessments in case of increased levels of liver blood parameters

~~In case of any of the below:~~

- ~~ALT or AST > 5x UNL~~
- ~~ALT or AST > 3x baseline value~~
- ~~ALT or AST > 3x UNL and total bilirubin > 2x UNL, where no alternative aetiology exists (Hy's Law)~~
- ~~Total bilirubin > 1.5 mg/dL~~
- ~~INR > 1.3~~

~~report the event according to section **Error! Reference source not found.** and Appendix B.~~

~~For all such events prompt repeat testing (at central laboratory) including ALT, AST, alkaline phosphatase, total bilirubin and INR should be done and discontinuation of trial product considered. Thereafter, repeat testing (at central laboratory) of ALT, AST, alkaline phosphatase and total bilirubin should be done regularly until the abnormalities return to normal or baseline state. Additional clinical information should be gathered to seek a possible cause of the observed laboratory test abnormalities.~~

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

- *ALT or AST > 7x UNL*
- *ALT or AST > 2x baseline value*
- *Total bilirubin > 2.0 mg/dL*
- *INR > 1.6*

For definition of baseline values, see section 17.

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 (Hy's Law)(see section 12.1.2)*
- *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 in subjects where the baseline values were ≥2x UNL but <5x UNL.*
- *ALT or AST increase to >2x baseline value AND the increase is accompanied by a concomitant total bilirubin increase to >2x baseline value OR concomitant INR increase by >0.2 from baseline.*

- *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 section 8.4.5, section 12 and Appendix B.

For all such events repeat testing should occur within 48 to 72 hours and work up for competing etiologies must be performed (ref. 53) 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 only if an alternative etiology is definitively identified and liver blood parameters have returned to pre-event levels.

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 prematurely discontinued (see section 6.4).

2.9 Section 17.4.1.2 Safety endpoints

- Change from baseline to 72 weeks in:
    - Biochemistry (creatinine, *eGFR*, creatinine phosphokinase, urea, bilirubin (total), alkaline phosphatase, ferritin, sodium, potassium, calcium (total), amylase, lipase)

2.10 Section 27 References

42.KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. http://www.kidney-international.org 3[1]. 2013.

51.KDOQI Clinical practice guideline for diabetes and CKD: 2012 update. Am J Kidney Dis - 2012; 60(5):850-886.

53.http://www.fda.gov/downloads/Drugs/.../Guidances/UCM174090.pdf

2.11 Appendix B

Event	Definition	Additional data collection	Event adjudication
Hepatic event	~~• ALT or AST > 5x UNL~~ ~~• ALT or AST > 3x baseline value~~ ~~• ALT or AST > 3x UNL and total bilirubin > 2x UNL (Biochemical Hy's Law)~~ ~~• Total bilirubin > 1.5 mg/dL~~ ~~• INR > 1.3~~ • *ALT or AST > 7x UNL* • *ALT or AST > 2x baseline value* • *Total bilirubin > 2.0 mg/dL* • *INR > 1.6* • *ALT or AST > 3x UNL and total bilirubin > 2x UNL, where no alternative aetiology exists (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 in subjects were the baseline values were ≥2x UNL but <5x UNL.* • *ALT or AST increase to >2x baseline value AND the increase is accompanied by a concomitant total bilirubin increase to >2x baseline value OR concomitant INR increase by > 0.2 from baseline.* • *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 • Liver transplant • Ascites requiring medical • intervention • Gastroesophageal variceal bleeding • Hepatic encephalopathy • Spontaneous bacterial peritonitis • Hepatic events leading to trial product discontinuation	If one of the hepatic events is observed during the trial the following additional information must be reported if available: • Signs and symptoms associated to the event • Risk factors • Relevant laboratory test results • Liver biopsy results • Diagnostic procedures performed including • imaging • Treatment given for the event • Possible cause(s) of the event	No

Protocol Amendment

no 2 to
Protocol, final version 1.0 dated 20 June 2016 and
Global protocol amendment number 1, version 1.0, dated 26 August 2016

Trial ID: NN9931-4296

Investigation of efficacy and safety of three dose levels of subcutaneous semaglutide once daily versus placebo in subjects with non-alcoholic steatohepatitis

Trial phase: Phase 2

Applicable to all countries

Amendment originator:

[redacted] Senior International Trial Manager

TrialOps 2, GLP-1 diabetes, NADs and complications

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1 Introduction including rationale for the protocol amendment

Please see below the rationales for development of this global protocol amendment:

- Since the trial population is at risk of developing type 2 diabetes, the protocol is updated to allow antidiabetic treatment of subjects who are diagnosed with type 2 diabetes during trial participation.
- Exclusion criterion 8 is updated for vitamin E and pioglitazone treatment to ensure stable dose for 90 days prior to screening or baseline liver biopsy. This is to ensure that the potential treatment effect of these compounds is stabilised prior to enrolment into the trial.
- Statistical section is updated to perform a supportive analysis of the primary endpoint without pooling the placebo arms. The supportive analysis of the primary endpoint has been added to further evaluate the appropriateness of pooling the placebo groups.
  Furthermore a sensitivity analysis of the primary endpoint where vitamin E use is included as a factor in the model has been included and additionally a subgroup analysis for subjects who use vitamin E versus subjects who do not use vitamin E has been included. The sensitivity and subgroup analyses with respect to vitamin E use have been added to assess the impact of vitamin E use on the primary endpoint and possible interaction with randomised treatment.
- Text regarding a new safety signal on retinopathy when subjects with type 2 diabetes are treated with semaglutide is included in the benefit-risk section of the protocol.

Additionally there are some updates of operational character included in order to either support any of the above or to make additional specifications.

In this protocol amendment:

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

2 Changes

2.1 Section 5.3 Treatment of subjects

Throughout the trial subjects cannot initiate treatment with:

- ~~Glucose-lowering agents other than trial product~~
- *GLP-1 RAs (other than trial product), SGLT-2 inhibitors and bolus (fast-acting) insulin*
- Vitamin E *or pioglitazone*

- Drugs with potential effect on steatosis (corticosteroids (topical and inhaled 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 subjects participate in any organised weight reduction programme throughout the trial.

For subjects treated with vitamin E or pioglitazone according to exclusion criterion 8, these medications must be kept at a stable dose throughout the trial.

2.2 New section: *Section 5.3.2 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 at the discretion of the investigator. However the following treatments must not be used: GLP-1 RAs (other than trial product), SGLT-2 inhibitors and bolus (fast-acting) insulin.

The antidiabetic medication prescribed by the investigator will not be provided nor reimbursed by Novo Nordisk.

~~5.3.2~~ *5.3.3* Missed dose

2.3 Section 6.3 Exclusion criteria

8. Treatment with vitamin E *or pioglitazone* which has not been at a stable dose in the period from ~~28~~ *90* days prior to screening or if recent biopsy is used from ~~28~~ *90* days prior to baseline liver biopsy until time of screening.

2.4 Section 8.2.3 Concomitant medication

The information collected for each concomitant medication includes trade name or generic name, indication, start date and stop date or continuation. *For vitamin E and pioglitazone the daily dose must be recorded as well.*

2.5 Section 8.2.7 Fundoscopy/Fundus photography

For subjects with type 2 diabetes dilated fundoscopy/fundus photography will be performed as specified in section 2. *Fundoscopy requires pharmacological dilation of both pupils.* Results of the dilated fundoscopy/fundus photography will be evaluated by the investigator and the investigator evaluation must be documented either on the dilated fundoscopy/fundus photography result report or in the subject's medical record.

2.6 Section 8.7.2 Assessments in case of increased levels of liver blood parameters

For all such events repeat testing ~~should~~ *must* occur within 48 to 72 hours and work up for competing etiologies must be performed[53] including:

2.7 Section 17 Statistical considerations

~~The three different placebo arms will be pooled into one placebo treatment arm in all planned analyses. This pooling assumes that there is no substantial effect of different semaglutide placebo volumes on the efficacy and safety endpoints. The validity of this assumption will be checked for the primary endpoint and treatment-emergent adverse events by evaluating summaries for each placebo arm. Should the placebo arms demonstrate substantial differences, appropriate sensitivity analyses will be included.~~

If not otherwise specified, the three different placebo arms will be pooled into one placebo arm in the statistical analyses. The pooling is based on the assumption that there is no substantial effect of different placebo volumes on the efficacy and safety endpoints. The validity of this assumption will be checked for the primary endpoint and treatment-emergent adverse events by evaluating descriptive statistics where each placebo arm is presented separately. In addition, the assumption will be evaluated based on estimates from a supportive analysis of the primary endpoint (see section 17.3).

The statistical analyses will in general consist of the following three pairwise treatment comparisons:

- semaglutide 0.4 mg versus placebo
- semaglutide 0.2 mg versus placebo
- semaglutide 0.1 mg 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. The problem of multiple testing will be taken into account with respect to the primary endpoint (see section~~17.2~~ *17.3*) but not for any of the secondary endpoints.

2.8 Section 17.3 Primary endpoint

Adjustment for baseline body weight as a continuous covariate may potentially give more precise estimates of the treatment effects. To investigate the influence of such an adjustment, a sensitivity analysis will be performed using a logistic regression model which includes treatment, baseline diabetes status, baseline fibrosis stage and diabetes-by-fibrosis interaction as factors and baseline body weight as a covariate.

