Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
NCT number	NCT03689374
Sponsor trial ID:	NN9535-4386
Official title of study:	Effect of semaglutide once-weekly versus insulin aspart three times daily, both as add on to metformin and optimised insulin glargine (U100) in subjects with type 2 diabetes A 52-week, multi-centre, multinational, open-label, active-controlled, two armed, parallel-group, randomised trial in subjects with type 2 diabetes
Document date*:	08 July 2020

*Document date refers to the date on which the document was most recently updated.
Note: The date in the header of Page 2 is the date of compilation of the documents and not of an update to content.

16.1.1 Protocol and protocol amendments

List of contents

Redacted protocol
Includes redaction of personal identifiable information only.

.

Protocol

Protocol title:

SUSTAIN 11

Effect of semaglutide once-weekly versus insulin aspart three times daily, both as add on to metformin and optimised insulin glargine (U100) in subjects with type 2 diabetes

A 52-week, multi-centre, multinational, open-label, active-controlled, two armed, parallel-group, randomised trial in subjects with type 2 diabetes

Substance: Semaglutide

Universal Trial Number: U1111-1200-0164

EUdraCT Number: 2017-003219-20

Trial phase: 3b

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

Protocol amendment summary of changes table

DOCUMENT HISTORY		
Document version	Date	Applicable in country(ies) and/or site(s)
Protocol version 3.0	08 Jul 2020	Germany
Protocol version 2.0	09 May 2018	All countries
Original protocol version 1.0	09 Jan 2018	All countries

Protocol version 3 (08-Jul-2020)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union[38].

Overall rationale for preparing protocol, version 3:

Is to accommodate the requirements provided by the German health authorities of implementing the precautionary measures set out by Novo Nordisk to ensure subject safety, trial integrity, and the safety of Novo Nordisk and site staff during the COVID-19 pandemic.
These measures will ensure data validity and regulatory requirements by alternative methods for collection of data for primary endpoint, patient safety by conversion of site visit to phone contact, ensuring alternative trial product dispensing and extending visit window on trial specific safety assessments i.e. eye examination.

Section # and name	**Description of change**	**Brief rationale**
Appendix 9, Country specific requirements	Updated with safety measures and other initiatives to protect subjects from immediate hazard due to the COVID-19 Pandemic.	As a response to the COVID-19 pandemic, Sponsor has provided the involved German sites with a set of guidelines in order to support the sites in handling patient safety and trial integrity during the pandemic. The guidelines are to assist the site in managing trial supplies to patients and collection of endpoint related data. The mitigating actions should only be used during the pandemic and if normal trial procedures cannot be followed due to epidemiological restrictions.

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1 Synopsis

Rationale:

Semaglutide may provide an efficacious, safe and simple alternative to bolus insulin for advancing basal insulin regimen in patients with late stage type 2 diabetes, with lower risk of hypoglycaemia and weight gain. The purpose of the current trial is to compare the effect on glycaemic control, body weight, safety (hypoglycaemia) and health-related quality of life of semaglutide versus insulin aspart, both as add-on to metformin and optimised insulin glargine (U100) treatment in subjects with inadequately controlled type 2 diabetes.

Objectives and endpoints

Primary objective

To compare the effect of semaglutide once-weekly on glycaemic control versus insulin aspart three times daily, both as add on to metformin and optimised insulin glargine (U100) in subjects with type 2 diabetes.

Secondary objectives

To demonstrate that semaglutide once-weekly lowers the risk of severe hypoglycaemic episodes compared to insulin aspart three times daily, both as add on to metformin and optimised insulin glargine (U100) in subjects with type 2 diabetes.

To compare the effect of semaglutide once-weekly versus insulin aspart three times daily, both as add on to metformin and optimised insulin glargine (U100) in subjects with type 2 diabetes with regards to:

- body weight
- lipids
- blood pressure
- health-related quality of life
- safety

Primary endpoint

Change from baseline to week 52 in HbA_{1c} (%-point)

Key secondary endpoints

Confirmatory secondary endpoints

- Time to first event adjudication committee confirmed severe hypoglycaemic episode (American Diabetes Association) from randomisation up to week 52 (days)

- Time to first event adjudication committee confirmed severe hypoglycaemic episode (American Diabetes Association) requiring hospitalisation, documented medical help, or is life threatening from randomisation up to week 52 (days)
- Change from baseline to week 52 in body weight (kg)

Estimand

The primary estimand is the treatment difference between semaglutide and insulin aspart at week 52 for all randomised subjects if all subjects remained on randomised treatment throughout the trial
Overall design:

This is a 52-week, multi-centre, multinational, open-label, active controlled, two armed, parallel, randomised trial with a 12-week run-in period in subjects with type 2 diabetes to secure a direct comparison between semaglutide once-weekly and insulin aspart three times daily.

At run-in, eligible subjects will discontinue pre-trial basal insulin and the additional oral antidiabetic drug (if applicable, including conversion from fixed drug combination medications with metformin to metformin only) and start treatment with insulin glargine U100.

Subjects treated with metformin and insulin glargine U100, who are not in glycaemic control (defined as HbA_{1c} of > 7.5% to ≤ 10% [> 58 mmol/mol to ≤ 86 mmol/mol]) after run-in, will be randomised in a 1:1 manner to receive add-on treatment with following treatments:

- semaglutide once-weekly
- insulin aspart three times daily

Key inclusion criteria

- Male or female, age ≥ 18 years at the time of signing informed consent.
- Diagnosed with type 2 diabetes ≥ 180 days prior to the day of screening.
- Treated with basal insulin once daily or twice daily for ≥ 90 days prior to the day of screening.
- Stable daily dose for 90 days prior to the day of screening of the following anti-diabetic drugs or combination regimens: Any metformin formulations (≥ 1500 mg to ≤ 3000 mg or maximum tolerated or effective dose documented in subject's medical record), alone or in combination (including fixed-dose drug combination) with up to one additional of the following oral antidiabetic drugs: sulfonylureas, meglitinides, dipeptidyl peptidase-4inhibitors or alpha-glucosidase inhibitors.
- HbA_{1c} of > 7.5% to ≤ 10.0% (>58 mmol/mol to ≤ 86 mmol/mol).

Key exclusion criteria

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

- Any of the following: myocardial infarction, stroke, hospitalization for unstable angina or transient ischaemic attack within the past 180 days prior to the day of screening.
- Subjects presently classified as being in New York Heart Association Class IV.
- Planned coronary, carotid or peripheral artery revascularisation known on the day of screening.
- Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria within the past 90 days prior to the day of screening. However, short term bolus insulin treatment for a maximum of 14 days prior to the day of screening is allowed.
- Uncontrolled and potentially unstable diabetic retinopathy or maculopathy. Verified by a pharmacologically pupil-dilated fundus examination performed by an ophthalmologist or an equally qualified health care provider (e.g. optometrist) within the past 90 days prior to run-in.

Randomisation criteria

To be randomised, all randomisation criteria must be answered "yes".

- HbA_{1c} of >7.5% to ≤10.0% (>58 mmol/mol to ≤86 mmol/mol) measured at V7.
- Treated with insulin glargine U100 and metformin (≥ 1500 mg to ≤ 3000 mg or maximum tolerated dose documented in subject's medical record) at randomisation (V8).
- The need and willingness to undergo treatment intensification with the treatments investigated in this trial with the aim to reach an HbA_{1c} of 6.5% to 7.5% (48 mmol/mol to 58 mmol/mol) (both inclusive), as assessed by the investigator at randomisation (V8).
- Absence of uncontrolled and potentially unstable diabetic retinopathy or maculopathy. Verified by a pharmacologically pupil-dilated fundus examination performed by an ophthalmologist or an equally qualified health care provider (e.g. optometrist) within 30 days prior to randomisation.

Number of subjects:

- Number of subjects planned to be screened: 3144
- Number of subjects planned to enter-run-in period: 2043
- Number of subjects planned to be randomised: 1736

Treatment group and duration:

The total duration of the trial will be approximately 71 weeks: 2 weeks for screening, a 12-week run-in period, a 52-week treatment period and a follow-up period of 5 weeks.

Trial products:

Investigational medicinal products:

- Insulin glargine (Lantus®) 100 U/mL, 3 mL pre-filled pen-injector (SoloStar®).
- Test product:
  - Semaglutide 1.34 mg/ml, 1.5 mL PDS290 pre-filled pen-injector for s.c. injection.
- Reference therapy:
  - Insulin aspart (NovoRapid®/NovoLog®)100 U/mL, 3 ml pre-filled pen –injector (FlexPen®).

2 Flowchart

	Screening	Run-in					Randomisation	Treatment																			End of treatment	Treatment discontinuation	Follow-up	Treatment discontinuation F-u
Visit (V)/phone contact (P)	V1	V2	P3	V4	P5 P6	V7	V8	P9 P10 P11	V12	P13	V14	P15	V16	P17	V18	P19 P20	V21	P22 P23	V24	P25 P26	V27	P28 P29	V30	P31 P32	V33	P34 P35	V36	V36A	P37	P37A
Timing of Visit (weeks)	-14	-12	- 10	-8	-6 -4	-2	0	1 2 3	4	6	8	10	12	14	16	18 20	22	24 26	28	30 32	34	36 38	40	42 44	46	48 50	52		57	
Visit Window (days)	±7	±3	±3	±3	±3	±3	0	±3	±7	±3	±7	±3	±7	±3	±7	±3	±7	±3	±7	±3	±7	±3	±7	±3	±7	±3	±7		+7	
SUBJECT RELATED INFORMATION AND ASSESSMENTS																														
Informed consent	X																													
In/exclusion criteria	X	X																												
Run-in exclusion criteria			X	X	X	X	X																							
Randomisation criteria							X																							
Randomisation							X																							
Discontinuation Criteria								X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Rescue criteria								X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Concomitant illness	X																													
Medical history	X																													
Diagnosis of diabetes	X																													
Diabetes history and complications	X																													

	Screening	Run-in					Randomisation	Treatment																			End of treatment	Treatment discontinuation	Follow-up	Treatment discontinuation F-U
Visit (V)/phone contact (P)	V1	V2	P3	V4	P5 P6	V7	V8	P9 P10 P11	V12	P13	V14	P15	V16	P17	V18	P19 P20	V21	P22 P23	V24	P25 P26	V27	P28 P29	V30	P31 P32	V33	P34 P35	V36	V36A	P37	P37A
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Visit Window (days)	±7	±3	±3	±3	±3	±3	0	±3	±7	±3	±7	±3	±7	±3	±7	±3	±7	±3	±7	±3	±7	±3	±7	±3	±7	±3	±7		+7	
Hypoglycaemia unawareness[a]	X																										X	X		
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Tobacco use[b]	X																													
Demography[c]	X																													
Childbearing potential	X																													
EFFICACY																														
Self-measured plasma glucose[d]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Glucose metabolism																														
HbA_{1c}	X					X	X		X		X		X		X				X				X				X	X		
Fasting plasma glucose							X		X		X		X		X				X				X				X	X		

[a] Information on hypoglycaemia unawareness will be recorded at screening according to Clarke's questionnaire, question 8.[1]. Clarke WL, Cox DJ, Gonder-Frederick LA, Julian D, Schlundt D, Polonsky W. Reduced awareness of hypoglycemia in adults with IDDM. A prospective study of hypoglycemic frequency and associated symptoms. Diabetes Care. 1995;18(4):517-22. The investigator must ask the subject in the following way: "Have you ever experienced a low blood glucose?" If answer is "Yes" then following question should be asked: "To what extent can you tell by your symptoms that your blood glucose is low?" Subjects answering 'never, rarely or sometimes' are considered as having impaired awareness of hypoglycaemia.

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

[c] Demography: date of birth or year of birth, sex, ethnicity and race (according to local regulation)

[d] Pre-breakfast SMPG from V2 to V36/V36A: All subjects. Pre-lunch, pre-dinner and pre-bedtime SMPG from V8 to V36/V36A: 4 point SMPG profile for subjects randomised to IAsp only.
-7 point SMPG profile at V8, V24, V36/V36A: All subjects

	Screening	Run-in					Randomisation	Treatment																			End of treatment	Treatment discontinuation	Follow-up	Treatment discontinuation F/U
Visit (V)/phone contact (P)	V1	V2	P3	V4	P5 P6	V7	V8	P9 P10 P11	V12	P13	V14	P15	V16	P17	V18	P19 P20	V21	P22 P23	V24	P25 P26	V27	P28 P29	V30	P31 P32	V33	P34 P35	V36	V36A	P37	P37A
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Visit Window (days)	±7	±3	±3	±3	±3	±3	0	±3	±7	±3	±7	±3	±7	±3	±7	±3	±7	±3	±7	±3	±7	±3	±7	±3	±7	±3	±7		+7	
Lipids							X												X								X	X		
Patient reported outcomes																														
SF-36v2™							X												X								X	X		
DQLCTQ-R							X												X								X	X		
TRIM-D							X												X								X	X		
Body measurements																														
Height							X																							
Body weight							X		X		X		X		X				X				X				X	X		
Waist Circumference							X												X								X	X		
SAFETY																														
Adverse events		X	X	X	X	X	X	X	X	X	X	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	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	X	X	X	X	X	X	X	X	X	X	X		
Physical examination	X																										X	X		
Vital signs	X						X												X				X				X	X		

	Screening	Run-in					Randomisation	Treatment																		End of treatment	Treatment discontinuation	Follow-up	Treatment discontinuation F/U
Visit (V)/phone contact (P)	V1	V2	P3	V4	P5 P6	V7	V8	P9 P10 P11	V12	P13	V14	P15	V16	P17	V18	P19 P20	V21	P22 P23	V24	P25 P26	V27	P28 P29	V30	P31 P32	V33	P34 P35	V36	V36A	P37	P37A
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Visit Window (days)	±7	±3	±3	±3	±3	±3	0	±3	±7	±3	±7	±3	±7	±3	±7	±3	±7	±3	±7	±3	±7	±3	±7	±3	±7	±3	±7		+7	
Biochemistry	X						X						X						X								X	X		
Urinalysis[e]	X						X												X								X	X		
Calcitonin	X																													
Pregnancy test[f]	X						X																						X	X
Eye examination[g]		X					X																				X	X		
TRIAL MATERIAL																														
Dispensing of trial product																														
Insulin aspart							X		X		X		X		X		X		X		X		X		X					
Insulin glargine		X		X		X	X		X		X		X		X		X		X		X		X		X					

[ee] Urine albumin to creatinine ratio

[ff] Only applicable for women of childbearing potential. At V1, serum pregnancy test will be taken. At V8 and P37/P37A and in case of a missed period, a urine pregnancy test will be taken.

[gg]
- An eye examination performed within 90 days prior to run-in is acceptable if available at Visit 2.
- The eye examination must be repeated within 30 days prior to randomisation and results must be available for evaluation at Visit 8.
- Results must be available at V36. An eye examination performed within 5 weeks prior to Visit 36 is acceptable.
- For Visit 36A the assessments can be performed in the period between Visit 36A and P37A, if available and reviewed no later than at P37A

	Screening	Run-in					Randomisation	Treatment																		End of treatment	Treatment discontinuation	Follow-up	Treatment discontinuation F/U
Visit (V)/phone contact (P)	V1	V2	P3	V4	P5 P6	V7	V8	P9 P10 P11	V12	P13	V14	P15	V16	P17	V18	P19 P20	V21	P22 P23	V24	P25 P26	V27	P28 P29	V30	P31 P32	V33	P34 P35	V36	V36A	P37	P37A
Timing of Visit (weeks)	-14	-12	-10	-8	-6 -4	-2	0	1 2 3	4	6	8	10	12	14	16	18 20	22	24 26	28	30 32	34	36 38	40	42 44	46	48 50	52		57	
Visit Window (days)	±7	±3	±3	±3	±3	±3	0	±3	±7	±3	±7	±3	±7	±3	±7	±3	±7	±3	±7	±3	±7	±3	±7	±3	±7	±3	±7		+7	
Semaglutide							X		X		X		X		X		X		X		X		X		X					
Drug accountability		X		X		X	X		X		X		X		X		X		X		X		X		X		X	X		
IWRS session	X	X		X		X	X		X		X		X		X		X		X		X		X		X		X	X		
REMINDERS																														
Hand out ID card	X																													
Hand out directions for use		X					X																							
Training in pen differentiation							X		X				X						X											
Training in trial product, pen-handling		X		X			X		X				X						X											
Hand out and instruct in diary		X		X		X	X		X		X		X		X		X		X		X		X		X					
Collect diary				X		X	X		X		X		X		X		X		X		X		X		X		X	X		
Hand out and instruct in BG-meter		X																												
Attend visit fasting[h]							X		X		X		X		X				X				X				X	X		

[hh] Fasting is defined as at least 8 hours prior to the visit, without food or liquids, except for water. Trial product and any medication which should be taken with or after a meal should be withheld on the day of the visit until blood samples have been obtained. If the subject is not fasting as required, the subject should be called in for a new visit within the visit window to have the fasting procedures done.