The use of vitamin E may affect the chance of NASH resolution. Therefore, a sensitivity analysis will be performed using a logistic regression model which includes vitamin E use at baseline (yes/no) as factor together with randomised treatment, baseline diabetes status, baseline fibrosis stage and diabetes-by-fibrosis interaction. Furthermore, a subgroup analysis will be performed using the same logistic regression model but with the addition of a term for the interaction between randomised treatment and vitamin E use.

Supportive analysis

As part of an evaluation of the appropriateness of pooling the three placebo arms, a supportive analysis will be performed using the same CMH test as in the primary analysis but without pooling the placebo arms. Each semaglutide arm will instead be compared with the placebo arm which received the same injection volume.

Exploratory analysis

The dose-response relationship with respect to the primary endpoint will be further explored by fitting a modified logistic regression model with baseline diabetes status, baseline fibrosis stage and diabetes-by-fibrosis interaction as factors and the log-transformed dose level and baseline body weight as covariates

2.9 Section 17.4.1.1 Efficacy endpoints

~~$NFS = -1.675 + 0.037 \times Age\ (years) + 0.094 \times BMI\ (kg/m^2) + 1.13 \times Hyperglycaemia\ (yes/no) + 0.99 \times AST/ALT + 0.013 \times Thrombocyte\ count\ (10^9/L) + 0.66 \times Albumin\ (g/dL)$~~

$$NFS = -1.675 + 0.037 \times Age\ (years) + 0.094 \times BMI\ (kg/m^2) + 1.13 \times Hyperglycaemia\ (yes/no) + 0.99 \times AST/ALT - 0.013 \times Thrombocyte\ count\ (10^9/L) - 0.66 \times Albumin\ (g/dL)$$

2.10 Section 18 Ethics

Identified risks

<u>*Diabetic retinopathy*</u>

A transient worsening of diabetic retinopathy is a recognised complication in selected patients with diabetes after initiation of intensive antidiabetic treatment (refs. 67-69). Risk factors for these events include long-standing poor glycaemic control and presence of proliferative retinopathy, and initial large improvements in blood glucose maybe an additional aggravating factor. Several studies have, however, documented long-term beneficial effects of intensive glycaemic treatment in reducing retinopathy progression (Refs. 70,71) even in intensively treated patients who experienced early worsening (Ref. 68). In a cardiovascular outcomes trial with s.c. semaglutide, results indicate an increased risk of events related to diabetic retinopathy in subjects treated with semaglutide

compared to placebo. As a precaution in this trial, all subjects with type 2 diabetes are required to have a fundus photography or dilated fundoscopy performed before enrolment into the trial; moreover, subjects with proliferative retinopathy or maculopathy requiring acute treatment will be excluded. As part of good diabetes management the investigator is encouraged to ensure adequate monitoring and treatment of diabetic retinopathy in subjects enrolled into the trial (Ref. 72).

2.11 Section 26 Indemnity statement

For Russia only: Federal law of 12 April 2010 No. 61-FZ 'On Medicinal Drugs' Circulation *and Order No. 200n dated April 01, 2016 of the Ministry of Health of the Russian Federation On Approval of Rules for Good Clinical Practice.*

2.12 Section 27 References

67. Dahl-Jørgensen K, Brinchmann-Hansen O, Hanssen KF, Sandvik L, Aagenaes O. Rapid tightening of blood glucose control leads to transient deterioration of retinopathy in insulin dependent diabetes mellitus: the Oslo study. Br Med J (Clin Res Ed). 1985;290(6471):811- 5.

68. Early worsening of diabetic retinopathy in the Diabetes Control and Complications Trial. Arch Ophthalmol. 1998;116(7):874-86.

69. Varadhan L, Humphreys T, Walker AB, Varughese GI. The impact of improved glycaemic control with GLP-1 receptor agonist therapy on diabetic retinopathy. Diabetes Res Clin Pract. 2014;103(3):e37-9.

70. Action to Control Cardiovascular Risk in Diabetes Follow-On (ACCORDION) Eye Study Group and the Action to Control Cardiovascular Risk in Diabetes Follow-On (ACCORDION) Study Group. Persistent Effects of Intensive Glycemic Control on Retinopathy in Type 2 Diabetes in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Follow-On Study. Diabetes Care. 2016;39(7):1089-100.

71. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998;352(9131):837-53.

72. Diabetes Care 2016, Standards of Medical Care in Diabetes

~~67~~ *73*. Rockey DC, Caldwell SH, Goodman ZD, Nelson RC, Smith AD, Diseases AAftSoL. Liver biopsy. Hepatology. 2009;49(3):1017-44.

~~68~~ *74*. International Committee of Medical Journal Editors. Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals; current version available at www.icmje.org.

Protocol Amendment

no 3 to
Protocol, final version 1.0 dated 20 June 2016 and
Global protocol amendment number 1, version 1.0, dated 26 August 2016 and
Global protocol amendment number 2, version 1.0, dated 29 November 2016

Trial ID: NN9931-4296

Investigation of efficacy and safety of three dose levels of subcutaneous semaglutide once daily versus placebo in subjects with non-alcoholic steatohepatitis

Trial phase: 2

Applicable to all countries

Amendment originator:

[redacted] Senior International Trial Manager

TrialOps 2, GLP-1 diabetes, NADs and complications

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1 Introduction including rationale for the protocol amendment

The below changes to liver biopsy assessment, bilirubin, HbA_{1c}, BMI, thyroid stimulating hormone and pre-screening are implemented in the trial protocol based on detailed and continuous monitoring of the progress of the current trial, in addition to scientific developments in the field of non-alcoholic steatohepatitis (NASH). This combined with the continuous accumulation of semaglutide safety and efficacy data is the reason behind this protocol amendment. The changes are in accordance with advice from external NASH experts and recommendations from the Liver Forum (forum for collaboration between academia, industry and Health Authorities on clinical development in NASH). As the field of NASH is quickly evolving, including an increasing number of clinical trials, the described changes should also lead to an improvement in the rate of recruitment.

Number of subjects to be screened:

The expected screen failure rate and hence planned number of screened subjects are updated based on actual numbers seen in the trial.

Eligibility criteria:

Inclusion criterion 5: This criterion is rephrased to emphasize that eligibility is solely based on central pathologist assessment of the baseline liver biopsy. This will not change how patients are entering the trial and is in line with eligibility criteria for ongoing global NASH trials[1, 2].

Exclusion criterion 5: Gilbert's syndrome is a common form of unconjugated hyperbilirubinemia caused by an inherited deficiency in the bilirubin-conjugating enzyme. The condition is highly prevalent ranging from 3% to 12% of the population depending on the mode of diagnosis[3]. A small study of patients with NASH reported a prevalence of Gilbert's syndrome of 7.5%[4]. Gilbert's syndrome is, however, regarded a benign trait, and clinical recognition is often incidental to routine laboratory investigations, revealing an elevated level of total bilirubin. Thus, exclusion criterion 5 will be changed to allow subjects into the trial with total bilirubin level >1.5 mg/dL if conjugated bilirubin is <1.5×upper limit of normal.

Exclusion criterion 10 and 12: Exclusion criterion 10 is being amended to allow patients in with HbA_{1c} of up to 10% to allow a slightly broader population, including more patients with type 2 diabetes to enter the trial. Given that the current trial is placebo-controlled and of long duration, the responsibility of the investigator to ensure glycaemic control of the patients will be reinforced by adding guidance to treatment of patients with type 2 diabetes with poorly controlled glycaemia to the protocol.

A significant proportion of patients with NASH and type 2 diabetes is treated with bolus insulin. To allow for these patients to enter the trial, exclusion criterion 12 will be deleted. In order to mitigate

the risk of hypoglycaemia, the protocol is amended to instruct the total daily insulin dose to be reduced by 30% at baseline in subjects with $HbA_{1c} \leq 8.0\%$ at the screening visit.

Exclusion criterion 15: Exclusion criterion 15 will be amended by removing the upper limit of BMI in order to allow patients with a BMI ≥45 kg/m^2 to be included in the trial.

The prevalence of non-alcoholic fatty liver disease (NAFLD) and NASH increases with increasing body mass index (BMI). An analysis of liver histology obtained from liver donors, autopsy findings, and clinical liver biopsies suggests that the prevalence rates of steatosis and NASH are approximately 15% and 3%, 65% and 20% and 85% and 40% respectively in non-obese, BMI 30.0–39.9 kg/m^2 and BMI ≥40 kg/m^2 subjects[5].

The recently completed semaglutide obesity trial, trial NN9536-4153, which included patients with a BMI > 30 kg/m^2 and investigated the same dose range as the current trial (0.05-0.4 mg/day), reported that the semaglutide safety profile was well-tolerated, with the most common adverse events being gastrointestinal (GI) adverse events[6]. This is in line with the previous experience with semaglutide[7].

Exclusion criteria 16: Thyroid function disorders are not considered a safety concern for semaglutide[7] and thus exclusion criterion 16 will be removed.

Subjects can be re-screened if they have previously screen failed solely due to lab parameters included in the eligibility criteria that are changed in this amendment (HbA_{1c}, total bilirubin or TSH).

Pre-screening:

Optional pre-screening activities including blood samples and imaging methods will be implemented in the present protocol amendment to pre-qualify patients and thereby potentially minimise the number of patients having a liver biopsy performed and the number of screen failed subjects. These activities will require that the subject signs a separate informed consent form. According to the joint clinical guideline for the management of NAFLD from the European liver, diabetes and obesity associations, surrogate blood markers of fibrosis e.g. NAFLD Fibrosis Score (NFS), FIB-4 or Enhanced Liver Fibrosis (ELF) test, should be calculated for NAFLD patients in order to rule out significant fibrosis (≥F2). If significant fibrosis cannot be ruled out, patients should be referred to transient elastography, and if significant fibrosis is confirmed the final diagnosis should be made by liver biopsy[8]. Similar strategies to identify and target liver biopsies to patients at greatest risk of having NASH with advanced fibrosis have previously been described[9, 10].

Footnote to primary end-point:

The first footnote (*) of the primary endpoint has been updated to clarify that resolution of NASH is defined as "no more than mild residual inflammatory cells (0 – 1) and no ballooning (0)". This is in line with the Health Authority recommendation (FDA and EMA) as communicated through the Liver Forum[11].

Other minor changes and clarifications have been included.
Since new protocol sections are added, the numbering for some protocol sections will change throughout the updated protocol once the amendment is implemented.

In this protocol amendment:

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

2 Changes

2.1 List of abbreviations

~~TSH thyroid stimulating hormone~~

2.2 Section 1 Summary

Trial population

A total of 372 subjects are planned to be randomised. Based on an assumption of a *65*~~50~~% screening failure rate, *1063*~~744~~ subjects are planned to be screened.

Key inclusion criteria

- 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 *except for protocol described pre-screening activities which require a separate informed consent*.

- ~~Local histological diagnosis of NASH followed by histological confirmation of NASH based on central pathologist evaluation of~~ *Histologic evidence of NASH based on central pathologist evaluation of* a liver biopsy obtained up to 21 weeks before screening.

Key exclusion criteria

- HbA1c > ~~9~~*10* % at screening.

- Body Mass Index (BMI) ≤ 25.0 ~~or ≥ 45.0~~ kg/m^2 at the screening visit *(visit 1)*.

2.3 Section 2 Flowchart

~~TSH~~

Attend visit fasting: *Added x for visit 10*

16) All visit 2 assessments must be carried out prior to first trial product dose

2.4 Section 4.2.1 Primary endpoint

- NASH resolution* without worsening of fibrosis** after 72 weeks (yes/no)

**) Resolution of NASH defined by the NASH Clinical research network (CRN) as "no more than mild residual inflammatory cells (0 – 1) and no ballooning (0)" based on comprehensive interpretation by two independent pathologists (central reading) blinded to treatment allocation.*

~~*) Resolution of NASH as defined by comprehensive interpretation by two independent pathologists (central reading) blinded to treatment allocation and with complete resolution captured by terms such as "no fatty liver disease" or "simple steatosis or isolated steatosis" and defined by the NASH Clinical research network (CRN) as "no more than mild residual inflammatory cells and no ballooning"~~

**) worsening defined by an increase of at least one stage of the Kleiner fibrosis classification

2.5 Section 4.2.2.2 Supportive secondary safety endpoints

Change from baseline to 72 weeks in:

- Pulse
- ECG
- Physical examination
- Haematology (haemoglobin, haematocrit, thrombocytes, erythrocytes, leucocytes, differential count)
- Biochemistry (creatinine, estimated glomerular filtration rate (eGFR), creatin~~in~~e phosphokinase, urea, bilirubin (total), alkaline phosphatase, ferritin, sodium, potassium, calcium (total), amylase, lipase)
- Hormones (calcitonin)

2.6 Section 5.1 Type of trial

A planned total of 372 subjects will be randomised. Based on an assumption of a *65*~~50~~% screening failure rate, *1063*~~744~~ subjects will be screened.

2.7 Section 5.3 Treatment of subjects

The conversion table below shows the connection between each volume matched dose level and the value shown in the display on the NovoPen® 4. Subjects must be instructed to administer the value shown in the display.

Injections may be administered in the thigh, abdomen or upper arm, at any time of day irrespective of meals. The injections should be administered at approximately the same time of day during the trial.

Throughout the trial subjects cannot initiate treatment with:

- GLP-1 RAs (other than trial product)~~,~~ *or* SGLT-2 inhibitors ~~and bolus (fast-acting) insulin~~
- Vitamin E or pioglitazone
- Drugs with potential effect on steatosis (corticosteroids (topical, ~~and~~ 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).

2.8 Section 5.3.1 Subjects treated with ~~basal~~ insulin

~~The following basal insulins are allowed:~~

- ~~Insulin glargine~~
- ~~Insulin detemir~~
- ~~Insulin degludec~~
- ~~Neutral protamine Hagedorn (NPH) insulin~~

~~Subjects treated with basal 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 ~~basal~~ insulin *and* ~~with~~ $HbA_{1c} \leq 8.0$ % at screening:
Subjects with $HbA_{1c} \leq 8.0$ % at screening (visit 1) should have the *total daily* insulin dose reduced by 30 % at start of trial product treatment to limit the potential risk of hypoglycaemia induced by the combination of insulin and semaglutide.

2.9 New section: *5.3.2 Treatment of subjects with poorly controlled glycaemia*

Subjects with type 2 diabetes and with persistent and unacceptable hyperglycaemia should be offered treatment intensification. If any HbA_{1c} value reported by central laboratory exceeds 9% from at least 4 weeks after end of dose escalation, the subject should be offered treatment intensification at the discretion of the investigator. However, the following treatment types must not be used: GLP-1 RAs (other than trial product) and SGLT-2 inhibitors. Subjects that are started on treatment intensification medication should continue to follow the protocol specified visit schedule and stay on trial product treatment unless the investigator judges that this will jeopardise the safety of the subject.

All treatment intensification medication given should be documented in medical records and reported in the eCRF. Treatment intensification medication will not be provided nor reimbursed by Novo Nordisk.

2.10 Section 5.3.~~2~~*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 at the discretion of the investigator. However the following treatments must not be used: GLP-1 RAs (other than trial product)~~,~~ *and* SGLT-2 inhibitors ~~and bolus (fast-acting) insulin~~.

5.3.~~3~~*4* Missed dose

5.3.4*5* Nutritional and physical activity counselling

2.11 Section 6.1 Number of subjects

Number of subjects planned to be screened: ~~744~~ *1063*.

Number of subjects planned to be randomised: 372 (~~50~~ *65*% screen failure rate).

2.12 Section 6.2 Inclusion criteria

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 *except for protocol described pre-screening activities which require a separate informed consent*.

5. ~~Local histological diagnosis of NASH followed by histological confirmation of NASH based on central pathologist evaluation of~~ *Histologic evidence of NASH based on central pathologist evaluation of* a liver biopsy obtained up to 21 weeks before screening.

2.13 Section 6.3 Exclusion criteria

5. Elevated total bilirubin (> 1.5 mg/dL) at screening. T*otal bilirubin level >1.5 mg/dL is allowed if conjugated bilirubin is <1.5×UNL.*

6. ~~Prothrombin time~~ *International normalized ratio* (INR) *of prothrombin time* > 1.3 at screening.

10. HbA1c > ~~9~~*10* % at screening.

~~12. Treatment with bolus (fast-acting) insulin in the period from 28 days prior to screening or if recent biopsy is used from 28 days prior to baseline liver biopsy until time of screening.~~

~~13~~*12*. Treatment with other glucose lowering agent(s) (apart from *GLP-1 RAs or SGLT-2 inhibitors* ~~what is listed in exclusion criterion 11 and 12~~) not stable in the period from 28 days prior to screening or if recent biopsy is used from 28 days prior to baseline liver biopsy until time of screening. Changes without clinical relevance in the opinion of the investigator are allowed.

~~14~~*13*. Diagnosis of type 1 diabetes according to medical records.

<u>Obesity related:</u>

~~15~~*14*. Body Mass Index (BMI) ≤ 25.0 ~~or ≥ 45.0~~ kg/m^2 at the screening visit (visit 1).

~~16. TSH > 6 mIU/L or < 0.4 mIU/L at screening.~~

~~17~~*15*. Treatment with orlistat, zonisamide, topiramate, phentermine, lorcaserin, bupropion and naltrexone alone or in combination or any other medication that could promote weight loss in the opinion of the investigator in the period from 28 days prior to screening or if recent biopsy is used from 28 days prior to baseline liver biopsy until time of screening.

~~18~~*16*. Participation in an organised weight reduction program (e.g. WeightWatchers®) in the period from 28 days prior to screening or if recent biopsy is used from 28 days prior to baseline liver biopsy until time of screening.

~~19~~*17*. Previous surgical treatment for obesity. However (1) liposuction and/or abdominoplasty if performed > 6 months before baseline liver biopsy is allowed or 2) lap banding where the band has been removed > 6 months before baseline liver biopsy is allowed 3) intragastric balloon where the balloon has been removed > 6 months before baseline liver biopsy is allowed.