	Screening	Run-in					Randomisation	Treatment																			End of treatment	Treatment discontinuation	Follow-up	Treatment discontinuation F/U
Visit (V)/phone contact (P)	V1	V2	P3	V4	P5 P6	V7	V8	P9 P10 P11	V12	P13	V14	P15	V16	P17	V18	P19 P20	V21	P22 P23	V24	P25 P26	V27	P28 P29	V30	P31 P32	V33	P34 P35	V36	V36A	P37	P37A
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Visit Window (days)	±7	±3	±3	±3	±3	±3	0	±3	±7	±3	±7	±3	±7	±3	±7	±3	±7	±3	±7	±3	±7	±3	±7	±3	±7	±3	±7		+7	
End of Treatment[i]																											X	X		
End of Trial[i]																													X	

[i] If a subject completes both the treatment and the trial at scheduled time, the End of Treatment form must be filled in at V36 and End of Trial form must be filled in at P37. If discontinuation of trial product before the end of treatment (V36), End of Treatment form must be filled-in when the discontinuation happens and End of Trial form at scheduled visit P37. In case of subject withdrawal, both End of Treatment form and End of Trial form must be filled in at the time of withdrawal from the trial.

3 Introduction

3.1 Trial rationale

According to the American Diabetes Association (ADA) and European Association for Study of Diabetes (EASD), treatment intensification should be considered for patients with type 2 diabetes (T2D) who do not reach ADA/EASD recommended glycated haemoglobin (HbA_{1c}) goal within 3-6 months of treatment with basal insulin in combination with oral antidiabetic drugs (OADs). Advancing to a combined injectable treatment can be achieved with the addition of a glucagon-like peptide-1 receptor agonist (GLP-1 RA), or bolus insulin to the treatment with basal insulin. Drug choice should be individualised and based on local guidelines and patient preferences, as well as various patient, disease, and drug characteristics, with the goal of improving blood glucose (BG) levels while minimizing side effects, especially hypoglycaemia.[2, 3]

Severe hypoglycaemia impacts heavily on the well-being, productivity, health-related quality and mental functioning of life of people with T2D. Severe hypoglycaemia represents a substantial cost burden, as it may involve costs related to ambulances, paramedics, and hospitalisation.[4]

It is recommended that the HbA_{1c} goals should be individualised and within the range of 6.5% to 7.5% (48 mmol/mol to 58 mmol/mol) for the majority of adult patients with T2D.[2, 3, 5] Less stringent HbA_{1c} goals may be appropriate for patients with a history of severe hypoglycaemia, limited life expectancy, advanced micro- or macrovascular complications, extensive comorbid conditions, or long-standing diabetes in whom the goal is difficult to achieve despite diabetes self-management education, appropriate glucose monitoring and effective doses of multiple glucose-lowering agents, including insulin.[2, 3]

The purpose of the current trial is to compare the effect on glycaemic control, body weight, safety and health-related quality of life of semaglutide versus insulin aspart (IAsp), both as add-on to metformin and optimised insulin glargine (IGlar U100) treatment in subjects with inadequately controlled T2D.

Semaglutide may provide an efficacious and simple alternative to bolus insulin for advancing basal insulin regimen in patients with late stage T2D, with lower risk of hypoglycaemia and weight gain.

3.2 Background

Semaglutide is a novel GLP-1 (Glucagon-like peptide-1) analogue with a half-life around 1 week (149 to 165 hours), suitable for once-weekly (OW) subcutaneous (s.c.) administration.[6] In the SUSTAIN clinical development programme, semaglutide demonstrated clinically relevant and superior reductions in HbA_{1c} and body weight versus placebo (monotherapy and add-on to basal insulin) and active comparators (exenatide, dulaglutide, sitagliptin and IGlar). The cardiovascular (CV) safety of semaglutide has been established in a 2-year CV outcomes trial (SUSTAIN 6) that showed clinically relevant CV risk reduction with semaglutide compared to placebo.[7]

Semaglutide added on to basal insulin in patients with inadequately controlled T2D demonstrated superior effects on glycaemic control, weight loss, treatment satisfaction and reduction in basal insulin dose compared to placebo.[8]

Basal-bolus therapy, involving the addition of rapid acting insulin at mealtime to ongoing basal insulin, is an effective treatment for lowering glucose levels but can be associated with a risk of hypoglycaemia and weight gain.[2, 3] The adherence to basal-bolus regimens may be perceived as complicated for the patient, and it may affect the patient's quality of life. Specifically, basal-bolus treatment with IGlar and IAsp is a widely prescribed and accepted T2D treatment regimen worldwide.

Recent trials evaluating the use of GLP-1 RAs with basal insulin, demonstrated equal or superior efficacy on glycaemic control compared to bolus insulin, with greater weight loss and less hypoglycaemia.[9-11] Limited information is available on comparison of once-weekly GLP-1 RAs to bolus insulin, confirming these findings.[12]

Patients with inadequately controlled T2D with basal insulin, stable dose of metformin with or without an additional OAD, are the target population for inclusion in this trial. As a consequence, these subjects will already have exhausted the option of treatment with diet and exercise in combination with OADs and basal insulin and qualify for further treatment intensification. Upon trial entry, all subjects will be transferred from their pre-trial basal insulin treatment to IGlar U100, provided by Novo Nordisk A/S as the investigational medicinal product (IMP).

Subjects treated with metformin and optimised IGlar U100 who have not reached adequate glycaemic control after 12 week run-in will have their treatment intensified with either semaglutide OW or IAsp TID.

The selected active comparator in this trial is IAsp. IAsp (NovoRapid® and NovoLog®) is a rapid-acting insulin analogue indicated for the treatment of diabetes mellitus providing postprandial glycaemic control by means of lowering total glucose excursion following a meal both in subjects with type 1 diabetes and T2D. In order to reflect usual clinical practice, the investigator can change bolus insulin during the trial.

All subjects included in the trial will be treated with IGlar U100 as the basal insulin. IGlar U100 (Lantus®) is a long-acting insulin analogue, indicated for treatment of diabetes mellitus in combination with oral antidiabetic agents and as part of a basal-bolus insulin regimen.

3.3 Benefit-risk assessment

3.3.1 Risks related to semaglutide

Based on the clinical development programme a causal relationship with semaglutide was suggested for the following risks (identified risks):

Gastrointestinal disorders
For semaglutide as for other GLP-1 RAs, the most frequently reported adverse reactions in clinical trials were gastrointestinal disorders, including nausea, diarrhoea and vomiting. In general, these reactions were mild or moderate in severity and of short duration. A dose dependency has been observed for most of the gastrointestinal disorders. Clinical trials have shown that a low starting dose and gradual dose escalation mitigates the risk of gastrointestinal AEs.

In patients treated with GLP-1 RAs, nausea, vomiting and diarrhoea may lead to significant dehydration. This should be considered when treating patients with impaired renal function as it may cause a deterioration of renal function. Subjects with GI (Gastrointestinal) AEs are recommended to drink plenty of fluids to avoid volume depletion.

Hypoglycaemia
Subjects treated with semaglutide in combination with a sulfonylurea or insulin have an increased risk of hypoglycaemia. The risk of hypoglycaemia can be lowered by reducing the dose of sulfonylurea or insulin when initiating treatment with semaglutide.

Diabetic retinopathy complications
In a 2-year clinical trial involving 3,297 subjects with type 2 diabetes and high cardiovascular risk, long duration of diabetes and poorly controlled blood glucose, adjudicated events of diabetic retinopathy complications occurred in more patients treated with semaglutide (3.0%) compared to placebo (1.8%). Diabetic retinopathy complications were a composite of: need for retinal photocoagulation, need for treatment with intravitreal agents, vitreous haemorrhage and onset of diabetes-related blindness. The absolute risk increase for diabetic retinopathy complications was larger among patients with a history of diabetic retinopathy at baseline. In the patients that did not have a documented history of diabetic retinopathy the number of events were similar for semaglutide and placebo.

In other clinical trials up to 1 year involving 4,807 patients with type 2 diabetes patients, adverse events related to diabetic retinopathy were reported in similar proportions of subjects treated with semaglutide (1.7%) and comparators (2.0%).

Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy. Long-term glycaemic control decreases the risk of diabetic retinopathy. Subjects with a history of diabetic retinopathy should be monitored for worsening and treated according to clinical guidelines.

Other risks
Patients treated with semaglutide may also experience cholelithiasis, decreased appetite, dizziness, dysgeusia, fatigue, increased heart rate, increased lipase and amylase, injection site reactions and weight decrease.

In addition, for the risks below, there is some basis for suspicion of an association with semaglutide, however, the relationship has not been confirmed (potential risks).

Allergic reactions
As in the case with all protein-based pharmaceuticals, treatment with semaglutide may evoke allergic reactions, including serious allergic reactions such as anaphylactic reactions.

Acute pancreatitis
Acute pancreatitis has been observed with the use of GLP-1 RAs. Patients should be informed of the characteristic symptoms of acute pancreatitis and if pancreatitis is suspected, semaglutide should be discontinued. If confirmed, semaglutide should not be restarted.

Malignant neoplasms
There is no indication of a causal relationship between semaglutide and malignant neoplasm based on the available data. However, it is not possible to draw any firm conclusions due to very low numbers.

- ***Pancreatic cancer***
  Patients with T2D have an increased risk of certain types of cancer such as pancreatic cancer. In the development programme, rates of pancreatic cancer was low and do not support a causal association with semaglutide, and no safety concerns related to the pancreas were identified in the nonclinical programme with semaglutide. However, pancreatic cancer has been classified as a potential class risk for all marketed GLP-1 receptor agonists by regulatory agencies.

- ***Medullary thyroid cancer***
  Thyroid C-cell tumours were seen in mice and rat carcinogenicity studies after daily exposure to semaglutide for 2 years. The rodent C-cell tumours are caused by a non-genotoxic, specific GLP-1 receptor mediated mechanism to which rodents are particularly sensitive. No C-cell tumours were observed in monkeys after 52 weeks exposure up to 27-fold above the clinical plasma exposure at 1.0 mg/week.

  The GLP-1 receptor is not expressed in the normal human thyroid and the risk of GLP-1 receptor-mediated C-cell changes in humans is considered to be low.

Other safety considerations

Drug interactions
Semaglutide delays gastric emptying and has the potential to impact the rate of absorption of concomitantly administered oral medicinal products. The potential effect of semaglutide on the absorption of co-administered oral medications was studied in trials at semaglutide 1 mg/week steady state exposure. No clinically relevant drug-drug interactions with semaglutide were observed based on the evaluated medications.

Semaglutide did not change the overall pharmacodynamics of warfarin as measured by the international normalised ratio (INR). However, upon initiation of semaglutide treatment in patients on warfarin and/or coumarin derivatives, frequent monitoring of INR is recommended.

Pregnancy, lactation and fertility
Studies in animals have shown reproductive toxicity. There are limited data from the use of semaglutide in pregnant women. Therefore, semaglutide should not be used during pregnancy. If a patient wishes to become pregnant, or pregnancy occurs, semaglutide should be discontinued. Semaglutide should be discontinued at least 2 months before a planned pregnancy due to the long half-life. In lactating rats, semaglutide was excreted in milk. As a risk to a breast-fed child cannot be excluded, semaglutide should not be used during breast-feeding

The effect of semaglutide on fertility in humans is unknown. Semaglutide did not affect male fertility in rats. In female rats, an increase in oestrous length and a small reduction in number of ovulations were observed at doses associated with maternal body weight loss.

3.3.2 Risks related to insulin

Hypoglycaemia
The most frequently reported adverse reaction of insulin therapy is hypoglycaemia. It may occur if the insulin dose is too high in relation to the insulin requirement. Patients, whose blood glucose control is greatly improved, e.g. by intensified insulin therapy, may experience a change in their usual warning symptoms of hypoglycaemia, and should be advised accordingly. Usual warning symptoms may disappear in patients with longstanding diabetes.

Other
Other events include injection site reactions, lipodystrophy at injection site, allergic reactions, oedema and medication errors for dual insulin therapy

Intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy.

For IGlar: fast improvement in BG control may be associated with acute painful neuropathy, which is usually reversible.

3.3.3 Benefits

In clinical trials semaglutide has provided superior glycaemic control in T2D and clinically relevant reductions in body weight as compared to commonly used marketed products and placebo. The CV safety of semaglutide has been established in a CV outcome trial (SUSTAIN 6) and the trial suggested a clinically relevant CV risk reduction with semaglutide compared to placebo.

IAsp is widely prescribed and accepted bolus insulin used in patients with T2D worldwide, with well characterised clinical profile.

During this trial it is expected that all patients will benefit from participation through intensified treatment regimen in both groups which includes frequent contact with the trial site, where patients are monitored and treated following careful medical examinations.

To ensure all patients have an adequate glycaemic control, investigators are encouraged to optimise glycaemic control throughout the trial in accordance with the individualised glycaemic goal and the titration guidelines.

Risk and benefit conclusion

The aim of this trial is to compare the effect of semaglutide to that of IAsp. Inclusion and exclusion criteria have been chosen to ensure that subjects enrolling in the trial have T2D at a stage where treatment intensification with either GLP-1RAs or prandial insulin is recommended by T2D treatment guidelines. Randomised subjects should benefit from treatment intensification with either semaglutide or IAsp. It is therefore concluded that the potential benefits from the trial will outweigh the potential risks for the semaglutide as well as the IAsp treated patients.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of semaglutide may be found in the current edition of the investigator's brochure.

Detailed information about IAsp is available in the current version of the local label.

Detailed information about IGlar is available in the current version of the local label for Lantus®.

4 Objectives and endpoints

4.1 Primary objective

To compare the effect of semaglutide once-weekly on glycaemic control versus insulin aspart three times daily (TID), both as add on to metformin and optimised insulin glargine (U100) in subjects with T2D.

4.2 Secondary objectives

To demonstrate that semaglutide once-weekly has a lower risk of severe hypoglycaemic episodes compared to IAsp TID, both as add on to metformin and optimised insulin glargine (U100) in subjects with T2D.

To compare the effect of semaglutide OW versus IAsp TID, both as add on to metformin and optimised insulin glargine (U100) in subjects with T2D with regards to:

- body weight
- lipids
- blood pressure
- health-related quality of life
- safety

4.3 Estimand

For all objectives the primary estimand is the treatment difference between semaglutide OW and IAsp TID for all randomised subjects if all subjects initiated and remained on randomised treatment throughout the trial.

Patients who are lost to follow-up, who have withdrawn consent, or who discontinue trial drug are assumed, in the time following this event, to behave like patients that remain in the trial and are treated with trial drug.

4.4 Endpoints

Definition of baseline
For each assessment, the baseline assessment is defined as the measurement at the randomisation visit (V8). However, if a visit 8 assessment is missing then the assessment from visit 7, if available, will be used as the baseline assessment.