General safety:

~~20~~*18*. For patients with type 2 diabetes only: Proliferative retinopathy or maculopathy requiring acute treatment verified by fundus photography or dilated fundoscopy performed within the past 90 days prior to randomisation.

~~21~~*19*. History or presence of pancreatitis (acute or chronic).

~~22~~*20*. Calcitonin ≥ 50 ng/L at screening.

~~23~~*21*. Family or personal history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma. Family is defined as a first degree relative.

~~24~~*22*. Presence or history of malignant neoplasms within the past 5 years prior to the day of screening. Basal and squamous cell skin cancer and any carcinoma in-situ are allowed.

~~25~~*23*. Surgery scheduled for the trial duration period, except for minor surgical procedures, in the opinion of the investigator.

~~26~~*24*. Any condition which, in the investigator's opinion might jeopardise subject's safety or compliance with the protocol.

~~27~~*25*. Language barrier, mental incapacity, unwillingness or inability to adequately understand or comply with study procedures.

~~28~~*26*. Known or suspected hypersensitivity to trial product or related products.

~~29~~*27*. Previous participation in this trial. Participation is defined as randomisation.

~~30~~*28*. Participation in any clinical trial of an approved or non-approved investigational medicinal product within 90 days before screening.

~~31~~*29*. Female who is pregnant, breast-feeding or intends to become pregnant or is of childbearing potential and not using an adequate contraceptive method (adequate contraceptive measures as required by local regulation or practice).

For EU countries: The following contraceptive measures are considered adequate:

- Combined estrogen and progestogen containing hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation :
  - oral
  - injectable
  - implantable
- Placement of an
  - intrauterine device (IUD)
  - intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Barrier methods of contraception (condom or occlusive cap with spermicidal foam/gel/film/cream/suppository) (**not applicable for Belgium, Denmark, Finland, Greece, Spain, Sweden**)
- Vasectomised partner (where partner is sole partner of subject) (**not applicable for Denmark**)
- True sexual abstinence (**not applicable for Denmark**). Sexual abstinence is defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

~~32~~*30*. Renal impairment measured as estimated Glomerular Filtration Rate (eGFR) value of eGFR < 30 ml/min/1.73 m2 as defined by Kidney Disease: Improving Global Outcomes (KDIGO).42

2.14 Section 6.4 Criteria for premature discontinuation of trial product

10. Treatment with other GLP-1 receptor agonists *or*~~,~~ SGLT-2 inhibitors ~~or bolus (fast-acting) insulin~~

2.15 Section 7 Milestones

Planned duration of recruitment period: *78* ~~51~~ weeks

2.16 Section 8.1.1 Screening, Re-screening and screen failures

Informed consent must be obtained before any trial related activity, see section 18.2. Separate informed consent forms for long-term storage of human samples and genotyping are available and informed consent must be obtained before activities related to any of these are undertaken.

Additionally a separate informed consent form for optional pre-screening is available. This must be signed before any optional pre-screening activities are performed (see section 8.1.2).

Re-screening

Re-screening of screening failures is allowed only once within the limits of the recruitment period. However, re-screening is NOT allowed if the subject has failed one of the inclusion/exclusion criteria related to laboratory parameters (*pathology and/or blood parameters* ~~histological NAS, NASH fibrosis stage, HBsAg, anti HIV, HCV-RNA, AST, ALT, total bilirubin, INR, HbA1c, calcitonin or TSH~~). In the event of re-screening, a new informed consent must be obtained and a new subject number must be allocated. All assessments and laboratory samples must be repeated.

2.17 New section: *8.1.2 Optional pre-screening*

The Investigator may, after obtaining separate informed consent, perform pre-screening of potential trial candidates. Pre-screening assessments include blood parameters and imaging (except for imaging methods with radiation involved).The purpose of such assessments is to assess trial eligibility potential.

Pre-screening assessments are not defined as trial-related procedures. Results of pre-screening assessments will not be collected in the trial database and will not be monitored. Concerns related to any pre-screening assessment must not be reported as an adverse event.

Pre-screening assessments (blood parameters and imaging) performed after signature of the separate informed consent can be reimbursed by Novo Nordisk A/S.

8.1.~~2~~*3* AUDIT questionnaire

2.18 Section 8.1.~~3~~*4* Fasting visits

Subjects must attend ~~some of the~~ *most* clinic visits in a fasting state (see section 2).

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 blood sampling has been performed. 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. Fasting procedures include body weight, Fibroscan® measurements and blood sampling *(FPG,*

fasting insulin, fasting glucagon, calcitonin and lipids (Total cholesterol, free fatty acids, HDL cholesterol, LDL cholesterol, triglycerides, VLDL cholesterol)).

Prior to Fibroscan® measurements, only two hours of fasting is required.

At visit 19, the subject must be fasting for two hours prior to the anti-semaglutide antibody sampling (see section 8.5.3.7).

8.1.4*5* Missed visits

8.1.~~5~~*6* Premature discontinuation of trial product

8.1.~~6~~*7* Withdrawn subjects

8.1.~~7~~*8* Subject training

2.19 Section 8.3.1 Liver biopsy

To be randomised, subjects must have *histologic evidence of NASH* ~~a local histological diagnosis of NASH followed by histological confirmation of NASH diagnosis~~ based on central pathologist evaluation of a liver biopsy. ~~Confirmation of~~ *Histologic evidence of* NASH ~~diagnosis~~ can be based on a liver biopsy obtained up to 21 weeks prior to screening. For subjects with no historical liver biopsy within 21 weeks prior to screening, a liver biopsy must be performed during the screening period. ~~The local NASH diagnosis and the confirmation~~ *The histologic evidence* of NASH ~~diagnosis~~ by central pathologist evaluation of the liver biopsy must be available prior to randomisation of the subject. ~~The local NASH diagnosis and the confirmation of NASH diagnosis by central pathologist evaluation can be done on the same liver biopsy sample.~~

2.20 Section 8.3.1.1 Central pathologist evaluation

The *histologic evidence of* NASH ~~diagnosis~~ and histology based scores will be centrally assessed by two independent pathologists with expertise and experience in NASH.

2.21 Section 8.3.2 Fibroscan measurements

Liver stiffness

At sites with Fibroscan® equipment available, measurements of liver stiffness must be performed at the specified visits (section 2). *Fibroscan measurements can be performed up to 2 weeks prior to each visit.*

Liver steatosis

At sites with Fibroscan® equipment available, measurements of liver steatosis must be performed at the specified visits (section 2). *Fibroscan measurements can be performed up to 2 weeks prior to each visit.*

2.22 Section 8.3.3.3 Body mass index

Body mass index will be calculated by the eCRF from visit 1 height data and must be in accordance with exclusion criterion ~~15~~*14*.

2.23 Section 8.5 Laboratory assessments

The laboratory analyses will be performed by a central laboratory except for *laboratory analyses for pre-screening*, analysis of anti-semaglutide antibodies and semaglutide plasma concentration analysis and some exploratory biomarkers which will be performed at specialised laboratories.

2.24 Section 8.5.3.1 Biochemistry

- Bilirubin, total
- *Bilirubin, conjugated*
- Calcium
- Creati~~ni~~ne phosphokinase
- Creatinine
- eGFR (per CKD-EPI formula)
- Lipase
- Potassium
- Sodium
- Alkaline phosphatase
- Amylase
- Albumin
- Ferritin
- Urea
- MELD score

2.25 Section 8.5.3.2 Hormones

- Calcitonin (see Appendix A)
- ~~Thyroid-stimulating hormone (TSH)~~

2.26 Section 17.4.1.2 Safety endpoints

- Change from baseline to 72 weeks in:
  - Pulse
  - ECG
  - Physical examination
  - Haematology (haemoglobin, haematocrit, thrombocytes, erythrocytes, leucocytes, differential count)
  - Biochemistry (creatinine, eGFR, creatin~~in~~e phosphokinase, urea, bilirubin (total), alkaline phosphatase, ferritin, sodium, potassium, calcium (total), amylase, lipase)
  - Hormones (calcitonin)

2.27 Section 18.1 Benefit-risk assessment of the trial

Other safety considerations

Teratogenicity (nonclinical embryo-foetal toxicity)

Semaglutide has been concluded teratogenic in rats. This effect is regarded to be caused by impairment of nutrient supply to the embryo across the inverted yolk sac with placental function. As the yolk sac does not play such a role for nutrition of the embryo in humans, this effect is unlikely to be relevant for humans. However, as a precaution subjects fulfilling exclusion criterion ~~31~~*29* will be excluded from trial participation. Furthermore, as specified in the flowchart, female subjects included in the trial will have pregnancy testing performed frequently during the entire duration of the trial.

2.28 Section 18.2 Informed consent

Separate informed consent forms for long-term storage of human samples and genotyping are available and informed consent must be obtained before activities related to any of these are undertaken.

Additionally a separate informed consent form for optional pre-screening is available. This must be signed before any optional pre-screening activities are performed (see section 8.1.2).

3 References

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Protocol Amendment

no 4 to

Protocol, final version 1.0 dated 20 June 2016 and

Global protocol amendment number 1, version 1.0, dated 26 August 2016 and

Global protocol amendment number 2, version 1.0, dated 29 November 2016 and

Global protocol amendment number 3, version 1.0, dated 25 August 2017 and

Local protocol amendment number 5 in Sweden, version 1.0, dated 09 January 2018

Trial ID:NN9931-4296

Investigation of efficacy and safety of three dose levels of subcutaneous semaglutide once daily versus placebo in subjects with non-alcoholic steatohepatitis

Trial phase: 2
Applicable to all countries

Table of Contents

1 Introduction including rationale for the protocol amendment

This amendment introduces a change to the sample size and a broadening of the patient inclusion criterion to include subjects with liver fibrosis stage 1 (F1). The sample size reduction is based on new data from trials in non-alcoholic steatohepatitis (NASH), which collectively suggest a lower placebo response rate than was assumed when this study was designed. The inclusion of patients with F1 reflects the view that some patients may be so-called "fast progressors" who could benefit from pharmacological treatment.

A change to allow re-test of INR is implemented based on an evaluation of the causes behind prolonged INR observed in the current trial.

Sample size reduction:

The planned sample size in this clinical trial is being reduced due to emerging placebo response data from competitor NASH trials in subjects with NASH as well as semaglutide data from a Novo Nordisk trial in subjects with obesity.

CENTAUR[1] was a 2-year, randomised, double-blind, placebo-controlled phase 2b trial to evaluate the effect of cenicriviroc in subjects with NASH and liver fibrosis. Resolution of NASH with no worsening of liver fibrosis at year 1 was a secondary endpoint in the trial and of 126 subjects receiving placebo treatment with evaluable biopsies at both baseline and after 1 year, only 9 (7%) subjects met this endpoint.

GOLDEN-505[2] was a 52-week, randomised, double-blind, placebo-controlled phase 2 trial to evaluate the effect of elafibranor in subjects with NASH. The primary endpoint was resolution of NASH with no worsening of fibrosis at 1 year, using protocol-defined and modified definitions. The modified definition is recommended by regulatory agencies and is the one used in the current trial. Out of 77 subjects receiving placebo treatment with evaluable biopsies at both baseline and end of trial, only 11 (14%) subjects met this modified endpoint.

Based on the results from the CENTAUR[1] and GOLDEN-505[2] trials, the assumed proportion of completers meeting the primary endpoint with placebo has been reduced from 20% to 17% in the sample size calculation for the current trial.

The effect of semaglutide in subjects with obesity has been investigated in a phase 2 dose finding trial (NN9536-4153)[3]. The trial was a 52-week, randomised, double-blind, placebo- and active-controlled trial in which 957 adults with obesity but without type 2 diabetes received once-daily s.c. injection of semaglutide in one of five different doses (0.05 mg/day to 0.4 mg/day), once-daily injection of liraglutide (3.0 mg/day) or once-daily placebo as add on to lifestyle counselling. The estimated mean body weight loss at 52 weeks was up to 13.8% with semaglutide compared to 7.8% with liraglutide and 2.3% with placebo. The LEAN[4] trial investigated overweight subjects with biopsy-confirmed NASH and showed that statistically significantly more subjects treated with

liraglutide (1.8 mg/day) compared to subjects treated with placebo obtained resolution of NASH with no worsening of fibrosis after 48 weeks of treatment. In the LEAN trial, subjects treated with liraglutide had a mean weight loss of 5.5% compared to 0.7% in subjects treated with placebo.

The observed effect on weight loss with higher doses of semaglutide suggests that semaglutide putatively has a greater effect on resolution of NASH than previously anticipated. This is supported by data showing that a greater extent of weight loss is associated with improvement in histologic features of NASH.[5] To be conservative, the assumed proportion of completers meeting the primary endpoint with semaglutide 0.4 mg/day remains unchanged in the sample size calculation, but with the adjusted placebo effect from 20% to 17% this will imply an increase of the assumed treatment difference from 25 to 28 percentage points.

Eligibility criteria:

Inclusion criterion 7: The patient inclusion criteria have been broadened to include subjects with F1. Some patients with F1 may be "fast progressors", who may benefit from pharmacological treatment. Although the presence of increasing number of metabolic disorders such as insulin resistance, type 2 diabetes, hypertension, dyslipidemia, and visceral obesity seems to increase the risk of progression[6], the current understanding is incomplete.
Indeed, the broadening of the patient population in the current trial is in line with other phase 2 NASH trials, for which most have included patients with fibrosis stage 0-3[2, 7] or 1-3[1]. Further, a subset of F1 patients may be included in phase 3, as seen in other development programmes[8, 9], and as such it is important to understand the effect of semaglutide in these subjects.

A review of published data from other trials in NASH including LEAN[4], FLINT[7], GOLDEN-505[2] and CENTAUR[1], which involved a range of different drug classes, gives no clear indication of a differential treatment effect according to baseline fibrosis stage. Therefore, the inclusion of subjects with F1 at baseline is not anticipated to impact on the power of achieving the main trial objectives of NN9931-4296.

As stated above sufficient data across fibrosis stages are needed, therefore the aim is to randomise a maximum of approximately 35% subjects with F1.

Exclusion criterion 6: This trial specifically excludes subjects with advanced liver disease i.e. liver cirrhosis as based on liver histology and clinical/biochemical parameters including international normalized ratio (INR) >1.3 (exclusion criterion 6).

INR is the ratio of measured prothrombin time over normal prothrombin time and it evaluates the extrinsic coagulation pathway (vitamin K dependent clotting factors II; V, VII, IX and X). These clotting factors are synthesised in the liver, thus INR is used as a marker of liver synthesis function.[10]

INR can be prolonged due to factors other than decreased liver synthetic function including vitamin K deficiency as seen in the setting of dietary restrictions or malabsorption.[10] Furthermore, INR may be prolonged due to pre-analytical events associated with sample collection and processing. INR analysis is sensitive to under-filling of the collection tube as this cause an increase in the anti-coagulant (in the tube) to blood ratio, which results in a falsely prolonged INR. In addition, INR may be prolonged if centrifugation of the sample is delayed or is too vigorous.[11]
Serum albumin is also a protein that is produced in the liver and therefore serum albumin concentration is also a marker of liver synthesis function. Conjugation of bilirubin takes place in the liver and therefore bilirubin is also a marker of liver function.[10]

To ensure patient safety whilst at the same time avoiding exclusion of subjects that may otherwise be eligible for experimental treatment of a disease with currently no approved treatment options, re-testing of INR is allowed. INR re-testing is allowed once in patients with a normal screening albumin within central laboratory reference range and screening bilirubin below the concentration described in exclusion criterion 5.

Exclusion criterion 9: This is rephrased to emphasize that medication known to affect steatosis is exclusionary. However, allows for short term treatment not evaluated to impact steatosis.

Subjects can be re-screened once within the recruitment period if they have screen failed prior to approval of this global protocol amendment 4 due to: INR eligibility criterion only and/or F1 only.

Other minor changes and clarifications have been included.
Since new references are added, the numbering for references will change throughout the updated protocol once the amendment is implemented.

In this protocol amendment:

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

2 Changes

2.1 Section 1 Summary

Randomisation will be stratified in five strata based on region (Japanese or non-Japanese) and, within the non-Japanse group, based on diabetes status at screening (with or without type 2 diabetes) and fibrosis stage for baseline liver biopsy (*F1/*F2 or F3).

Trial population

A total of *288*~~372~~ subjects are planned to be randomised. Based on an assumption of a 65% screening failure rate, *823*~~1063~~ subjects are planned to be screened.

Key inclusion criteria

- NASH fibrosis stage *1,* 2 or 3 according to the NASH CRN fibrosis staging system based on central pathologist evaluation.

2.2 Section 5.1 Type of trial

A planned total of *288*~~372~~ subjects will be randomised. Based on an assumption of a 65% screening failure rate, *823*~~1063~~ subjects will be screened.

2.3 Section 5.2 Rationale for trial design

Randomisation will be stratified in five strata based on region (Japanese or non-Japanese) and, within the non-Japanese group, based on diabetes status at screening (with or without type 2 diabetes) and fibrosis stage for baseline liver biopsy (*F1*/F2 or F3).

2.4 Section 6.1 Number of subjects

Number of subjects planned to be screened: *823*~~1063~~.

Number of subjects planned to be randomised: *288*~~372~~ (65% screen failure rate).

Number of subjects expected to complete the trial on or off trial product: *259*~~335~~ (10% trial withdrawal rate).

Number of subjects expected to complete the trial on trial product: *245*~~316~~ (15% total trial product discontinuation rate).

The aim is that between 30 and 70% of subjects should have NASH and type 2 diabetes.

To ensure that a sufficient number of subjects with F2 and F3 are included in the trial the aim is to randomise a maximum of approximately 35% subjects with F1.

2.5 Section 6.2 Inclusion criteria

7. NASH fibrosis stage *1,* 2 or 3 according to the NASH CRN fibrosis staging system based on central pathologist evaluation

2.6 Section 6.3 Exclusion criteria

9. Treatment ~~with drugs with potential~~ *or anticipated initiation (for more than 14 consecutive days) of medications known to have an* effect on steatosis~~;~~ *(e.g. treatment with* Corticosteroids (topical and inhaled are allowed), Methotrexate, Tamoxifen, Valproic acid, Amiodarone or Tetracycline*)* in the period from 28 days prior to screening or if recent biopsy is used from 28 days prior to baseline liver biopsy until time of screening.