4.4.1 Primary endpoint

- Change from baseline to week 52 in HbA_{1c} (%-point)

4.4.2 Secondary endpoints

4.4.2.1 Confirmatory secondary endpoints

- Time to first event adjudication committee (EAC) confirmed severe hypoglycaemic episode (ADA) from randomisation up to week 52 (days)
- Time to first EAC confirmed severe hypoglycaemic episode (ADA) requiring hospitalisation, documented medical help, or is life threatening from randomisation up to week 52 (days)
- Change from baseline to week 52 in body weight (kg)

4.4.2.2 Supportive secondary endpoints

- Change from baseline to week 52 in:
  - Fasting plasma glucose (FPG) (mmol/L)
  - 7-point self-measured plasma glucose profile
    - Mean 7-point profile (mmol/L)
    - Mean post-prandial increment (over all meals) (mmol/L)
  - Systolic and diastolic blood pressure (mmHg)
  - Fasting blood lipids (total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides) (mmol/L)
  - Body mass index (BMI) (kg/m2)
  - Waist circumference (cm)
  - Body weight (%)
  - Pulse (bpm)
- Number of EAC confirmed severe hypoglycaemic episodes (ADA) from randomisation to week 52
- Number of EAC confirmed severe (ADA) or blood glucose confirmed, symptomatic hypoglycaemic episodes (PG < 3.1 mmol/L (56 mg/dL)) from randomisation to week 52
- Number of EAC confirmed severe (ADA) or blood glucose confirmed, symptomatic hypoglycaemic episodes (PG ≤ 3.9 mmol/L (70 mg/dL)) from randomisation to week 52
- Number of EAC confirmed severe hypoglycaemic episodes (ADA) requiring hospitalisation, documented medical help, or is life threatening from randomisation to week 52

Supportive secondary HRQoL endpoints

Change from baseline to week 52 in the following scores for the selected patient-reported outcomes (PRO):

- 36-item Short Form Health Survey version 2 (SF-36v2™)
  - Physical Component Summary (PCS) score (range:7.32-70.14)
  - Mental Component Summary (MCS) score (range: 5.79-69.91)
  - Physical Functioning (PF) domain score (range:19.26-57.54)

- Role-Physical (RP) domain score (range: 21.23-57.16)
- Bodily Pain (BP) domain score (range: 21.68-62.00)
- General Health (GH) domain score (range: 18.95-66.50)
- Vitality (VT) domain score (range: 22.89-70.42)
- Social Functioning (SF) domain score (range: 17.23-57.34)
- Role-Emotional (RE) domain score (range: 14.39-56.17)
- Mental Health (MH) domain score (range: 11.63-63.95)

The ten scores related to SF-36v2™ are measured on a scale from 5.79-70.42, and calculated using the 2009 General U.S. Population.
Higher scores are indicative of a better health state.

- Diabetes Quality Of Life Clinical Trial Questionnaire (DQLCTQ-R)
  - Physical functioning domain score
  - Energy / fatigue domain score
  - Health distress domain score
  - Mental health domain score
  - Satisfaction domain score
  - Treatment satisfaction domain score
  - Treatment flexibility domain score
  - Frequency of symptoms domain score

The eight scores related to DQLCTQ-R are measured on a scale from 0-100.
Higher scores are indicative of better health state.

4.4.2.3 Exploratory endpoints

Exploratory responder endpoints

- $HbA_{1c} \leq 7.5\%$ (58 mmol/mol) at week 52 (Y/N)
- $HbA_{1c} < 7.0\%$ (53 mmol/mol) at week 52 (Y/N) (ADA)
- $HbA_{1c} \leq 6.5\%$ (48 mmol/mol) at week 52 (Y/N) (AACE)
- $HbA_{1c} \leq 7.5\%$ (58 mmol/mol) at week 52 without an EAC confirmed severe hypoglycaemic episode (ADA) from randomisation to week 52 (Y/N)
- $HbA_{1c} \leq 7.5\%$ (58 mmol/mol) at week 52 without an EAC confirmed severe hypoglycaemic episode (ADA) requiring hospitalisation, documented medical help, or is life threatening from randomisation to week 52 (Y/N)
- Weight loss $\geq 5\%$ at week 52 (Y/N)
- Weight loss $\geq 10\%$ at week 52 (Y/N)

Exploratory PRO endpoints

Change from baseline to week 52 in the scores for the Treatment Related Impact Measure for Diabetes (TRIM-D):

- TRIM-D Total Score
- Treatment Burden Domain Score
- Daily Life Domain Score
- Diabetes Management Domain Score
- Compliance Domain Score
- Psychological Health Domain Score

The six scores related to TRIM-D are measured on a scale from 0-100.
Higher scores are indicative of better health state (less negative impact).

5 Trial design

5.1 Overall design

This is a 52-week, multi-centre, multinational, open-label, active controlled, two armed, parallel, randomised trial with a 12-week run-in period in subjects with T2D. The total duration of the trial will be approximately 71 weeks: 2 weeks for screening, a 12-week run-in period, a 52-week treatment period and a follow-up period of 5 weeks.

At run-in, eligible subjects will discontinue pre-trial basal insulin and the additional OAD (if applicable, including conversion from fixed drug combination medications with metformin and DPP-4i (Dipeptidyl peptidase-4 inhibitor) to metformin only) and start treatment with IGlar U100.

During run-in, subjects will be treated with metformin and IGlar U100. During run-in metformin can be optimised within the dose range of ≥ 1500 mg to ≤ 3000 mg. The IGlar U100 dose will be optimised as described in the Appendix 8.

Subjects treated with metformin and IGlar U100 who are not in glycaemic control (defined as HbA_{1c} of > 7.5% to ≤ 10% [> 58 mmol/mol to ≤ 86 mmol/mol]) after run-in, will be randomised 1:1 to receive add-on treatment with semaglutide OW or IAsp TID. For details of the dosing of IGlar, IAsp and semaglutide, refer to Appendix 8. A schematic overview of the trial design is shown below.

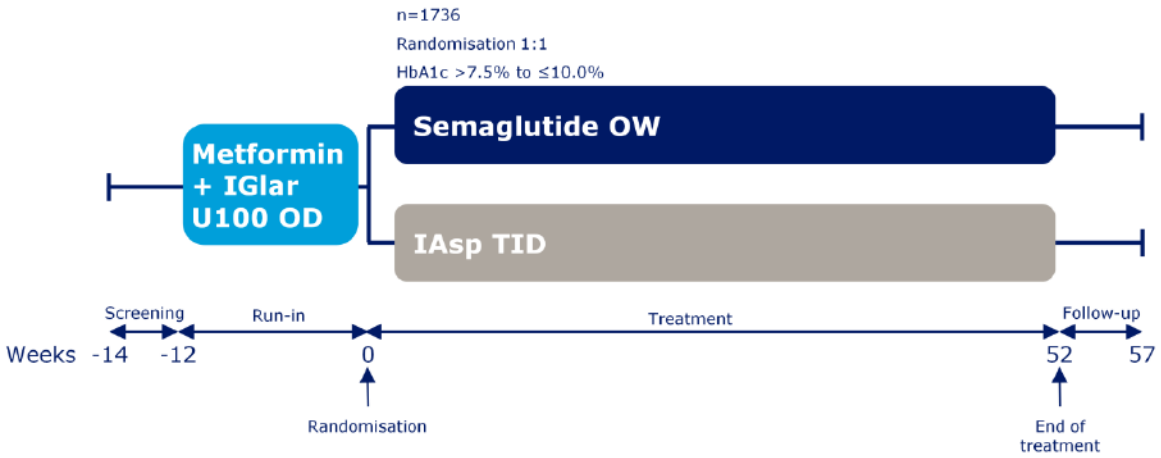

Figure 5-1 Trial design

The trial includes a screening visit to assess the subject's eligibility, additional visits and phone contacts during run-in and treatment period, and a follow-up phone contact at week 57 to ensure the capture of adverse events (AEs) during wash-out of semaglutide OW. The visit schedule described

in Section 2 is chosen to secure an optimal insulin titration and semaglutide OW dose adjustment according to a predefined treatment algorithm.

5.2 Subject and trial completion

Approximately 3144 subjects will be screened to achieve 1736 subjects randomly assigned to trial products. Approximately 2043 subjects are planned to be included in the run-in period.

Trial period completion for a subject

Trial period completion is defined as when the randomised subject has completed the final scheduled visit ('end of trial' according to the flowchart, Section 2).'Date of trial completion' is the date the subject completed the final scheduled visit.

Treatment period completion for a subject

Treatment period completion is defined as when the randomised subject has received the required treatment, and attended the 'end of treatment' visit (V36) according to the flowchart, Section 2.

5.3 End of trial definition

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

5.4 Scientific rationale for trial design

The trial has been designed as a parallel-group, two-armed, open-label, randomised trial to secure a direct comparison between semaglutide OW and IAsp TID.

A 12-week run-in period is included in order to ensure the dose optimisation of IGlar after the transfer of all subjects from their pre-trial basal insulin to IGlar and after the discontinuation of the additional OAD to metformin (if applicable). Only subjects with inadequate glycaemic control at randomisation (per central laboratory HbA_{1c} value obtained at the last visit during run-in, V7) will be initiated onto the add-on treatment with semaglutide or IAsp.

The trial is open-label due to the different requirements in number and timing of the injections, BG self-monitoring and the dose escalation/titration algorithms for semaglutide and IAsp.

Randomised treatment duration will be 52 weeks to ensure adequate time to compare the full effect and safety of randomised treatments. Robust assessment of effect on glycaemic control, body weight, safety and Health Related Quality of Life (HRQoL) endpoints is ensured with the treatment duration of 52 weeks.

Titration algorithms for insulins and dose adjustment guidance for semaglutide, including individualised glycaemic goals as well as rescue criteria are in place to ensure optimal glycaemic control for all subjects included in the trial. To ensure uniformity between the sites, as well as to

ensure that the subjects receive an optimal treatment, titration algorithms have been developed specifying recommended dose adjustments at different self-measured plasma glucose (SMPG) and HbA_{1c} levels. To optimise and maintain glycaemic control the investigator should throughout the trial be in bimonthly contact with the subjects to ensure adequate treatment. For further details, please see Appendix 8.

The follow-up period is 5 weeks to ensure safety data collection during wash-out of semaglutide due to its long half-life.

5.5 Justification for dose

For the details on the route of administration, initiation and dose adjustments of IMPs (IGlar U100, semaglutide and IAsp) please refer to Section 7.1 and Appendix 8.

6 Trial population

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

6.1 Inclusion criteria

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

1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial.
2. Male or female, age ≥ 18 years at the time of signing informed consent.
3. Diagnosed with type 2 diabetes ≥ 180 days prior to the day of screening.
4. Treated with basal insulin once daily (OD) or twice daily (BID) for ≥ 90 days prior to the day of screening.
5. Stable daily dose for 90 days prior to the day of screening of the following anti-diabetic drugs or combination regimens: Any metformin formulations (≥ 1500 mg to ≤ 3000 mg or maximum tolerated or effective dose documented in subject's medical record), alone or in combination (including fixed-dose drug combination) with up to one additional of the following OADs: sulfonylureas, meglitinides, DPP-4 inhibitors or alpha-glucosidase inhibitors.
6. HbA_{1c} of > 7.5% to ≤ 10.0% (>58 mmol/mol to ≤ 86 mmol/mol)
7. The need and willingness to undergo treatment intensification with the treatments investigated in this trial with the aim to reach an HbA_{1c} of 6.5% to 7.5% (48 mmol/mol to 58 mmol/mol) (both inclusive), as assessed by the investigator.
8. Ability and willingness to adhere to the protocol including performance of SMPG profiles according to the protocol.
9. Ability and willingness to eat at least 3 meals (breakfast, lunch and dinner) every day during the trial.

6.2 Exclusion criteria

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

1. Known or suspected hypersensitivity to trial product(s) or related products.
2. Previous participation in this trial. Participation is defined as signed informed consent.
3. Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using highly effective contraceptive methods as required by local regulation or practice.
4. Receipt of any investigational medicinal product within 30 days before screening except from IGlar.
5. Any disorder which in the investigator's opinion might jeopardise the subject's safety or compliance with the protocol.

6. Personal or first degree relative(s) history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma.
7. History or presence of pancreatitis (acute or chronic).
8. Any of the following: myocardial infarction, stroke, hospitalization for unstable angina or transient ischaemic attack within the past 180 days prior to the day of screening.
9. Subjects presently classified as being in New York Heart Association Class IV.
10. Planned coronary, carotid or peripheral artery revascularisation known on the day of screening.
11. Renal impairment measured as estimated Glomerular Filtration Rate (eGFR) <30 ml/min/1.73 m^2 as defined by KDIGO 2012.[13]
12. Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria within the past 90 days prior to the day of screening. However, short term bolus insulin treatment for a maximum of 14 days prior to the day of screening is allowed.
13. Uncontrolled and potentially unstable diabetic retinopathy or maculopathy. Verified by a pharmacologically pupil-dilated fundus examination performed by an ophthalmologist or an equally qualified health care provider (e.g. optometrist) within the past 90 days prior to run-in.
14. 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.

6.3 Lifestyle restrictions

Not applicable

6.4 Run-in exclusion criteria

The subject must be excluded from the trial during the run-in period, if the following applies after screening and before or at randomisation:

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. Any disorder which in the investigator's opinion might jeopardise subject's safety
6. Pancreatitis (acute or chronic)
7. Any of the following: myocardial infarction, stroke or hospitalization for unstable angina or transient ischaemic attack
8. New York Heart Association (NYHA) Class IV
9. Planned coronary, carotid or peripheral artery revascularisation

10. Treatment with any medication for the indication of diabetes or obesity except metformin and IGlar U100. However, short-term bolus insulin treatment for a maximum of 14 days is allowed.
11. Pre-breakfast SMPG values taken on three consecutive days or any of the FPG samples analysed by the central laboratory exceed the limit of 15.0 mmol/L (270 mg/dL), from screening to randomisation and:
    - no treatable intercurrent cause for the hyperglycaemia (e.g. non-compliance) is identified,

    and
    - confirmatory FPG obtained and analysed by the central laboratory exceeds the limit of 15.0 mmol/L (270 mg/dL).

6.5 Randomisation criteria

To be randomised, all randomisation criteria must be answered "yes".

1. HbA_{1c} of >7.5% to ≤10.0% (>58 mmol/mol to ≤86 mmol/mol) measured at V7.
2. Treated with IGlar U100 and metformin (≥ 1500 mg to ≤ 3000 mg or maximum tolerated dose documented in subject's medical record) during the run-in and at randomisation (V8).
3. The need and willingness to undergo treatment intensification with the treatments investigated in this trial with the aim to reach an HbA_{1c} of 6.5% to 7.5% (48 mmol/mol to 58 mmol/mol) (both inclusive), as assessed by the investigator at randomisation (V8).
4. Absence of uncontrolled and potentially unstable diabetic retinopathy or maculopathy. Verified by a pharmacologically pupil-dilated fundus examination performed by an ophthalmologist or an equally qualified health care provider (e.g. optometrist) within 30 days prior to randomisation.

Re-sampling is not allowed if the subject has failed the randomisation criteria related to HbA_{1c}.

6.6 Screen failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are not eligible for participation according to in/exclusion criteria. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet requirements from regulatory authorities. Minimal information includes demography, date of informed consent, screen failure details, eligibility criteria, and any SAE. A screen failure session must be made in the IWRS (Interactive Web Response System).

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

6.7 Run-in failures

Run-in failures are defined as subjects who are not eligible to be randomised (i.e. has met one of the run-in exclusion criteria or has not met all of the randomisation criteria). Consequently, the run-in failure must be registered in the IWRS and a run-in failure form must be completed in the electronic case report form (eCRF) together with the reason for not continuing in the trial. The last date of trial product must be captured in the eCRF. No follow-up visit should take place and no additional assessments are needed. SAEs and non-serious AEs from run-in failures must be recorded by the investigator in the eCRF. Follow-up of AEs must be carried out according to Appendix 4.

7 Treatments

7.1 Treatments administered

7.1.1 Investigational medicinal products

- All trial products listed in Table 7-1 are considered IMP.
- Trial product must only be used, if it appears clear and colourless.

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

Trial product name:	Insulin glargine (Lantus®) 100 U/mL (IMP)	Semaglutide 1.34 mg/ml (IMP, test product)	Insulin aspart (NovoRapid®/NovoLog®)100 U/mL (IMP, reference therapy)
Dosage form:	solution for injection	solution for injection	solution for injection
Route of administration:	Subcutaneous	Subcutaneous	Subcutaneous
Dosing instructions:	Once daily For details, see Appendix 8	Once-weekly For details, see Appendix 8	Three times daily For details, see Appendix 8
Packaging	3 mL pre-filled pen-injector (SoloStar®)	1.5 ml pre-filled PDS290 pen-injector	3 ml pre-filled pen – injector (FlexPen®)

- Subjects must be trained in handling the pen-injectors when dispensed the first time and training must be repeated during the trial as indicated per flowchart Section 2. The investigator may choose to observe the subject when administering the first dose.
- The investigator must document that directions for use (DFU) are given verbally and in writing the first time trial product is dispensed and again during the trial as needed.
- The subject should be advised to discard the injection needle after each injection and store the pen without an injection needle attached. Needles to be used with the trial product should be provided throughout the trial as needed.
- If alternative bolus insulin is required per investigator's discretion it will be reimbursed by Novo Nordisk A/S.

7.1.2 Non-investigational medicinal products

After signing the informed consent, subjects should continue metformin treatment. During run-in optimisation of metformin within the dose range of ≥ 1500 mg to ≤ 3000 mg or maximum tolerated dose is allowed. From randomisation (V8) and throughout the entire trial the dose of metformin should be maintained at the same level and with same frequency unless safety concern related to the background medication arises. For subjects using fixed drug combination treatment with metformin

pre-trial, transfer to metformin-only formulation should be performed at run-in. All locally available metformin formulations are allowed.

In addition, metformin:

- is considered a non-investigational medicinal product (NIMP)
- will not be supplied or reimbursed by Novo Nordisk A/S, unless required according to local regulations.
- should be used in accordance with the current approved label in the individual country.
- the dose must not exceed the maximum approved dose in the individual country.

7.1.3 Auxiliary supplies

- The following auxiliary supplies will be provided by Novo Nordisk:
  - Needles for the pen-injectors
  - DFU for the pen-injectors
  - BG meter and related auxiliaries
- Subjects will be instructed in how to use the BG-meter and the instructions will be repeated during the trial as needed.
- Only needles provided by Novo Nordisk must be used for administration of trial product.

7.2 Dose modification

Dose modification of IMPs is performed in relation to individualised SMPG, overall HbA_{1c} goals, local guidelines and in accordance with the trial requirements listed in Appendix 8. Subjects randomised to semaglutide should follow the recommended dose escalation regimen in order to lower the risk of gastrointestinal AEs. Please see further details in Appendix 8.

7.3 Method of treatment assignment

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

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

7.4 Blinding

This is an open-label trial.

7.5 Preparation/Handling/Storage/Accountability

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

Table 7-2 Trial product storage conditions

Trial product name	Storage conditions (not-in-use)	In-use conditions	In-use time[a]
Semaglutide 1.34 mg/ml	Store in refrigerator (2°C-8°C) Do not freeze Protect from light	In-use conditions will be available on the trial product label.	In-use conditions will be available on the trial product label.
Insulin aspart 100 U/ml			
Insulin glargine 100 U/ml			

[a] For semaglutide, in-use time starts when the product is taken out of the refrigerator in the subject's home. For IAsp and IGlar, in-use time starts when the product is taken out of the refrigerator in the subject's home for start of use or for carrying as a spare.

- Each trial site will be supplied with sufficient trial products for the trial on an on-going basis controlled by the IWRS. Trial product will be distributed to the trial sites according to screening, run-in and randomisation numbers.
- The investigator must confirm that appropriate temperature conditions have been maintained during transit for all trial products received and any discrepancies are reported and resolved before use of the trial products.
- All trial products must be stored in a secure, controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.
- The investigator must inform Novo Nordisk immediately if any trial product has been stored outside specified conditions. Additional details regarding handling of temperature deviations can be found in the 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.
- Subjects must return all used, partly used and unused trial products as instructed by the investigator.
- The investigator is responsible for drug accountability and record maintenance (i.e. receipt, accountability and final disposition records).
- Drug accountability should be performed in the IWRS by registering pen-injectors as returned either as used/partly used, unused or as lost.
- Destruction of trial products can be performed on an ongoing basis and will be done according to local procedures after accountability is finalised by the site and reconciled by the monitor.

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

7.6 Treatment compliance

Throughout the trial, the investigator will remind the subjects to follow the trial procedures and requirements to ensure subject compliance. The investigator will at each contact (visit or phone contact) assess the subject's compliance by evaluating the glycaemic control and adherence to the visit schedule and completion of the subject's diary, including the SMPG profiles, dose and hypoglycaemia reporting. In addition, subject compliance will be assessed by monitoring of drug accountability. 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.

7.7 Concomitant medication

Any medication other than the trial product(s) that the subject is receiving at the time of screening or receives during the trial must be recorded along with:

- Trade name or generic name
- Indication
- Dates of administration including start and stop dates or continuation
- Only applicable for anti-diabetic medication: start date of current dose and total daily dose

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

At the run-in visit (Visit 2), pre-trial basal insulin and OAD treatment (except for metformin) must be discontinued and a stop date recorded in the eCRF.

7.8 Rescue medication

It is important for trial integrity that only subjects who actually need treatment intensification according to Section 8.2 are started on rescue medication. Rescue medication should be prescribed at the investigator's discretion as add-on to randomised treatment and according to ADA/EASD treatment guidelines.[3, 14]

Subjects who are started on rescue medication should continue to follow the protocol-specified visit schedule.

Rescue medication (initiation of new antidiabetic medication) and any changes hereto must be recorded on the concomitant medication form in the eCRF.
Choice of rescue medication, at the discretion of the investigator, could include the addition of thiazolidinediones, sodium–glucose cotransporter inhibitors, meglitinides, or alpha-glucosidase inhibitors. Addition of sulfonylureas, other incretin-based therapies (e.g. GLP-1 RA or DDP-4 inhibitors) or prandial insulin are prohibited.
Rescue medication is considered NIMP and will not be provided by Novo Nordisk A/S.

7.9 Treatment after the end of the trial

When discontinuing trial products, the subject should be transferred to a suitable marketed product at the discretion of the investigator. The long half-life of semaglutide must be taken into consideration when selecting anti-diabetic treatment after discontinuation of trial product.

8 Discontinuation/Withdrawal criteria

All efforts should be made to keep subjects on trial products.

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

Efforts must be made to have the randomised subjects, who discontinue trial product, attend visit 36A as soon as possible (preferably the same day) to undertake procedures, which are similar to those at visit 36. Phone contact 37A should be scheduled 5 weeks after the last date on trial product.

If discontinuation of trial product is decided during a scheduled visit after randomisation, the visit will be converted into a Visit 36A and trial procedures must be performed accordingly. Randomised subjects should continue with the originally scheduled site contacts after Phone contact 37A and up to and including Phone contact 37. If necessary, in order to retain the subject in the trial, site visits can be replaced by phone contacts after Phone contact 37A. However, all attempts should be made to ensure that Visit 36 is performed as a site visit and includes all planned assessments.

Randomised subjects should stay in the trial irrespective of lack of adherence to randomised treatment, lack of adherence to visit schedule, missing assessments or discontinuation of trial product for any reason.

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

8.1 Discontinuation of trial treatment

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

1. Safety concern related to trial product or unacceptable intolerability
2. Pregnancy
3. Intention of becoming pregnant
4. Simultaneous participation in another clinical trial of an approved or non-approved investigational medicinal product.
5. Confirmation of acute pancreatitis (only applicable for subjects treated with semaglutide)

See the flowchart Section 2 for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

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

Upon discontinuation of trial product(s), the randomised subject should be switched to a suitable marketed product at the discretion of the investigator, while taking into consideration the long half-life of semaglutide. It is the investigator's responsibility to ensure optimal glycaemic control for the subjects who discontinue trial product.

8.1.1 Treatment discontinuation in case of randomisation in violation of the eligibility criteria

A subject who does not fulfil the eligibility (inclusion/exclusion/run-in exclusion/randomisation) criteria must not be randomised. Randomisation in violation of any of the eligibility criteria is a GCP non-compliance and must be reported to the sponsor without delay. This will be handled as an important protocol deviation, and the IEC/IRB and regulatory authorities must be notified according to local requirements. If there is no safety concerns, trial treatment may be continued or resumed at the discretion of the investigator after agreement with the sponsor's global medical expert.

8.1.2 Temporary discontinuation of trial treatment

If acute pancreatitis is suspected, temporary treatment discontinuation of semaglutide should promptly be initiated at the discretion of the investigator. If acute pancreatitis is confirmed, trial product should not be restarted.

8.2 Rescue criteria

Subjects with persistent and unacceptable hyperglycaemia should be offered treatment intensification. To allow time for dose escalation to maximum dose and to observe the expected effect of treatment on glycaemic parameters, rescue criteria will be applied at week 8 and onwards.

6. Pre-breakfast SMPG values taken on three consecutive days or if any of the FPG samples analysed by the central laboratory exceed the limit of:
   - 15.0 mmol/L (270 mg/dL) week 8 to end of week 12
   - 13.3 mmol/L (240 mg/dL) from week 13 to end of treatment,
     and
   - if no treatable intercurrent cause for the hyperglycaemia (e.g. non-compliance) has been identified.

   In such case, the subject must be called for a confirmatory FPG measurement as soon as possible. A confirmatory FPG must be obtained and analysed by the central laboratory. If this FPG exceeds the limits described above subject fulfils the rescue criterion.
7. HbA_{1c} (at central laboratory) > 8.5% (> 69.4 mmol/mol), from week 26 to end of treatment.

In case one of the criteria above is fulfilled, increase in the dose of the IMP(s) (IGlar U100 and/or IAsp/semaglutide) should be considered as the first choice in accordance with Appendix 8 and will not be considered as rescue medication.

In case further dose increase of the IMP(s) is not possible due to safety concern or unacceptable intolerability, subject should be started on rescue medication. Please refer to Section 7.8 for further details.

8.3 Withdrawal from the trial

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

If a subject withdraws consent, the investigator must ask the subject if he/she is willing, as soon as possible, to have assessment performed according to visit 36A. See the flowchart for data to be collected.

If a subject has already prematurely discontinued from trial product and previously attended V36A and P37A, no further visits should be attended.

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

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

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

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

8.3.1 Replacement of subjects

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

8.4 Lost to follow-up

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

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

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the trial.

- Before a subject is deemed lost to follow-up, the investigator must make every effort to regain contact with the subject (where possible, at least three telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). If attempts have failed, family members or other contacts consented by the subject can be contacted for alternative contact details. These contact attempts should be documented in the subject's source document.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the trial with a primary reason of lost to 'follow-up'.

9 Trial assessments and procedures

- Trial procedures and their timing are summarised in the flowchart, Section 2.
- Informed consent must be obtained before any trial related activity, see Appendix 3
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria.
- The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reason for screen failure, as applicable.
- At screening, subjects will be provided with a card stating that they are participating in a trial and giving contact details of relevant trial site staff.
- Adherence to the trial design requirements, including those specified in the flowchart, is essential and required for trial conduct.
- The investigator should inform the subjects' primary physician about the patients' participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.
- Subjects should be asked to provide contact information for persons, e.g. relatives, primary care provider etc., whom investigator can contact in case of issues when trying to contact the subject during the trial.
- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule.
- Source data of clinical assessments performed and recorded in the CRF must be available and will usually be the subject's medical records. Additional recording to be considered source data includes, but is not limited to laboratory reports, diary recordings and PRO questionnaires.
- Review of completed diaries, PRO questionnaires, laboratory reports, eye and physical examinations etc. must be documented either on the documents or in the subject's medical records. If clarification of entries or discrepancies in the diary or PRO questionnaires is needed, the subject must be questioned and a conclusion made in the subject's source documents. Care must be taken not to bias the subject.
- Repeat samples may be taken for technical issues and unscheduled samples or assessments may be taken for safety reasons. Please refer to Appendix 2 for further details on laboratory samples.

9.1 Efficacy assessments

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

9.1.1 Self-measured plasma glucose

At Visit 2, subjects will be provided with a BG meter including auxiliaries as well as instructions for use, if needed. The subjects will be instructed in how to use the device and the instruction should be repeated as necessary during the trial.

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

The BG meter provided by Novo Nordisk should be used for the measurements required in the protocol, as described in Section 2 and Appendix 8.

Subjects 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 and value. Relevant data from the diary as specified in Appendix 8 must be transcribed into the CRF during or following the contact. If obtained via phone and a discrepancy is later detected, the values in the CRF must be corrected.

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

Once daily pre-breakfast SMPG
All subjects in the trial should perform pre-breakfast SMPG every day from Visit 2 to Visit 36. SMPG values measured before breakfast should be performed in a fasting condition.

4-point SMPG profile
Subjects randomised to IAsp should perform 4-point profiles every day after randomisation. The measurements should be performed at the following time points:

- Before breakfast
- Before lunch
- Before main evening meal (dinner)
- At bedtime

SMPG values measured before breakfast, lunch, main evening meal, and at bedtime should be performed before any injection of bolus insulin and just before the start of the meal (breakfast, lunch or main evening meal). SMPG values measured before breakfast should be performed in a fasting condition. The 4-point profile is part of the 7-point profiles which are measured prior to selected site visits.

7-point SMPG profile

All subjects will be instructed to perform 7-point SMPG profiles in the week prior to V8, V24 and V36 according to the time points listed below:

- Before breakfast
- 90 minutes after the start of breakfast
- Before lunch
- 90 minutes after the start of lunch
- Before main evening meal (dinner)
- 90 minutes after the start of main evening meal (dinner)
- At bedtime

SMPG values measured before breakfast, lunch, main evening meal and at bedtime should be performed before any insulin injection and just before the start of the meal (breakfast, lunch or main evening meal). SMPG values measured before breakfast should be performed in a fasting condition. The measurements will be used to evaluate the glucose profile.

9.1.2 Clinical efficacy laboratory assessments

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

9.1.3 Patient reported outcomes

The following PRO questionnaires will be used in the trial:

- 36-item Short Form Health Survey version 2 (SF-36v2™)
- Treatment related impact measure for diabetes (TRIM-D)
- Diabetes Quality of Life Clinical Trial Questionnaire (DQLCTQ-R)

The questionnaires should be completed by the subject as specified in the flowchart (see Section 2). It takes approximately 20 minutes to complete the questionnaires. Subjects should be given the opportunity to complete the questionnaires by themselves without interruption. All results from the PROs must be transferred into the eCRF.

SF-36v2™

The SF-36v2™ questionnaire (standard version) will be used to assess subjects overall HRQoL and can also be used to estimate quality adjusted life years which is used in cost effectiveness calculations. This questionnaire contains 36 items and measures the individual overall HRQoL on 8 domains; physical functioning, role functioning, body pain, general health, vitality, social functioning, role emotional and mental health.

TRIM-D

The TRIM-D questionnaire will be used to assess the treatment impact and burden for subjects. The questionnaire contains 28 items and provides an overall score (TRIM-D score) as well as a score of

each of the 5 domains; Treatment burden, Daily life, Diabetes management, Compliance and Psychological health.

DQLCTQ-R
The DQLCTQ-R questionnaire will be used to assess subjects' HRQoL. The questionnaire contains 57 items and measures and provide scores for each of the 8 included domains; Physical Function, Energy/Fatigue, Health Distress, Mental Health, Satisfaction, Treatment Satisfaction, Treatment Flexibility and Frequency of Symptoms.