2.7 Section 6.7 Rationale for trial population

The trial population will consist of patients with NASH and a fibrosis stage of *F1*~~F2~~-F3. Patients with F0 ~~and F1~~ will be excluded as they do not have fibrosis ~~(F0) or are less progressed in the disease spectrum, why less benefit may be achieved on fibrosis (F1)~~. Furthermore, subjects with fibrosis stage 4 (cirrhosis) will be excluded from the trial as an important endpoint addressing worsening in fibrosis cannot be addressed in this population (the Kleiner classification has a maximum score of 4).

2.8 Section 7 Milestones

Planned duration of recruitment period: *103*~~78~~ weeks

2.9 Section 8.1.1 Screening, re-screening and screen failures

Re-screening

Re-screening of screening failures is allowed only once within the limits of the recruitment period. However, re-screening is NOT allowed if the subject has failed one of the inclusion/exclusion criteria related to laboratory parameters (pathology and/or blood parameters). In the event of re-screening, a new informed consent must be obtained and a new subject number must be allocated. All assessments and laboratory samples must be repeated.
For subjects meeting exclusion criterion number 6, re-test of INR is allowed once within the limits of the screening period for that subject. To be eligible for INR re-test the subject must have a screening albumin within central laboratory reference range. Re-test of INR does not require a new informed consent or new subject number.

2.10 Section 11 Randomisation procedure and breaking of blinded codes

Randomisation will be controlled by the IWRS and stratified in five strata defined by region, diabetes status and fibrosis stage for baseline liver biopsy according to the criteria below:

- Japanese

- Non-Japanese, with type 2 diabetes, fibrosis stage *1/*2
- Non-Japanese, with type 2 diabetes, fibrosis stage 3
- Non-Japanese, without type 2 diabetes, fibrosis stage *1/*2
- Non-Japanese, without type 2 diabetes, fibrosis stage 3

2.11 Section 17.1 Sample size calculation

The sample size calculation is based on an aim to detect a difference in the probability of achieving NASH resolution (without worsening in fibrosis) between the highest semaglutide dose and the pooled placebo arm at 5% significance level, using Pearson chi-square test with normal approximation. The power is set to 90%.

It is expected that some subjects will respond to standard care. In the LEAN trial, 2 (9%) of 22 placebo subjects had improvement in liver histology. In the FLINT[56] and PIVENS[57] trials, clearance of NASH was a secondary endpoint and the corresponding numbers were 13 (13%) of 98 subjects and 17 (21%) of 83 subjects, respectively. However, these figures also included patients that had worsening of fibrosis. *In the more recent trials, CENTAUR[58] and GOLDEN-505[59] , the numbers were 9 (7%) of 126 subjects and 11 (14%) of 77 subjects, respectively, for an endpoint that was defined in the same way as the primary endpoint in the present trial.* As a conservative assumption, it is anticipated that up to *17*~~20~~% of the placebo completers will achieve resolution of NASH with no worsening of fibrosis.

It is uncertain how many subjects on semaglutide should be expected to achieve resolution of NASH. In the LEAN trial, an improvement was found in 9 (39%) of 23 subjects who received liraglutide 1.8 mg. *Results from semaglutide trials in subjects with T2D and/or obesity suggest a greater effect of semaglutide on glycaemic control and body weight loss compared to liraglutide.* In communication with medical advisers, a treatment difference of 20-30 percentage points was deemed to be a realistic target as well as clinically relevant. Therefore, it is assumed that 45% of the subjects who complete treatment with semaglutide 0.4 mg achieve resolution of NASH.

Based on the previous NASH trials, 15% of the randomised subjects are anticipated to prematurely discontinue trial product before week 72. These will be included in the main analysis either by using the observed outcome at week 72 (if the outcome is known) or by using imputation (if the outcome is not known). In either case, it is assumed that none of these subjects will achieve resolution of NASH.

Based on the assumptions above, the required number of randomised subjects per arm for the 3 semaglutide arms and the pooled placebo arm is found to be *70*~~91~~. Since the number in the pooled placebo arm needs to be divisible by 3, the number of subjects in each arm is adjusted to *72*~~93~~. Hence, the total number of subjects to be randomised is *288*~~372~~.

In order to investigate the influence of the values of the model parameters such as treatment difference and rate of premature discontinuation of trial product on the calculation, sample sizes have been calculated for different alternative scenarios. The results can be seen in Table 17-1.

Table 17-1 Sample size calculations for different scenarios - number of subjects per arm

Probability of achieving resolution of NASH			
Semaglutide completers	Placebo completers	Rate of premature discontinuation	N per arm
50%	*17~~20~~%*	10%	*49~~61~~*
		15%	*53~~66~~*
		20%	*58~~72~~*
45%	*17~~20~~%*	10%	*65~~84~~*
		15%	*70~~91~~*
		20%	*77~~99~~*
40%	*17~~20~~%*	10%	*92~~126~~*
		15%	*99~~137~~*
		30%	*108~~176~~*

2.12 Section 17.3 Primary endpoint

The primary endpoint is the binary outcome NASH resolution without worsening in fibrosis after 72 weeks (yes/no).The primary analysis will be based on the Cochran-Mantel-Haenszel (CMH) test[59] which will be performed separately for the comparisons between each of the semaglutide arms and placebo. The test will adjust for baseline diabetes status (with or without T2D) and baseline fibrosis stage (*F1*, F2 or F3).

2.13 Section 27 References

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Protocol Amendment

no 5 to
Protocol, final version 1.0 dated 20 June 2016 and
Global protocol amendment number 1, version 1.0, dated 26 August 2016 and
Global protocol amendment number 2, version 1.0, dated 29 November 2016

Trial ID: NN9931-4296

Investigation of efficacy and safety of three dose levels of subcutaneous semaglutide once daily versus placebo in subjects with non-alcoholic steatohepatitis

Trial phase: 2

Applicable to Sweden

Amendment originator:

[redacted] Local Trial Manager

Novo Nordisk Scandinavia AB, Sweden

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1 Introduction including rationale for the protocol amendment

The below changes to liver biopsy assessment, bilirubin, HbA_{1c} and BMI are implemented in the trial protocol based on detailed and continuous monitoring of the progress of the current trial, in addition to scientific developments in the field of non-alcoholic steatohepatitis (NASH). This combined with the continuous accumulation of semaglutide safety and efficacy data is the reason behind this protocol amendment. The changes are in accordance with advice from external NASH experts and recommendations from the Liver Forum (forum for collaboration between academia, industry and Health Authorities on clinical development in NASH). As the field of NASH is quickly evolving, including an increasing number of clinical trials, the described changes should also lead to an improvement in the rate of recruitment.
This local Swedish protocol amendment is following the global protocol amendment that was submitted to the authorities in Sweden earlier. Medical Product Agency did not agree with two of changes (TSH in screening and pre-screening process) and the amendment was rejected. These changes are changed back to their original now in this amendment. The other changes that were not reason for rejection by the Medical Product Agency are included as it was submitted earlier.

Number of subjects to be screened:

The expected screen failure rate and hence planned number of screened subjects are updated based on actual numbers seen in the trial.

Eligibility criteria:

Inclusion criterion 5: This criterion is rephrased to emphasize that eligibility is solely based on central pathologist assessment of the baseline liver biopsy. This will not change how patients are entering the trial and is in line with eligibility criteria for ongoing global NASH trials[1, 2].

Exclusion criterion 5: Gilbert's syndrome is a common form of unconjugated hyperbilirubinemia caused by an inherited deficiency in the bilirubin-conjugating enzyme. The condition is highly prevalent ranging from 3% to 12% of the population depending on the mode of diagnosis[3]. A small study of patients with NASH reported a prevalence of Gilbert's syndrome of 7.5%[4]. Gilbert's syndrome is, however, regarded a benign trait, and clinical recognition is often incidental to routine laboratory investigations, revealing an elevated level of total bilirubin. Thus, exclusion criterion 5 will be changed to allow subjects into the trial with total bilirubin level >1.5 mg/dL if conjugated bilirubin is <1.5×upper limit of normal.

Exclusion criterion 10 and 12: Exclusion criterion 10 is being amended to allow patients in with HbA_{1c} of up to 10% to allow a slightly broader population, including more patients with type 2 diabetes to enter the trial. Given that the current trial is placebo-controlled and of long duration, the responsibility of the investigator to ensure glycaemic control of the patients will be reinforced by

adding guidance to treatment of patients with type 2 diabetes with poorly controlled glycaemia to the protocol.

A significant proportion of patients with NASH and type 2 diabetes is treated with bolus insulin. To allow for these patients to enter the trial, exclusion criterion 12 will be deleted. In order to mitigate the risk of hypoglycaemia, the protocol is amended to instruct the total daily insulin dose to be reduced by 30% at baseline in subjects with $HbA_{1c} \leq 8.0\%$ at the screening visit.

Exclusion criterion 15: Exclusion criterion 15 will be amended by removing the upper limit of BMI in order to allow patients with a BMI ≥ 45 kg/m^2 to be included in the trial.