9.1.4 Body measurements

- Height is measured without shoes in centimetres or inches and recorded to nearest ½cm or ¼inch.
- Body weight should be measured without shoes and only wearing light clothing and recorded in the eCRF in kilogram or pound [kg/lb], with a precision of 1/10 unit, (e.g. 45.2 kg / 137.2 lb). BMI will be calculated in the eCRF.
- The waist circumference is defined as the minimal abdominal circumference located midway between the lower rib margin and the iliac crest and will be measured using a non-stretchable measuring tape. The measurement of waist circumference should be performed and recorded in the eCRF to the nearest ½ cm or ¼inch using the same measuring tape throughout the trial. The waist circumference should be measured in a standing position with an empty bladder and wearing light clothing with accessible waist. The subject should be standing with arms down their side and feet together. The tape should touch the skin but not compress soft tissue. The subject should be asked to breathe normally and the measurement should be taken when the subject is breathing out gently.

9.2 Adverse events

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

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

9.2.1 Time period and frequency for collecting AE and SAE information

All AEs will be collected from after run-in (V2) and until the follow-up visit, at the time points specified in the flowchart (Section 2). Medical occurrences with onset between informed consent and day of run-in or conditions detected as part of screening procedures need to be recorded, if applicable, on the medical history/concomitant illness form in the CRF (not the AE CRF).

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

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

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

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

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

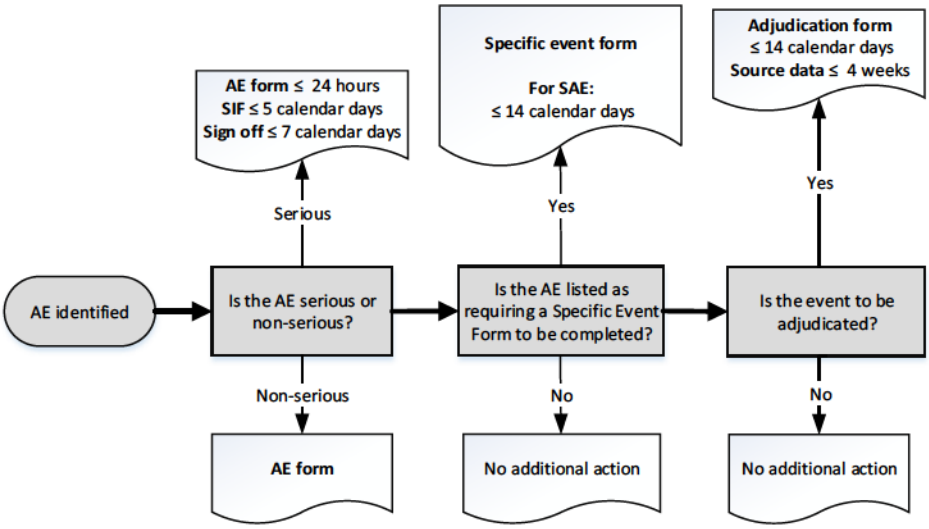

Figure 9-1 Decision tree for determining the event type and the respective forms to complete with associated timelines

Table 9-1 AEs requiring additional data collection (via specific event form) and events for adjudication

Event type	Description	AE requiring additional event form	Event for adjudication (9.2.1.1)	Adjudication outcome
Acute gallbladder disease	Events of symptomatic acute gallbladder disease (including gallstones and cholecystitis)	X		
Death	All-cause death		X	• Death associated with severe hypoglycaemic episode (ADA), • Death associated with acute pancreatitis • Death not associated with severe hypoglycaemia or acute pancreatitis
Severe hypoglycaemic episode (ADA)	An episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. Plasma glucose (PG) 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		X	Severe hypoglycaemic episode (ADA)
Malignant neoplasm	Malignant neoplasm by histopathology or other substantial clinical evidence	X		
Acute pancreatitis	Diagnosis requires at least two of the following: 1) abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back) 2) serum lipase (and/or amylase) at least three times greater than the upper limit of normal 3) characteristic findings of acute pancreatitis on imaging.	X	X	Acute pancreatitis (according to Atlanta classification[15])
Diabetic retinopathy	New onset or worsening of diabetic retinopathy	X		
Medication error	Administration of wrong drug.	X		

	Wrong route, such as intramuscular instead of s.c. or accidental administration of a lower or higher dose than intended where clinical consequences for the patient were likely to happen, although they did not necessarily occur. Intentional drug errors related to trial product are misuse/abuse and should be reported as AEs and not as medication errors.			

9.2.1.1 Events for adjudication

To increase the validity of the endpoints and ensure a standardised and uniform assessment of severe hypoglycaemic episodes, acute pancreatitis and all deaths, these events will undergo adjudication. Table 9-1 lists the AEs that are subject to event adjudication including an elaborate definition of the event types. The reporting timelines are listed in Figure 9-2.

Event adjudication will be performed for events in randomised subjects including events with an onset date on the day of randomisation and onwards.

These events are reviewed by an independent external event adjudication committee in a blinded manner; refer to Appendix 3 for further details.

Events relevant for adjudication are identified as described below:

1. Investigator-reported events for adjudication: Severe hypoglycaemic episode or hypoglycaemic episode reported as SAE as well as Acute Pancreatitis
2. Deaths (AEs reported with fatal outcome)
3. PT Search (standardized screening): All AEs not directly reported by the investigator as requiring adjudication, will undergo screening and evaluation to identify potential events for adjudication. The investigator can be queried to provide additional information related to the reported AE, e.g. alternative aetiology, underlying cause(s) and/or clinical details.
4. EAC-identified events: When reviewing source documents provided for another event for adjudication, the EAC can identify additional events in scope for adjudication that were not initially reported by the investigator. In these instances, the investigator will be notified of the newly identified event and has the option to report the EAC-identified event. Regardless of whether the investigator decides to report the event or not, it will undergo adjudication. Occasionally, EAC-identified events may require the investigator to collect additional source documents, which should be provided by uploading to the event adjudication system (EAS).

With the exception of EAC-identified events, an adjudication form for the specific event types in question should be completed in the CRF within 14 calendar days of the investigator's first knowledge of the event. Copies of collected source documents should be labelled with trial ID, subject and AE number, redacted (anonymised of personal identifiers, trial drug, dose, route of

administration, number of drug administrations etc.) and uploaded to the EAS within 4 weeks according to instructions outlined in the event adjudication site manual. If no, or insufficient source documents are provided to the adjudication supplier, the investigator can be asked to complete a clinical narrative to serve as supporting documentation and upload this to the EAS.

If new information becomes available for an event sent for adjudication, it is the responsibility of the investigator to ensure the new information is uploaded to the EAS as the new information may result in re-adjudication of the event.

A site manual will be provided to each site detailing how to provide the relevant documentation to the adjudication vendor. In addition, the anonymization requirements will also be described in the site manual.

9.2.2 Method of detecting AEs and SAEs

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

9.2.3 Follow-up on AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, or if the event is otherwise explained (e.g. chronic condition) or the subject is lost to follow-up (as defined in Section 8.4).Unresolved non-serious AEs should be followed until end of trial. Further information on follow-up procedures is given in Appendix 4.

9.2.4 Regulatory reporting requirements for SAEs

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

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

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Novo Nordisk policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g. summary or listing of SAEs), from Novo Nordisk will review and then file it

along with the investigator's brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.2.5 Cardiovascular and death events

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

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

The following Disease-Related Events (DREs) are common in subjects with type 2 diabetes and can be serious/life threatening:

- Hypoglycaemic episodes

Definitions, classification and reporting requirements are described in Appendix 7

All events of hypoglycaemia must be reported on the hypoglycaemic episode form. Please refer to Appendix 7 for details.

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

9.2.7 Pregnancies and associated adverse events

Details of pregnancies in female subjects will be collected after the first-trial-related activity after obtaining informed consent and until pregnancy outcome.

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

Pregnancy outcome should be documented in the subject's medical record. Abnormal pregnancy outcome (e.g. spontaneous abortion, foetal death, stillbirth, congenital anomalies and ectopic pregnancy) is considered an SAE. The investigator will report information on the patient and the pregnancy outcome until the newborn infant is one month of age in accordance with European Medicines Agency (EMA) and Committee for Medicinal Products for Human Use (CHMP).[16]

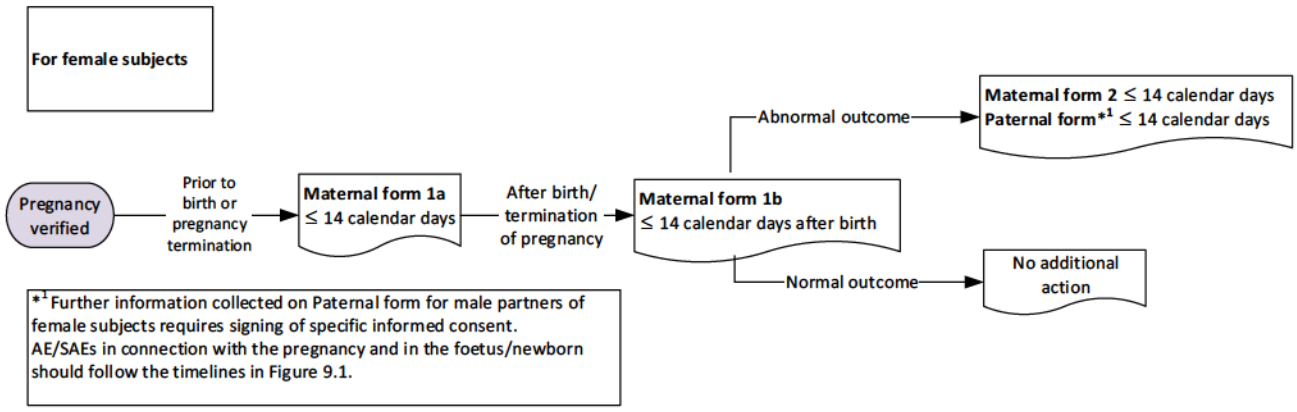

Figure 9-2 Decision tree for determining the forms to complete with associated timelines for pregnancy.

9.2.8 Medical device incidents (including malfunctions)

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

9.2.9 Technical complaints

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

9.3 Treatment of overdose

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

In the event of an overdose, the investigator should closely monitor the subject for overdose-related AE/SAE and laboratory abnormalities.

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

Insulin

A specific overdose for insulin cannot be defined; however, hypoglycaemia may develop over sequential stages if too high doses relative to the patient's requirement are administered. Mild episodes of hypoglycaemia can usually be treated with oral carbohydrates. Adjustments in dose of the medicinal product, meal patterns, or physical activity may be needed. More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/s.c. glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycaemia may recur after apparent clinical recovery.

Semaglutide
Overdoses of up to 4 mg of semaglutide in a single dose/in one week have been reported in clinical trials. The most commonly reported adverse reaction was nausea. All patients recovered without complications. In the event of overdose, appropriate supportive treatment should be initiated according to the patients' clinical signs and symptoms. A prolonged period of observation and treatment for these symptoms may be necessary, taking into account the long half-life of semaglutide of approximately one week.

For more information on overdose, also consult the current version of the semaglutide investigator's brochure and the current version of the local label for Lantus® and NovoRapid®/NovoLog®.

9.4 Safety assessments

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

A **concomitant illness** is any illness that is present at the start of the trial (i.e. at the first visit) or found as a result of a screening procedure or other trial procedures performed before exposure to trial product.
Medical history is a medical event that the subject has experienced in the past. Only relevant concomitant illness and medical history as judged by the investigator should be reported. Diabetes history and related complications should be reported separately in the diabetes history/complication form.

The information collected for concomitant illness and medical history should include diagnosis, date of onset and date of resolution or continuation, as applicable.

In case of an abnormal and clinically significant finding, the investigator must record the finding on the Medical History/Concomitant Illness form if it is present at screening. Any new finding fulfilling the AE definition (see Appendix 4) during the trial and any clinically significant worsening from run-in (Visit 2) must be reported as an AE (see Section 9.2).

9.4.1 Physical examinations

- A physical examination will include assessments of the general appearance, thyroid gland and the Cardiovascular, Respiratory, Gastrointestinal, Musculoskeletal and Neurological systems.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

9.4.2 Vital signs

- Pulse rate, as well as diastolic and systolic blood pressure will be assessed.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the subject in a quiet setting without distractions (e.g. television, cell phones).

- Blood pressure at screening will consist of 3 diastolic and systolic blood pressure measurements with intervals of at least 1 minute.
- Pulse at screening will also consist of 3 measurements.
- All blood pressure and pulse readings must be entered in the CRF and the average of the 3 blood pressure readings will be calculated in the CRF.
- At the subsequent visits, the blood pressure and pulse should only be measured once.
- Blood pressure and pulse measurements will be assessed while the subject is in a sitting position with a completely automated device. Manual techniques will be used only if an automated device is not available.

9.4.3 Clinical safety laboratory assessments

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

9.4.4 Eye examination

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

Results of an eye examination performed as per flow chart (see Section 2) by an ophthalmologist, or another suitable qualified certified health care provider must be available and evaluated by the investigator at Visit 2 at the latest to assess eligibility.

The eye examination should be performed as a fundus photography (e.g. 2-field 60 degree or better, colour or red-free) or by slit-lamp biomicroscopy examination (e.g. using a pre-corneal or corneal contact lens examination) and performed with pharmacologically dilated pupils.

If the subject had such an eye examination performed within 90 days prior to run-in (Visit 2), the investigator may base his/her evaluation upon the results of that examination. The examination must be repeated before randomisation if the subject has experienced worsening of visual function since the last examination. If the applicable eye examination was performed before the subject signed the informed consent form, it must be documented that the reason for performing the examination was not related to this trial.

The examination must be repeated within 30 days prior to randomisation and results must be available for evaluation at Visit 8.

After randomisation an eye examination performed according to above must be performed at Visit 36 or within 5 weeks prior to this. The investigator should indicate the outcome of each eye examination. Relevant findings prior to randomisation must be recorded as concomitant illness/medical history. While relevant findings occurring after randomisation should be reported as

an AE, if applicable according to Section 9.2. Results must be available and evaluated by the investigator at Visit 36. For subjects who discontinue trial treatment, the eye examination should be performed both at V36A and V36. At V36A the assessment can be performed in the period between V36A and P37A, but the results should be available and reviewed no later than at P37A.

9.5 Pharmacokinetics

Not applicable

9.6 Pharmacodynamics

Not applicable

9.7 Genetics

Not applicable

9.8 Biomarkers

Not applicable

10 Statistical considerations

10.1 Sample size determination

The primary endpoint is change from baseline to week 52 in HbA_{1c}, and both non-inferiority and subsequently superiority are planned to be tested. The confirmatory secondary endpoints are time to first EAC confirmed severe hypoglycaemic episode (ADA) from randomisation up to week 52, time to first EAC confirmed severe hypoglycaemic episode requiring hospitalisation, documented medical help, or is life threatening from randomisation up to week 52, and change from baseline to week 52 in body weight. For these endpoints superiority will be tested. The type-I error rate will be controlled in the strong sense across the primary and the confirmatory secondary hypotheses at an overall alpha (two-sided) of 0.05. Multiplicity control and criteria for confirming hypotheses is described in Section 10.3 below.

The trial is designed to have 85% power to jointly establish non-inferiority, with respect to glycaemic control, and to confirm superiority on EAC confirmed severe hypoglycaemic episodes (ADA), and to confirm superiority on EAC confirmed severe hypoglycaemic episodes (ADA) requiring hospitalisation, documented medical help, or is life threatening, of semaglutide compared to IAsp. The superiority hypotheses for both severe hypoglycaemic endpoints are the determining factor for the sample size. This means that the power for HbA_{1c} non-inferiority is indirectly obtained with the number of subjects needed to confirm superiority on both severe hypoglycaemic endpoints.

Primary endpoint

With 1736 subjects randomised to ensure sufficient joint power (85%) for the hypotheses for the confirmatory severe hypoglycaemic endpoints, there is >99.9% power for confirming that semaglutide is non-inferior to IAsp on change from baseline to week 52 in HbA_{1c}. This is based on a 1:1 randomisation, a two-sided significance level of 0.05, a t-test, an assumption of no treatment difference, a non-inferiority margin of 0.3%-point, and a standard deviation (SD) of 1.1%-point. Both semaglutide and IAsp have a large effect on glycaemic control, thus a conservative approach motivates the assumed treatment difference of 0.0%-point, and the assumed SD is based on the SUSTAIN program. With the above assumptions, the marginal power for establishing superiority of semaglutide versus IAsp on change from baseline to week 52 in HbA_{1c} corresponds to the type-I error.