The prevalence of non-alcoholic fatty liver disease (NAFLD) and NASH increases with increasing body mass index (BMI). An analysis of liver histology obtained from liver donors, autopsy findings, and clinical liver biopsies suggests that the prevalence rates of steatosis and NASH are approximately 15% and 3%, 65% and 20% and 85% and 40% respectively in non-obese, BMI 30.0–39.9 kg/m^2 and BMI ≥ 40 kg/m^2 subjects[5].

The recently completed semaglutide obesity trial, trial NN9536-4153, which included patients with a BMI > 30 kg/m^2 and investigated the same dose range as the current trial (0.05-0.4 mg/day), reported that the semaglutide safety profile was well-tolerated, with the most common adverse events being gastrointestinal (GI) adverse events[6]. This is in line with the previous experience with semaglutide[7].

Subjects can be re-screened if they have previously screen failed solely due to lab parameters included in the eligibility criteria that are changed in this amendment (HbA_{1c}, total bilirubin).

Footnote to primary end-point:

The first footnote (*) of the primary endpoint has been updated to clarify that resolution of NASH is defined as “no more than mild residual inflammatory cells (0 – 1) and no ballooning (0)”. This is in line with the Health Authority recommendation (FDA and EMA) as communicated through the Liver Forum[11].

Other minor changes and clarifications have been included.
Since new protocol sections are added, the numbering for some protocol sections will change throughout the updated protocol once the amendment is implemented.

In this protocol amendment:

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

2 Changes

2.1 List of abbreviations

TSH ***(Applicable for Sweden)*** thyroid-stimulating hormone

2.2 Section 1 Summary

Trial population

A total of 372 subjects are planned to be randomised. Based on an assumption of a *65*~~50~~% screening failure rate, *1063*~~744~~ subjects are planned to be screened.

Key inclusion criteria

- 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 *except for protocol described pre-screening activities which require a separate informed consent*.

  Applicable for Sweden: *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.*

- ~~Local histological diagnosis of NASH followed by histological confirmation of NASH based on central pathologist evaluation of~~ *Histologic evidence of NASH based on central pathologist evaluation of* a liver biopsy obtained up to 21 weeks before screening.

Key exclusion criteria

- HbA1c > ~~9~~*10* % at screening.
- Body Mass Index (BMI) ≤ 25.0 ~~or ≥ 45.0~~ kg/m^2 at the screening visit *(visit 1)*.

2.3 Section 2 Flowchart

TSH ***(Sweden only)***

Attend visit fasting: *Added x for visit 10*

16) All visit 2 assessments must be carried out prior to first trial product dose

2.4 Section 4.2.1 Primary endpoint

- NASH resolution* without worsening of fibrosis** after 72 weeks (yes/no)

**) Resolution of NASH defined by the NASH Clinical research network (CRN) as "no more than mild residual inflammatory cells (0 – 1) and no ballooning (0)" based on comprehensive interpretation by two independent pathologists (central reading) blinded to treatment allocation.*

~~*) Resolution of NASH as defined by comprehensive interpretation by two independent pathologists (central reading) blinded to treatment allocation and with complete resolution captured by terms such as "no fatty liver disease" or "simple steatosis or isolated steatosis" and defined by the NASH Clinical research network (CRN) as "no more than mild residual inflammatory cells and no ballooning"~~

**) worsening defined by an increase of at least one stage of the Kleiner fibrosis classification

2.5 Section 4.2.2.2 Supportive secondary safety endpoints

Change from baseline to 72 weeks in:

- Pulse
- ECG
- Physical examination
- Haematology (haemoglobin, haematocrit, thrombocytes, erythrocytes, leucocytes, differential count)
- Biochemistry (creatinine, estimated glomerular filtration rate (eGFR), creatin~~in~~e phosphokinase, urea, bilirubin (total), alkaline phosphatase, ferritin, sodium, potassium, calcium (total), amylase, lipase)
- Hormones (calcitonin)

2.6 Section 5.1 Type of trial

A planned total of 372 subjects will be randomised. Based on an assumption of a *65*~~50~~% screening failure rate, *1063*~~744~~ subjects will be screened.

2.7 Section 5.3 Treatment of subjects

The conversion table below shows the connection between each volume matched dose level and the value shown in the display on the NovoPen® 4. Subjects must be instructed to administer the value shown in the display.

Injections may be administered in the thigh, abdomen or upper arm, at any time of day irrespective of meals. The injections should be administered at approximately the same time of day during the trial.

Throughout the trial subjects cannot initiate treatment with:

- GLP-1 RAs (other than trial product)~~,~~ *or* SGLT-2 inhibitors ~~and bolus (fast-acting) insulin~~
- Vitamin E or pioglitazone
- Drugs with potential effect on steatosis (corticosteroids (topical, ~~and~~ 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).

2.8 Section 5.3.1 Subjects treated with ~~basal~~ insulin

~~The following basal insulins are allowed:~~

- ~~Insulin glargine~~
- ~~Insulin detemir~~
- ~~Insulin degludec~~
- ~~Neutral protamine Hagedorn (NPH) insulin~~

~~Subjects treated with basal 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 ~~basal~~ insulin *and* ~~with~~ $HbA_{1c} \leq 8.0$ % at screening:
Subjects with $HbA_{1c} \leq 8.0$ % at screening (visit 1) should have the *total daily* insulin dose reduced by 30 % at start of trial product treatment to limit the potential risk of hypoglycaemia induced by the combination of insulin and semaglutide.

2.9 New section: *5.3.2 Treatment of subjects with poorly controlled glycaemia*

Subjects with type 2 diabetes and with persistent and unacceptable hyperglycaemia should be offered treatment intensification. If any HbA_{1c} value reported by central laboratory exceeds 9% from at least 4 weeks after end of dose escalation, the subject should be offered treatment intensification at the discretion of the investigator. However, the following treatment types must not be used: GLP-1 RAs (other than trial product) and SGLT-2 inhibitors. Subjects that are started on treatment intensification medication should continue to follow the protocol specified visit schedule

and stay on trial product treatment unless the investigator judges that this will jeopardise the safety of the subject.

All treatment intensification medication given should be documented in medical records and reported in the eCRF. Treatment intensification medication will not be provided nor reimbursed by Novo Nordisk.

2.10 Section 5.3.~~2~~*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 at the discretion of the investigator. However the following treatments must not be used: GLP-1 RAs (other than trial product)~~,~~ *and* SGLT-2 inhibitors ~~and bolus (fast-acting) insulin~~.

5.3.~~3~~*4* Missed dose

5.3.~~4~~*5* Nutritional and physical activity counselling

2.11 Section 6.1 Number of subjects

Number of subjects planned to be screened: ~~744~~ *1063*.

Number of subjects planned to be randomised: 372 (~~50~~ *65*% screen failure rate).

2.12 Section 6.2 Inclusion criteria

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 *except for protocol described pre-screening activities which require a separate informed consent*.

Applicable for Sweden*: 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.*

5. ~~Local histological diagnosis of NASH followed by histological confirmation of NASH based on central pathologist evaluation of~~ *Histologic evidence of NASH based on central pathologist evaluation of* a liver biopsy obtained up to 21 weeks before screening.

2.13 Section 6.3 Exclusion criteria

5. Elevated total bilirubin (> 1.5 mg/dL) at screening. T*otal bilirubin level >1.5 mg/dL is allowed if conjugated bilirubin is <1.5×UNL.*

6. ~~Prothrombin time~~ *International normalized ratio* (INR) *of prothrombin time* > 1.3 at screening.

10. HbA1c > ~~9~~*10* % at screening.

~~12. Treatment with bolus (fast-acting) insulin in the period from 28 days prior to screening or if recent biopsy is used from 28 days prior to baseline liver biopsy until time of screening.~~

~~13~~*12*. Treatment with other glucose lowering agent(s) (apart from *GLP-1 RAs or SGLT-2 inhibitors* ~~what is listed in exclusion criterion 11 and 12~~) not stable in the period from 28 days prior to screening or if recent biopsy is used from 28 days prior to baseline liver biopsy until time of screening. Changes without clinical relevance in the opinion of the investigator are allowed.

~~14~~*13*. Diagnosis of type 1 diabetes according to medical records.

Obesity related:

~~15~~*14*. Body Mass Index (BMI) ≤ 25.0 ~~or ≥ 45.0~~ kg/m^2 at the screening visit (visit 1).

~~16. TSH > 6 mIU/L or < 0.4 mIU/L at screening.~~

~~17~~*15*. Treatment with orlistat, zonisamide, topiramate, phentermine, lorcaserin, bupropion and naltrexone alone or in combination or any other medication that could promote weight loss in the opinion of the investigator in the period from 28 days prior to screening or if recent biopsy is used from 28 days prior to baseline liver biopsy until time of screening.

~~18~~*16*. Participation in an organised weight reduction program (e.g. WeightWatchers®) in the period from 28 days prior to screening or if recent biopsy is used from 28 days prior to baseline liver biopsy until time of screening.

~~19~~*17*. Previous surgical treatment for obesity. However (1) liposuction and/or abdominoplasty if performed > 6 months before baseline liver biopsy is allowed or 2) lap banding where the band has been removed > 6 months before baseline liver biopsy is allowed 3) intragastric balloon where the balloon has been removed > 6 months before baseline liver biopsy is allowed.

General safety:

~~20~~*18*. For patients with type 2 diabetes only: Proliferative retinopathy or maculopathy requiring acute treatment verified by fundus photography or dilated fundoscopy performed within the past 90 days prior to randomisation.

~~21~~*19*. History or presence of pancreatitis (acute or chronic).

~~22~~*20*. Calcitonin ≥ 50 ng/L at screening.

~~23~~*21*. Family or personal history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma. Family is defined as a first degree relative.

~~24~~*22*. Presence or history of malignant neoplasms within the past 5 years prior to the day of screening. Basal and squamous cell skin cancer and any carcinoma in-situ are allowed.

~~25~~*23*. Surgery scheduled for the trial duration period, except for minor surgical procedures, in the opinion of the investigator.

~~26~~*24*. Any condition which, in the investigator's opinion might jeopardise subject's safety or compliance with the protocol.

~~27~~*25*. Language barrier, mental incapacity, unwillingness or inability to adequately understand or comply with study procedures.

~~28~~*26*. Known or suspected hypersensitivity to trial product or related products.

~~29~~*27*. Previous participation in this trial. Participation is defined as randomisation.

~~30~~*28*. Participation in any clinical trial of an approved or non-approved investigational medicinal product within 90 days before screening.

~~31~~*29*. Female who is pregnant, breast-feeding or intends to become pregnant or is of childbearing potential and not using an adequate contraceptive method (adequate contraceptive measures as required by local regulation or practice).

For EU countries: The following contraceptive measures are considered adequate:

- Combined estrogen and progestogen containing hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation :
  - oral
  - injectable
  - implantable
- Placement of an
  - intrauterine device (IUD)
  - intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Barrier methods of contraception (condom or occlusive cap with spermicidal foam/gel/film/cream/suppository) (**not applicable for Belgium, Denmark, Finland, Greece, Spain, Sweden**)
- Vasectomised partner (where partner is sole partner of subject) (**not applicable for Denmark**)

- True sexual abstinence (**not applicable for Denmark**). Sexual abstinence is defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

~~32~~*30*. Renal impairment measured as estimated Glomerular Filtration Rate (eGFR) value of eGFR < 30 ml/min/1.73 m2 as defined by Kidney Disease: Improving Global Outcomes (KDIGO).42

31. ***Applicable for Sweden:*** *TSH > 6 mIU/L or < 0.4 mIU/L at screening.*

2.14 Section 6.4 Criteria for premature discontinuation of trial product

10. Treatment with other GLP-1 receptor agonists *or*~~,~~ SGLT-2 inhibitors ~~or bolus (fast-acting) insulin~~

2.15 Section 7 Milestones

Planned duration of recruitment period: *78* ~~51~~ weeks

2.16 Section 8.1.1 Screening, Re-screening and screen failures

Informed consent must be obtained before any trial related activity, see section 18.2. Separate informed consent forms for long-term storage of human samples and genotyping are available and informed consent must be obtained before activities related to any of these are undertaken.

Additionally a separate informed consent form for optional pre-screening is available. This must be signed before any optional pre-screening activities are performed (see section 8.1.2).

Re-screening

Re-screening of screening failures is allowed only once within the limits of the recruitment period. However, re-screening is NOT allowed if the subject has failed one of the inclusion/exclusion criteria related to laboratory parameters (*pathology and/or blood parameters* ~~histological NAS, NASH fibrosis stage, HBsAg, anti HIV, HCV-RNA, AST, ALT, total bilirubin, INR, HbA1c, calcitonin or TSH~~). In the event of re-screening, a new informed consent must be obtained and a new subject number must be allocated. All assessments and laboratory samples must be repeated.

2.17 New section: *8.1.2 Optional pre-screening (Not applicable for Sweden)*

The Investigator may, after obtaining separate informed consent, perform pre-screening of potential trial candidates. Pre-screening assessments include blood parameters and imaging (except for imaging methods with radiation involved).The purpose of such assessments is to assess trial eligibility potential.

Pre-screening assessments are not defined as trial-related procedures. Results of pre-screening assessments will not be collected in the trial database and will not be monitored. Concerns related to any pre-screening assessment must not be reported as an adverse event.

Pre-screening assessments (blood parameters and imaging) performed after signature of the separate informed consent can be reimbursed by Novo Nordisk A/S.

8.1.~~2~~*3* AUDIT questionnaire

2.18 Section 8.1.~~3~~*4* Fasting visits

Subjects must attend ~~some of the~~ *most* clinic visits in a fasting state (see section 2).

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 blood sampling has been performed. 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. Fasting procedures include body weight, Fibroscan® measurements and blood sampling *(FPG, fasting insulin, fasting glucagon, calcitonin and lipids (Total cholesterol, free fatty acids, HDL cholesterol, LDL cholesterol, triglycerides, VLDL cholesterol))*.

Prior to Fibroscan® measurements, only two hours of fasting is required.

At visit 19, the subject must be fasting for two hours prior to the anti-semaglutide antibody sampling (see section 8.5.3.7).

8.1.4*5* Missed visits

8.1.~~5~~*6* Premature discontinuation of trial product

8.1.~~6~~*7* Withdrawn subjects

8.1.~~7~~*8* Subject training

2.19 Section 8.3.1 Liver biopsy

To be randomised, subjects must have *histologic evidence of NASH* ~~a local histological diagnosis of NASH followed by histological confirmation of NASH diagnosis~~ based on central pathologist evaluation of a liver biopsy. ~~Confirmation of~~ *Histologic evidence of* NASH ~~diagnosis~~ can be based on a liver biopsy obtained up to 21 weeks prior to screening. For subjects with no historical liver biopsy within 21 weeks prior to screening, a liver biopsy must be performed during the screening period. ~~The local NASH diagnosis and the confirmation~~ *The histologic evidence* of NASH ~~diagnosis~~ by central pathologist evaluation of the liver biopsy must be available prior to randomisation of the

subject. ~~The local NASH diagnosis and the confirmation of NASH diagnosis by central pathologist evaluation can be done on the same liver biopsy sample.~~

2.20 Section 8.3.1.1 Central pathologist evaluation

The *histologic evidence of* NASH ~~diagnosis~~ and histology based scores will be centrally assessed by two independent pathologists with expertise and experience in NASH.

2.21 Section 8.3.2 Fibroscan measurements

Liver stiffness

At sites with Fibroscan® equipment available, measurements of liver stiffness must be performed at the specified visits (section 2). *Fibroscan measurements can be performed up to 2 weeks prior to each visit.*

Liver steatosis

At sites with Fibroscan® equipment available, measurements of liver steatosis must be performed at the specified visits (section 2). *Fibroscan measurements can be performed up to 2 weeks prior to each visit.*

2.22 Section 8.3.3.3 Body mass index

Body mass index will be calculated by the eCRF from visit 1 height data and must be in accordance with exclusion criterion ~~15~~*14*.

2.23 Section 8.5 Laboratory assessments

The laboratory analyses will be performed by a central laboratory except for *laboratory analyses for pre-screening*, analysis of anti-semaglutide antibodies and semaglutide plasma concentration analysis and some exploratory biomarkers which will be performed at specialised laboratories.

2.24 Section 8.5.3.1 Biochemistry

- Bilirubin, total
- *Bilirubin, conjugated*
- Calcium
- Creati~~ni~~ne phosphokinase
- Creatinine
- eGFR (per CKD-EPI formula)
- Lipase
- Potassium
- Sodium

- Alkaline phosphatase
- Amylase
- Albumin
- Ferritin
- Urea
- MELD score

2.25 Section 8.5.3.2 Hormones

- Calcitonin (see Appendix A)
- ***For Sweden:*** *Thyroid-stimulating hormone (TSH)*

2.26 Section 17.4.1.2 Safety endpoints

- Change from baseline to 72 weeks in:
  - Pulse
  - ECG
  - Physical examination
  - Haematology (haemoglobin, haematocrit, thrombocytes, erythrocytes, leucocytes, differential count)
  - Biochemistry (creatinine, eGFR, creatin~~in~~e phosphokinase, urea, bilirubin (total), alkaline phosphatase, ferritin, sodium, potassium, calcium (total), amylase, lipase)
  - Hormones (calcitonin)

2.27 Section 18.1 Benefit-risk assessment of the trial

Other safety considerations

Teratogenicity (nonclinical embryo-foetal toxicity)

Semaglutide has been concluded teratogenic in rats. This effect is regarded to be caused by impairment of nutrient supply to the embryo across the inverted yolk sac with placental function. As the yolk sac does not play such a role for nutrition of the embryo in humans, this effect is unlikely to be relevant for humans. However, as a precaution subjects fulfilling exclusion criterion ~~31~~*29* will be excluded from trial participation. Furthermore, as specified in the flowchart, female subjects included in the trial will have pregnancy testing performed frequently during the entire duration of the trial.

2.28 Section 18.2 Informed consent

Separate informed consent forms for long-term storage of human samples and genotyping are available and informed consent must be obtained before activities related to any of these are undertaken.

Additionally a separate informed consent form for optional pre-screening is available. This must be signed before any optional pre-screening activities are performed (see section 8.1.2).

3 References

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