Confirmatory secondary endpoints

Time to first EAC confirmed severe hypoglycaemic episode (ADA) from randomisation up to week 52

The power calculation for the superiority hypothesis for this endpoint is based on the following assumptions

- First EAC confirmed severe hypoglycaemic episode (ADA) occur at an incidence rate of 4.0 per 100 patient years of risk time (PYR) in the IAsp group
- First EAC confirmed severe hypoglycaemic episode (ADA) occur at an incidence rate of 1.0 per 100 PYR in the semaglutide group, corresponding to a hazard ratio of 0.25
- 10% of the subjects randomised to IAsp will prematurely discontinue trial medication uniformly during the 52 weeks of treatment
- 15% of the subjects randomised to semaglutide will prematurely discontinue trial medication uniformly during the 52 weeks of treatment

The assumptions for the incidence rate of severe hypoglycaemia are based on the previously conducted clinical trials with similar population, titration and duration: DUAL VII (NN9068-4185)[17], BEGIN Basal-Bolus T2D (NN1250-3582)[18], AWARD-4[19], DEVOTE (EX1250-4080)[20] and SUSTAIN 5 (NN9535-3627)[8]. In these trials, the following incidence rates of or proportion of subjects experiencing severe hypoglycaemic episodes were observed for IAsp and semaglutide respectively:

IAsp

- *DUAL VII* (26 weeks, NN IDegLira titration algorithm): 253 subjects treated with IGlar and IAsp 2-4x/day whereof 4 subjects experienced a severe hypoglycaemic episode (ADA). With a total exposure of 119.3 years this gives an incidence rate of 3.4 per 100 PYR.
- *BEGIN BASAL BOLUS* T2D (52 weeks, NN insulin titration algorithm): 251 subjects treated with IGlar and IAsp TID whereof 11 subjects experienced a severe hypoglycaemic episode (ADA). With a total exposure of 228.8 years this gives an incidence rate of 4.8 per 100 PYR.
- *AWARD-4* (52 weeks, titration algorithm adapted based on Riddle and Bergenstahl): 296 subjects treated with IGlar and Lispro TID whereof 15 subjects experienced a severe hypoglycaemic episode (investigator's clinical judgement). This gives a proportion of 5.1%.
- *DEVOTE* (2 years, NN insulin titration algorithm and individualised titration) 1755 subjects with a pre-randomisation treatment of basal-bolus insulin (including bolus only and pre-mix) where treated with IGlar whereof 151 subjects experienced an EAC confirmed severe hypoglycaemic episode (ADA). With a mean observation time of 1.98 years this gives an incidence rate of 4.3 per 100 PYR.

Semaglutide

- *SUSTAIN 5* (30 weeks, no enforced titration): 132 subjects treated with basal insulin and semaglutide OW 0.5 mg whereof 0 subjects experienced a severe hypoglycaemic episode (ADA). 131 subjects treated with basal insulin and semaglutide OW 1.0 mg whereof 2 subjects experienced a severe hypoglycaemic episode (ADA). With a total exposure across treatments of 116.1 years this gives an incidence rate of 1.2 per 100 PYR across treatment groups.

Based on these results and using a conservative approach to accommodate the uncertainty in the incidence rates, an incidence rate of 4.0 per 100 PYR in the IAsp group, mainly based on the EAC confirmed severe hypoglycaemic episodes in DEVOTE, and an incidence rate of 1.0 per 100 PYR in the semaglutide group are assumed. With 1736 randomised subjects, a 1:1 randomisation, a two-sided significance level of 0.05, and a log-rank test, this yields a marginal power of 96.8%.

Time to first EAC confirmed severe hypoglycaemic episode (ADA) requiring hospitalisation, documented medical help, or is life threatening from randomisation up to week 52

Based on the observations from the DEVOTE trial, a total of 95 subjects experienced an EAC confirmed severe hypoglycaemic episode (according to ADA) that fulfilled the additional requirement that these events were either SAEs (covering events requiring hospitalisation or life threatening events), or the subject experiencing this event was unconscious, in coma or had a seizure, or required medical assistance or was treated with I.V. glucose or glucagon. This corresponds to an observed incidence rate of 2.7 per 100 PYR. The assumption of uniform loss functions of 15% for the semaglutide arm and 10% for the IAsp arm, as well as the ratio of 1:4 between the semaglutide and the IAsp assumed incidence rates, used for power calculations for the first EAC confirmed severe hypoglycaemic episode (ADA), are maintained for this endpoint. Based on these assumptions, the power calculation for this endpoint is based on an assumed incidence rate of 0.675 per 100 PYR for semaglutide and 2.7 per 100 PYR for IAsp. With 1736 randomised subjects, a 1:1 randomisation, a two-sided significance level of 0.05, and a log-rank test, this yields a marginal power of 87.9%.

Change from baseline to week 52 in body weight

With 1736 subjects randomised to ensure sufficient joint power (85%) for the confirmatory severe hypoglycaemic endpoints, there is >99.9% marginal power for confirming that semaglutide is superior to IAsp on change from baseline to week 52 in body weight. This is based on a 1:1 randomisation, a two-sided significance level of 0.05, a t-test, an assumed treatment difference of 2.0 kg, and a SD of 4.0 kg. The assumed treatment difference and the SD is based on the SUSTAIN program.

The joint (effective) power is calculated under the assumption of independence of endpoints by multiplying the respective marginal powers successively. Since some of these endpoints/tests are positively correlated, the assumption of independence is viewed as conservative. With the above assumptions, a joint power of 85% for confirming non-inferiority in HbA_{1c}, and superiority on both severe hypoglycaemic endpoints will require a total of 1736 randomised subjects, i.e. 868 subjects randomised in each arm, when comparing semaglutide to IAsp. Table 10-1summarises the assumptions that the sample size calculation is based on as well as providing an overview of the marginal and joint power for each hypothesis.

Table 10-1

Hypothesis	Assumptions	Randomised subjects	Marginal power	Joint power
HbA_{1c}, non-inferiority	Treatment difference: 0.0%-point Standard deviation: 1.1%-point Non-inferiority margin: 0.3%-point	1736	>99.9%	>99.9%
EAC confirmed severe hypoglycaemic episodes (ADA), superiority	Hazard ratio: 0.25 Incidence rate for semaglutide: 1.0 per 100 PYR Incidence rate for IAsp: 4.0 per 100 PYR 10% uniform loss for IAsp 15% uniform loss for semaglutide	1736	96.8%	96.8%
EAC confirmed severe hypoglycaemic episodes (ADA) requiring hospitalisation, documented medical help, or is life threatening, superiority	Hazard ratio: 0.25 Incidence rate for semaglutide: 0.675 per 100 PYR Incidence rate for IAsp: 2.7 per 100 PYR 10% uniform loss for IAsp 15% uniform loss for semaglutide	1736	87.9%	85.0%
Body weight, superiority	Treatment difference: 2.0 kg Standard deviation: 4.0 kg	1736	>99.9%	85.0%
HbA_{1c}, superiority	Treatment difference: 0.0%-point Standard deviation: 1.1%-point	1736	Less than or equal to Type I error per assumption	

The sample size calculations above are sensitive to the assumptions made for the incidence rates and true hazard ratios for the severe hypoglycaemic endpoints. Table 10-2illustrates this with eight alternative set of assumptions.

Table 10-2 Power with different incidence rates for severe hypoglycaemic episodes for the IAsp treatment group

Scenarios	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Base case	Scenario 5	Scenario 6	Scenario 7	Scenario 8
Time to first EAC confirmed severe hypoglycaemic episode (ADA)									
Incidence rate per 100 PYR: semaglutide	1.0	1.0	1.0	1.0	**1.0**	1.0	1.0	1.0	1.0
Incidence rate per 100 PYR: IAsp	3.5	3.75	4.25	4.5	**4.0**	4.0	4.0	4.0	4.0
HR	0.29	0.27	0.24	0.22	**0.25**	0.25	0.25	0.25	0.25
Marginal power	91.7%	94.7%	98.0%	98.8%	**96.8%**	96.8%	96.8%	96.8%	96.8%
Expected number of first events: semaglutide	9	9	9	9	**9**	9	9	9	9

Expected number of first events: IAsp	30	32	37	39	**35**	35	35	35	35
Time to first EAC confirmed severe hypoglycaemic episode (ADA) requiring hospitalisation, documented medical help, or is life threatening									
Incidence rate per 100 PYR: semaglutide	0.675	0.675	0.675	0.675	**0.675**	0.675	0.675	0.675	0.675
Incidence rate per 100 PYR: IAsp	2.7	2.7	2.7	2.7	**2.7**	2.1	2.4	3.0	3.3
HR	0.25	0.25	0.25	0.25	**0.25**	0.32	0.28	0.25	0.20
Marginal power	87.9%	87.9%	87.9%	87.9%	**87.9%**	68.1%	79.8%	93.1%	96.2%
Expected number of first events: semaglutide	6	6	6	6	**6**	6	6	6	6
Expected number of first events: IAsp	24	24	24	24	**24**	19	21	26	29
Randomised subjects	1736	1736	1736	1736	**1736**	1736	1736	1736	1736
Joint power	80.6%	83.3%	86.2%	86.9%	**85.0%**	65.9%	77.2%	90.1%	93.1%

10.2 Definition of analysis sets

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

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

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

Per protocol (PP) analysis set: includes all subjects in the FAS who fulfil the following criteria:

- Have not violated any inclusion criteria
- Have not fulfilled any exclusion criteria
- Have not fulfilled any run-in exclusion criteria
- Have not violated any randomisation criteria
- Have a valid HbA_{1c} measurement at the randomisation visit (V8) and/or the last run-in visit (V7)
  Is on trial product at visit 21 and have at least one valid HbA_{1c} measurement at or after visit 21

Subjects will be analysed according to the trial product received for the majority of the period they were on treatment.

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

- date of end-of-trial follow-up visit
- date of death
- date when subject withdrew consent
- date of last contact for subjects lost to follow-up

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

- The follow-up visit (P37)
- The premature discontinuation follow-up visit (P37A)
- The last date on randomised treatment regimen + 42 days
- The end-date for the 'in-trial' observation period

The follow-up visit is scheduled to take place 5 weeks after the last date on trial product corresponding to approximately five half-lives of semaglutide OW. The visit window for the follow-up visit is +7 days, a total of 42 days.

For efficacy and other safety assessments (hypoglycaemic episodes, laboratory assessments, body measurements, SMPG, PRO questionnaires, and vital signs) the 'on-treatment' observation period ends at the last date on trial product with a visit window of +7 days in accordance to the trial flow chart. Hence, for these assessments, the 'on-treatment' observation period reflects the period in which subjects are treated.

Due to inherently similar pharmacological characteristics of different bolus insulins, subjects randomised to IAsp who have changed to a different bolus insulin will be considered as being on randomised treatment. In this case the last date on randomised trial regimen will be the last date on any bolus insulin.

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

Before data are locked for statistical analysis, a review of all data will take place. Neither subjects nor observations should be excluded from data. If subjects or observations are excluded, the reasons for their exclusion must be documented before database lock and described in the clinical trial report. Any decision to exclude either a subject or single observations from the statistical analysis is the joint responsibility of the members of the Novo Nordisk study group.

10.3 Statistical analyses

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

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 comparison presented from a statistical analysis will be semaglutide versus IAsp.

If no statistical analysis is specified, data will be presented using relevant summary statistics. Accordingly, adverse events will be summarised descriptively. Data collected before randomisation (V8) will only be summarised descriptively.

Data transformations

Some of the continuous parameters will be log-transformed prior to statistical analysis. The output tables and figures will show the results of the analysis back-transformed to the original scale, implying that log-treatment-differences are reported as treatment ratios.

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

Multiplicity control and criteria for confirming hypotheses

In order to preserve the overall type-I error the conclusion of non-inferiority and superiority of semaglutide versus IAsp will be evaluated hierarchically according to the sequence below, and starting with the first hypothesis. In this testing sequence it is necessary to fulfil the test criteria, which is to reject the corresponding null hypothesis in order to go to the next step. If the corresponding null hypothesis is not rejected, the testing will stop and no further conclusions will be drawn. The treatment difference is defined as μ = (semaglutide minus IAsp). The hazard ratio (HR) is for the comparison of semaglutide vs. IAsp.

1. HbA_{1c} non-inferiority of semaglutide vs. IAsp
   - H_0: $\mu \geq 0.3$%-point against H_a: $\mu < 0.3$%-point

2. Superiority of semaglutide vs. IAsp on EAC confirmed severe hypoglycaemic episodes (ADA)
   - H_0: HR ≥ 1.0 against H_a: HR < 1.0

3. Superiority of semaglutide vs. IAsp on EAC confirmed severe hypoglycaemic episodes (ADA) requiring hospitalisation, documented medical help, or is life threatening
   - H_0: HR ≥ 1.0 against H_a: HR < 1.0

4. Superiority of semaglutide vs. IAsp on body weight
   - H_0: $\mu \geq 0.0$ kg against H_a: $\mu < 0.0$ kg

5. Superiority of semaglutide vs. IAsp on HbA_{1c}
   - H_0: $\mu \geq 0.0$%-point against H_a: $\mu < 0.0$%-point

Non-inferiority and superiority of semaglutide versus IAsp will be considered confirmed if the associated H_0 is rejected.

The non-inferiority margin of 0.3%-point is chosen based on the EMA guideline[21] and the effect of faster-acting insulin aspart (FIAsp) on glycaemic effect seen in a similar trial (NN1218-4049) where FIAsp was used in a basal-bolus regimen versus basal insulin therapy, both in combination with metformin.[22] In this trial FIAsp showed an HbA_{1c} treatment difference to placebo of -0.94%-point. FIAsp is non-inferior to IAsp in terms of lowering HbA_{1c} levels.[23] Hence, based on this trial, the chosen margin of 0.3%-point provides assurance that semaglutide has an effect compared to placebo greater than 0 with a clinically relevant size. With regards to the constancy assumption, controlled clinical trials have consistently established that IAsp is an effective anti-diabetic drug. Therefore, lack of trial sensitivity with IAsp as comparator is not anticipated to be an issue in this trial.

10.3.1 Primary endpoint

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

Primary analysis

According to the primary estimand, the primary analysis will be estimated based on the FAS using post-baseline measurements up to and including week 52 from the 'on-treatment' observation period. Imputation of missing data will be handled using multiple imputation assuming that missing data is missing at random (MAR). Missing data will be imputed using observed data within each of the two groups defined by the randomised treatment (semaglutide/IAsp). It is hereby assumed that the likely values of what the missing data would have been, if available, are best described by information from subjects who receive the same treatment.

Technically, missing values will be imputed as follows:

- Intermittent missing values are imputed using a Markov Chain Monte Carlo (MCMC) method, in order to obtain a monotone missing data pattern. This imputation is done for each of the treatment groups separately and 500 copies of the dataset will be generated.
- A sequential conditional linear regression approach for imputing monotone missing values at planned visits will be implemented starting with the first visit after baseline and sequentially continuing to the last planned visit at week 52. A model used to impute missing values at each planned visit will be fitted for each of the randomised treatment groups using observed data. The model will include the baseline and post-baseline HbA_{1c} values observed prior to the visit in question as covariates. The resulting 500 complete datasets will furthermore be used for the subsequent tipping analysis to evaluate the robustness of the primary analysis.
- An analysis of covariance (ANCOVA) with treatment as categorical effect and baseline HbA_{1c} as a covariate will be used to analyse HbA_{1c} values at week 52 for each of the 500 complete data sets. Rubin's rule[24] will be used to combine the analysis results in order to draw inference.

From this analysis, the estimated treatment difference between semaglutide and IAsp at week 52 will be presented together with the associated two-sided 95% confidence interval (CI) and two-sided p-value.

Sensitivity analyses

The aim of the below pre-specified sensitivity analysis is to investigate the robustness of the conclusions from the primary analysis and to stress test the missing at random assumption.

Tipping point analysis

The tipping point analysis is based on the FAS using the 'on-treatment' observation period. In this analysis, subjects from the semaglutide group with missing observations will be given a penalty, i.e., it is assumed that subjects with missing observations who are randomised to semaglutide will receive a treatment that is less beneficial than subjects with observed values who are randomised to semaglutide. The 500 complete datasets created for the primary analysis will be re-used for the tipping-point analysis. For each of these datasets, penalty values are added stepwise to the imputed change from baseline at week 52 for subjects randomised to semaglutide, followed by performing an ANCOVA. The addition of the penalty values and subsequent analysis steps should be repeated with increasing penalty values until a significant result in the corresponding superiority and non-inferiority analyses are no longer significant.

Retrieved dropout analysis

The retrieved dropout analysis will be based on the FAS using the 'in-trial' observation period. Missing data will be imputed using the same approach as described for the primary analysis of the primary estimand. However the imputation will be done within the same group defined not only by

the randomised treatment (semaglutide/ IAsp) but also by the treatment status (still on randomised treatment at week 52 yes/no) (4 groups in total). It is hereby assumed that the likely values of what the missing data would have been if available are best described by information from subjects who at week 52 are similar in terms of randomised treatment and treatment status. This analysis will be performed for both non-inferiority and superiority testing.

Per protocol analysis

The per protocol analysis is based on the PP analysis set using the 'on-treatment ' observation period. This analysis will be carried out for non-inferiority testing only. The statistical analysis will be the same as the primary analysis for the primary estimand.

10.3.2 Secondary endpoints

10.3.2.1 Confirmatory secondary endpoints

The confirmatory secondary endpoints are time to first EAC confirmed severe hypoglycaemic episode (ADA), time to first EAC confirmed severe hypoglycaemic episode (ADA) requiring hospitalization, documented medical help, or is life threatening and change from baseline to week 52 in body weight.

Confirmatory analyses

The statistical analysis of time to first EAC confirmed severe hypoglycaemic episode (ADA) will be based on the FAS using the 'on-treatment' observation period. The hazard ratio comparing semaglutide versus IAsp will be estimated from a Cox proportional hazards model with treatment group (semaglutide, IAsp) as fixed factor together with the two-sided 95% CI and the two-sided p-value. Subjects who have not experienced an EAC confirmed severe hypoglycaemic episode (ADA) within the 'on-treatment' observation period will be considered censored with the censoring date given by the end-date of the 'on-treatment' observation period. Superiority will be tested according to the statistical analysis approach to multiplicity described in Section 10.3.

The statistical analysis of time to first EAC confirmed severe hypoglycaemic episode (ADA) requiring hospitalization, documented medical help, or is life threatening will be analysed in the same manner as the confirmatory endpoint time to first EAC confirmed severe hypoglycaemic episode (ADA) as described above. This analysis will be based on the FAS and the 'on-treatment' observation period.

For each time-to-event endpoint, a Kaplan-Meier plot with numbers of subjects at risk at specific time points for each treatment group will be presented.

According to the primary estimand, body weight will be analysed using the same approach as described in Section 10.3.1. Body weight will be tested for superiority according to the statistical

analysis approach to multiplicity described in Section 10.3. Baseline and post-baseline body weight will be used as covariates instead of HbA_{1c}.

Sensitivity analyses

An in-trial sensitivity analysis will be performed to evaluate the robustness of the conclusions from the statistical analysis of time to first EAC confirmed severe hypoglycaemic episode (ADA). This in-trial analysis is based on the FAS using the 'in-trial' observation period. Subjects who have not experienced an EAC confirmed severe hypoglycaemic episode (ADA) within the 'in-trial' observation period will be considered censored with the censoring date given by the in-trial end-date. The statistical analysis will be the same as the statistical analysis for the primary estimand.

Moreover, the time to first EAC confirmed severe hypoglycaemic episode (ADA) requiring hospitalization, documented medical help, or is life threatening will be analysed using the same model as described above but using all data collected in the 'in-trial' observation period instead.

The tipping point sensitivity analysis pre-specified to evaluate the robustness of the conclusions from the primary analysis of HbA_{1c} will also be performed to evaluate the robustness of the conclusions from the body weight superiority test. In addition, the retrieved dropout sensitivity analysis will also be performed for body weight.

10.3.2.2 Supportive secondary endpoints

The following continuous supportive secondary endpoints are considered. Change from baseline to week 52 in:

- Fasting plasma glucose (mmol/L)
- Mean 7-point self-measured plasma glucose profile (mmol/L)
- Mean post-prandial increment (over all meals) (mmol/L)
- Systolic and diastolic blood pressure (mmHg)
- Fasting blood lipids (total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides) (mmol/L)
- Body mass index (BMI) (kg/m^2)
- Waist circumference (cm)
- Body weight (%)

The above continuous endpoints will be analysed separately using a similar model approach as for the primary endpoint with the associated baseline value as covariate instead of HbA_{1c} for their respective analyses. These analyses will be based on the FAS and the 'on-treatment' observation period.

Fasting blood lipid endpoints will be log-transformed prior to analysis with the associated log-transformed baseline value as a covariate.

Pulse rate

Change from baseline to week 52 in pulse rate (bpm) will be analysed using an analysis similar to the primary analysis of the primary endpoint but with the baseline pulse rate value as covariate instead of HbA_{1c}. This analysis will be based on the SAS using the 'on-treatment' observation period.

Hypoglycaemic episodes

The supportive secondary safety endpoints related to hypoglycaemic episodes are:

- Number of EAC confirmed severe hypoglycaemic episodes (ADA) from randomisation to week 52
- Number of EAC confirmed severe (ADA) or blood glucose confirmed, symptomatic hypoglycaemic episodes (PG < 3.1 mmol/L (56 mg/dL)) from randomisation to week 52
- Number of EAC confirmed severe (ADA) or blood glucose confirmed, symptomatic hypoglycaemic episodes (PG ≤ 3.9 mmol/L (70 mg/dL)) from randomisation to week 52
- Number of EAC confirmed severe hypoglycaemic episodes (ADA) requiring hospitalisation, documented medical help, or is life threatening from randomisation to week 52

The number hypoglycaemic episodes of the above types will be analysed using a negative binomial regression model with a log-link function and the logarithm of the time period covered by the subject's 'on-treatment' observation period as offset. The model will include treatment as a fixed factor and baseline HbA_{1c} as a covariate. This analysis will be based on the FAS using the 'on-treatment' observation period. The results will be described by the rate ratio between treatments and the associated 95% CI and p-value for no treatment difference.

Moreover, the above types of number of hypoglycaemic episodes will also be analysed based on the 'in-trial' observation period, still using the above mentioned model, however using all data collected in the 'in-trial' observation period.

Supportive secondary HRQoL endpoints

Change from baseline to week 52 in the following scores for the selected PROs:

- 36-item Short Form Health Survey version 2 (SF-36v2™)
  - Physical Component Summary (PCS) score (range:7.32-70.14)
  - Mental Component Summary (MCS) score (range: 5.79-69.91)
  - Physical Functioning (PF) domain score (range:19.26-57.54)
  - Role-Physical (RP) domain score (range: 21.23-57.16)
  - Bodily Pain (BP) domain score (range: 21.68-62.00)
  - General Health (GH) domain score (range: 18.95-66.50)
  - Vitality (VT) domain score (range: 22.89-70.42)
  - Social Functioning (SF) domain score (range: 17.23-57.34)

- Role-Emotional (RE) domain score (range: 14.39-56.17)
- Mental Health (MH) domain score (range: 11.63-63.95)

The ten scores related to SF-36v2™ are measured on a scale from 5.79-70.42, and calculated using the 2009 General U.S. Population. Higher scores are indicative of a better health state.

- Diabetes Quality Of Life Clinical Trial Questionnaire (DQLCTQ-R)
  - Physical functioning domain score
  - Energy / fatigue domain score
  - Health distress domain score
  - Mental health domain score
  - Satisfaction domain score
  - Treatment satisfaction domain score
  - Treatment flexibility domain score
  - Frequency of symptoms domain score

  The eight scores related to DQLCTQ-R are measured on a scale from 0-100. Higher scores are indicative of a better health state.

The PRO questionnaires, SF-36v2™ and DQLCTQ-R, will be used to evaluate the objective regarding Quality of Life. Each of the PRO endpoints will be analysed separately as the other continuous supportive secondary endpoints using a similar model approach as for the primary endpoint with the associated baseline value as covariates. These analyses will be based on the FAS and the 'on-treatment' observation period.

10.3.3 Exploratory endpoints

Exploratory responder endpoints

- $HbA_{1c} \leq 7.5\%$ at week 52 (Y/N)
- $HbA_{1c} < 7.0\%$ (53 mmol/mol) at week 52 (Y/N) (ADA)
- $HbA_{1c} \leq 6.5\%$ (48 mmol/mol) at week 52 (Y/N) (AACE)
- $HbA_{1c} \leq 7.5\%$ at week 52 without an EAC confirmed severe hypoglycaemic episode (ADA) from randomisation to week 52 (Y/N)
- $HbA_{1c} \leq 7.5\%$ at week 52 without an EAC confirmed severe hypoglycaemic episode (ADA) requiring hospitalisation, documented medical help, or is life threatening from randomisation to week 52 (Y/N)
- Weight loss $\geq 5\%$ at week 52 (Y/N)
- Weight loss $\geq 10\%$ at week 52 (Y/N)

The above seven binary endpoints will be analysed using a logistic regression model with treatment as fixed effects and baseline response as covariate (i.e. baseline HbA_{1c} for binary HbA_{1c} endpoints, baseline weight for weight endpoints). These analyses will be based on the FAS and the 'on-treatment' observation period. To account for missing data, the analysis will be made using a sequential multiple imputation approach as described below:

- The binary endpoints will be derived based on the 500 imputed datasets from the primary analysis of HbA_{1c} and confirmatory analysis of body weight. For the responder endpoints related to hypoglycaemic episodes, the number of hypoglycaemic episodes for the remaining unobserved part of the observation period will be imputed and subsequently the total number of hypoglycaemic episodes will be dichotomised. This will be done using a Bayes negative binomial log-link model with baseline HbA_{1c} as covariate, and the logarithm of the time period covered by the subject's 'on-treatment' observation period as offset.
- Each of the complete data set will be analysed with the described logistic regression model. Estimated odds ratios will be log transformed and inference will be drawn using Rubin's rule[24].

The results will be back-transformed and described by the odds ratio between treatments and the associated 95% CI and p-value for no treatment difference.

Exploratory PRO endpoints

Change from baseline to week 52 in the following scores for the following PRO:

- Treatment Related Impact Measure For Diabetes (TRIM-D)
  - TRIM-D Total Score
  - Treatment Burden Domain Score
  - Daily Life Domain Score
  - Diabetes Management Domain Score
  - Compliance Domain Score
  - Psychological Health Domain Score

The six scores related to TRIM-D are measured on a scale from 0-100.
Higher scores are indicative of better health state (less negative impact).

The PRO questionnaire, TRIM-D, will be analysed as the other PRO questionnaires described in Section 10.3.2.2.

10.3.4 Other analyses

A total of four additional analyses regarding hypoglycaemic episodes will be performed. These consider:

- Time to first EAC confirmed severe (ADA) or blood glucose confirmed, symptomatic hypoglycaemic episode (PG < 3.1 mmol/L (56 mg/dL)) from randomisation up to week 52 (days)
- Time to first EAC confirmed severe (ADA) or blood glucose confirmed, symptomatic hypoglycaemic episode (PG ≤ 3.9 mmol/L (70 mg/dL)) from randomisation up to week 52 (days)

These analyses will be performed in the same manner as the confirmatory analysis of the endpoint time to first EAC confirmed severe hypoglycaemic episode (ADA) as described in Section 10.3.2.1. These analyses will be based on FAS and the 'on-treatment' observation period. Moreover, these analyses will also be performed using FAS and all data collected in the 'in-trial' observation period.

10.4 Pharmacokinetic and/or pharmacodynamic modelling

Not applicable for this trial.

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12 Appendices

Appendix 1 Abbreviations and Trademarks

ADA	American Diabetes Association
AE	Adverse event
BG	Blood glucose
BID	Twice daily
BMI	Body mass index
CI	Confidence interval
CLAE	Clinical laboratory adverse event
CV	Cardiovascular
DPP-4i	Dipeptidyl peptidase-4 inhibitor
DFU	Directions for use
DQLCTQ-R	Diabetes Quality Of Life Clinical Trial Questionnaire-revised
DRE	Disease-Related Event
DUN	Dispensing unit number
EAC	Event adjudication committee
EAS	Event adjudication system
EASD	European Association for Study of Diabetes
(e)CRF	(Electronic) case report form
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
FAS	Full analysis set
FDAAA	U.S. Food and Drug Administration Amendments Act
FPG	Fasting plasma glucose
GCP	Good Clinical Practice
GLP-1	Glucagon-like peptide-1
GLP-1 RA	Glucagon-like peptide-1 receptor agonist
HbA_{1c}	Glycated haemoglobin
hCG	Human chorionic gonadotropin
HDL	High-density lipoprotein

HRQoL	Health related quality of life
IAsp	Insulin aspart
ICH	International Council for Harmonisation
IEC	Independent ethics committee
IGlar	Insulin glargine
IMP	Investigational medicinal product
INR	International Normalised Ratio
IRB	Institutional review board
IWRS	Interactive web response system
KDIGO	Kidney Disease: Improving Global Outcomes
LDL	Low-density lipoprotein
MedDRA	Medical Dictionary for Regulatory Activities
NIMP	Non-investigational medicinal product
NYHA	New York Heart Association
OAD	Oral antidiabetic drugs
OD	Once daily
OW	Once-weekly
PCD	Primary completion date
PG	Plasma glucose
PP	Per protocol
PRO	Patient reported outcome
s.c.	Subcutaneous
SAE	Serious adverse event
SAP	Statistical analysis plan
SF-36v2™	36-item Short Form Health Survey version 2
SIF	Safety information form
SMPG	Self-measured plasma glucose
SUSAR	Suspected unexpected serious adverse reaction
T2D	Type 2 diabetes
TID	Three times daily
TMM	Trial materials manual

TRIM-D	Treatment Related Impact Measure For Diabetes
WOCBP	Woman of child bearing potential

Appendix 2 Clinical laboratory tests

- Blood samples have to be obtained, and sent to the central laboratory, where the tests detailed in Table 12-1 and Table 12-2 will be performed.
- Additional tests may be performed at any time during the trial as determined necessary by the investigator or required by local regulations. Only laboratory samples specified in the protocol should be sent to the central laboratory for analysis; if additional laboratory sampling is needed, e.g. to follow up on AEs, this must be done at a local laboratory.
- The investigator must review all laboratory results for concomitant illnesses and AEs.
- Laboratory samples will be destroyed on an ongoing basis and no later than at finalisation of the clinical trial report.

Table 12-1 Protocol-required efficacy laboratory assessments

Laboratory assessments	Parameters
Glucose metabolism	• FPG[1] • HbA_{1c}
Lipids	• Total Cholesterol • High density lipoprotein (HDL) cholesterol • Low density lipoprotein (LDL) cholesterol • Triglycerides
NOTES : [1]A FPG result ≤3.9 mmol/L (70 mg/dL) in relation to planned fasting visits should not be reported as a hypoglycaemic episode but as a clinical laboratory adverse event (CLAE) at the discretion of the investigator (Appendix 4).	

Table 12-2 Protocol-required safety laboratory assessments

Laboratory assessments	Parameters
Biochemistry	• Creatinine • eGFR calculated by the central laboratory based on the creatinine value using the CKD-EPI equation
Urinalysis	• Urine albumin to creatinine ratio
Hormones	• Calcitonin (only for screening purposes)
Pregnancy Testing	• Serum or urine human chorionic gonadotropin (hCG) pregnancy test (for WOCBP)

All trial-required laboratory assessments will be performed by a central laboratory, with the exception of urine pregnancy testing, which will be performed locally.

Appendix 3 Trial governance considerations

1) Regulatory and ethical considerations

- This trial will be conducted in accordance with the protocol and with the following:
- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki[25] and applicable ICH Good Clinical Practice (GCP) Guideline[26]
- ISO 14155[27]
- Applicable laws and regulations
- The protocol, informed consent form, investigator's brochure (as applicable) and other relevant documents (e.g. advertisements), must be submitted to an IRB/IEC and reviewed and approved by the IRB/IEC before the trial is initiated.
- Regulatory authorities will receive the clinical trial application, protocol amendments, reports on SAEs, and the clinical trial report according to national requirements.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the trial design, except for changes necessary to eliminate an immediate safety hazard to trial subjects.
- Before a trial site is allowed to start screening subjects, written notification from Novo Nordisk must be received.

The investigator will be responsible for:

- providing written summaries of the status of the trial annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC and/or regulatory authorities
- notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- providing oversight of the conduct of the trial at the site and adherence to requirements of ICH guidelines, the IRB/IEC, and all other applicable local regulations
- keeping a log of staff and delegation of tasks.
- ensuring submission of the clinical trial report (CTR) synopsis to the IRB/IEC.

2) Financial disclosure

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

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

3) Informed consent process

- The investigator or his/her representative will explain the nature of the trial to the subject and answer all questions regarding the trial.
- The investigator must ensure the subject ample time to come to a decision whether or not to participate in the trial.
- Subjects must be informed that their participation is voluntary.
- Subjects will be required to sign and date a statement of informed consent that meets the requirements of local regulations, ICH guidelines[26], Declaration of Helsinki[25] and the IRB/IEC or trial site.
- The medical record must include a statement that written informed consent was obtained before any trial related activity and the date when the written consent was obtained. The authorised person obtaining the informed consent must also sign and date the informed consent form before any trial related activity.
- The responsibility of seeking informed consent must remain with the investigator, but the investigator may delegate the task of informing to a medically qualified person, in accordance with local requirements.
- Subjects must be re-consented to the most current version of the informed consent form(s) during their participation in the trial.
- A copy of the informed consent form(s) must be provided to the subject.

4) Information to subjects during trial

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

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

5) Data protection

- Subjects will be assigned a 6-digit unique identifier, a subject number. Any subject records or datasets that are transferred to Novo Nordisk will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.
- The subject and any biological material obtained from the subject will be identified by subject number, visit number and trial ID. Appropriate measures such as encryption or

leaving out certain identifiers will be enforced to protect the identity of subjects as required by local, regional and national requirements.

- The subject must be informed that his/her personal trial related data will be used by Novo Nordisk in accordance with local data protection law. The disclosure of the data must also be explained to the subject.
- The subject must be informed that his/her medical records may be examined by auditors or other authorised personnel appointed by Novo Nordisk, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

6) Committee structure

Novo Nordisk safety committee
Novo Nordisk will constitute an internal safety committee to perform ongoing safety surveillance.

Event adjudication committee
An independent external event adjudication committee (EAC) is established to perform ongoing blinded adjudication of selected types of events and deaths (see Table 9-1 and Appendix 4). The EAC will evaluate events sent for adjudication using pre-defined definitions and guidelines in accordance with the EAC Charter. The evaluation is based on review of pre-defined clinical data collected by the investigational sites.

The EAC is composed of permanent members covering all required medical specialities. EAC members must disclose any potential conflicts of interest and must be independent of Novo Nordisk. The EAC will have no authorisations to impact on trial conduct, trial protocol or amendments.

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

The AEs for adjudication are listed in Section 9.2.

Adjudication of severe hypoglycaemic events is performed to ensure a standardised and uniform assessment hereby increasing the validity of these important endpoints. Adjudication of acute pancreatitis is performed due to the fact that treatment with GLP-1 agonists has been associated with acute pancreatitis, thus Novo Nordisk monitors this event type closely.

7) Publication policy

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

trial shall remain the sole property of Novo Nordisk and is to be considered confidential information.

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

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

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

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

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

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

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

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

Authorship of publications should be in accordance with the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals by the International Committee of Medical Journal Editors[28].

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

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

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

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

8) Dissemination of clinical trial data

Information of the trial will be disclosed at clinicaltrials.gov and novonordisk-trials.com. It will also be disclosed according to other applicable requirements such as those of the International Committee of Medical Journal Editors (ICMJE)[29], the U.S. Food and Drug Administration Amendments Act (FDAAA)[30], European Commission Requirements[31, 32] and other relevant recommendations or regulations. If a subject requests to be included in the trial via the Novo Nordisk e-mail contact at these web sites, Novo Nordisk may disclose the investigator's contact details to the subject. As a result of increasing requirements for transparency, some countries require public disclosure of investigator names and their affiliations.

The Primary Completion Date (PCD) is the last assessment of the primary endpoint, and is for this trial Last Subject First Treatment (V2) + 64 weeks corresponding to 'end of treatment' visit (V36). If the last subject is withdrawn early, the PCD is considered the date when the last subject would have completed 'end of treatment' visit (V36). The PCD determines the deadline for results disclosure at clinicaltrials.gov according to FDAAA.

9) Data quality assurance

Case Report Forms (CRFs)

- Novo Nordisk or designee is responsible for the data management of this trial including quality checking of the data.
- All subject data relating to the trial will be recorded on electronic CRFs unless transmitted electronically to Novo Nordisk or designee (e.g. laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF and for ensuring that all relevant questions are answered, and that no empty data field exists.
- The following will be provided as paper CRFs:
    - Pregnancy forms
- The following will be provided as paper CRFs to be used when access to the CRF is revoked or the CRF is temporarily unavailable:
    - AE forms
    - SIFs
    - Technical complaint forms (also to be used to report complaints that are not subject related, e.g. discovered at trial site before allocation)

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

Monitoring

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

- Trial monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorised site personnel are accurate, complete and verifiable from source documents; that the safety and rights of subjects are being protected, to monitor drug accountability and collect completed paper CRF pages, if applicable, and that the trial is being conducted in accordance with the currently approved protocol and any other trial agreements, ICH GCP, and all applicable regulatory requirements.
- Monitoring will be conducted using a risk based approach including risk assessment, monitoring plans, centralised monitoring (remote assessment of data by Novo Nordisk) and visits to trial sites.
- Monitors will review the subject's medical records and other source data e.g. the diaries and PROs, to ensure consistency and/or identify omissions compared to the CRF.

Protocol compliance

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

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

10) Source documents

- All data entered in the CRF must be verifiable in source documentation other than the CRF.
- The original of the completed diaries and/or PROs must not be removed from the trial site, unless they form part of the CRF and a copy is kept at the site.
- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the trial site.
- Data reported on the paper CRF or entered in the electronic CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records. Also, current medical records must be available.
- It must be possible to verify subject's medical history in source documents such as subject's medical record.
- The investigator must document any attempt to obtain external medical information by noting the date(s) when information was requested and who was contacted.
- Definition of what constitutes source data can be found in a source document agreement at each trial site. There will only be one source document defined at any time for any data element.

11) Retention of clinical trial documentation

- Records and documents, including signed informed consent forms, pertaining to the conduct of this trial must be retained by the investigator for 15 years after end of trial unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of Novo Nordisk. No records may be transferred to another location or party without written notification to Novo Nordisk.
- The investigator must be able to access his/her trial documents without involving Novo Nordisk in any way. If applicable, electronic CRF and other subject data will be provided in an electronic readable format to the investigator before access is revoked to the systems supplied by Novo Nordisk. Site-specific CRFs and other subject data (in an electronic readable format or as paper copies or prints) must be retained by the trial site. If the provided electronic data (e.g. the CD-ROM) is not readable during the entire storage period, the investigator can request a new copy. A copy of all data will be stored by Novo Nordisk.
- Subject's medical records must be kept for the maximum period permitted by the hospital, institution or private practice

12) Trial and site closure

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

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

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

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

13) Responsibilities

The investigator is accountable for the conduct of the trial at his/her site and must ensure adequate supervision of the conduct of the trial at the trial site. If any tasks are delegated, the investigator must maintain a log of appropriately qualified persons to whom he/she has delegated specified trial-

related duties. The investigator must ensure that there is adequate and documented training for all staff participating in the conduct of the trial. It is the investigator's responsibility to supervise the conduct of the trial and to protect the rights, safety, and well-being of the subjects.
A qualified physician, who is an investigator or a subinvestigator for the trial, must be responsible for all trial-related medical decisions.

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

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

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

If the investigator is no longer able to fulfil the role as investigator (e.g. if he/she moves or retires) a new investigator will be appointed in consultation with Novo Nordisk.
The investigator and other site personnel must have sufficient English skills according to their assigned task(s).

14) Indemnity statement

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

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

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

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

Events meeting the AE definition
• Any abnormal laboratory test results or safety assessments, including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. • A CLAE: a clinical abnormal laboratory finding which is clinically significant, i.e. an abnormality that suggests a disease and/or organ toxicity and is of a severity that requires active management. Active management includes active treatment or further investigations, for example change of medicine dose or more frequent follow-up due to the abnormality. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • Signs, symptoms or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms or the clinical sequelae of a suspected overdose of trial product regardless of intent. • A "lack of efficacy" or "failure of expected pharmacological action" constitutes an AE or SAE. Also, the signs, symptoms and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition.
Events NOT meeting the AE definition
• Pre-existing conditions, anticipated day-to-day fluctuations of pre-existing conditions, including those identified during screening or other trial procedures performed before exposure to trial product. Note: pre-existing conditions should be recorded as medical history/concomitant illness. • Pre-planned procedures, unless the condition for which the procedure was planned has worsened from the first trial related activity after the subject has signed the informed consent.

Definition of an SAE
An SAE is an AE that fulfils at least one of the following criteria:
• **Results in death**
• **Is life-threatening** The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death, if it were more severe.
• **Requires inpatient hospitalisation or prolongation of existing hospitalisation** • Hospitalisation signifies that the subject has been detained at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious. • Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE. Note: ▪ Hospitalisations for administrative, trial related and social purposes do not constitute AEs and should therefore not be reported as AEs or SAEs. ▪ Hospital admissions for surgical procedures, planned before trial inclusion, are not considered AEs or SAEs.
• **Results in persistent disability/incapacity**

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

- **Is a congenital anomaly/birth defect**

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

Description of AEs requiring additional data collection (via specific event form) and events for adjudication.

AEs requiring additional data collection and events for adjudication are described in Section 9.2

Medication error:
A medication error concerning trial products is defined as:

- Administration of wrong drug.
  Note: Use of wrong DUN is not considered a medication error unless it results in a confirmed administration of wrong drug.
- Wrong route of administration, such as intramuscular instead of s.c.

Accidental administration of a lower or higher dose than intended. The administered dose must deviate from the intended dose to an extent where clinical consequences for the trial subject were likely to happen as judged by the investigator, although they did not necessarily occur.

AE and SAE recording

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

Assessment of severity

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

- **Mild**: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- **Moderate**: An event that causes sufficient discomfort and interferes with normal everyday activities.
- **Severe**: An event that prevents normal everyday activities.

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

Assessment of causality

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

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

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

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

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

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

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

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

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 SIF. Novo Nordisk may need to report this adverse event to relevant regulatory authorities.

Final outcome

The investigator will select the most appropriate outcome:

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

Follow-up of AE and SAE

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

New or updated information will be recorded in the CRF.

SAE reporting via electronic CRF

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

SAE reporting via paper CRF

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

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

Appendix 5 Contraceptive guidance and collection of pregnancy information

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

Definitions

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

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

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

Contraception guidance

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

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

Table 12-3 Highly effective contraceptive methods

Highly effective contraceptive methods that are user dependent [a and b] Failure rate of <1% per year when used consistently and correctly.
Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation • oral • intravaginal • transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation • oral • injectable
Highly effective methods that are user independent [b]
• Implantable progestogen only hormonal contraception associated with inhibition of ovulation • Intrauterine Device • Intrauterine hormone-releasing System • Bilateral tubal occlusion
Vasectomised partner A vasectomised partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
Sexual abstinence[b] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial product. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject.
Notes: [a]Failure rates may differ from < 1% per year, if not used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical trials. [b]Contraception should be utilised during the treatment period and for at least 35 days after the last dose of trial product.

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

1) known intolerance to the highly effective methods mentioned in Table 12-3 or where the use of any of the listed highly effective contraceptive measures are contraindicated in the individual subject, and/or

2) if the risk of initiating treatment with a specific highly effective method outweighs the benefit for the female.

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

Pregnancy testing

- WOCBP should only be included after a negative highly sensitive pregnancy test.

- Urine pregnancy testing should be performed at follow-up visit according to the flowchart.
- Additional urine pregnancy testing should be performed during the treatment period, if required locally (Appendix 9).
- Pregnancy testing should be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

Collection of pregnancy information

Female subjects who become pregnant

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

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

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

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

Examples of technical complaints:

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

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

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

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

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

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

Appendix 7 Hypoglycaemic episodes

Novo Nordisk classification of hypoglycaemia

In normal physiology, symptoms of hypoglycaemia occur below a PG level of 3.1 mmol/L (56 mg/dL)[33]. Therefore, Novo Nordisk has included hypoglycaemia with PG levels below this cut-off point in the definition of BG confirmed hypoglycaemia.

Novo Nordisk uses the following classification (Table 12-1) in addition to the ADA classification[34]:

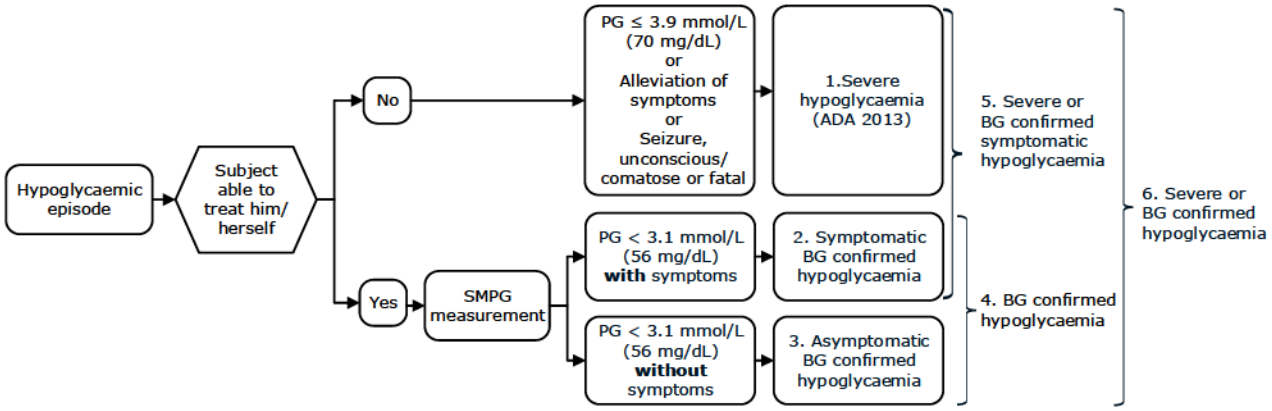
8. Severe hypoglycaemia according to the ADA classification[34].
9. Symptomatic BG confirmed hypoglycaemia: An episode that is BG confirmed by PG value <3.1 mmol/L (56 mg/dL) **with** symptoms consistent with hypoglycaemia.
10. Asymptomatic BG confirmed hypoglycaemia: An episode that is BG confirmed by PG value <3.1 mmol/L (56 mg/dL) **without** symptoms consistent with hypoglycaemia.
11. BG confirmed hypoglycaemia: The union of 2. and 3.
12. Severe or BG confirmed symptomatic hypoglycaemia: The union of 1. and 2.
13. Severe or BG confirmed hypoglycaemia: The union of 1, 2. and 3.

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

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

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

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



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

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

Figure 12-1 Novo Nordisk classification of hypoglycaemia

ADA classification[34] of hypoglycaemia

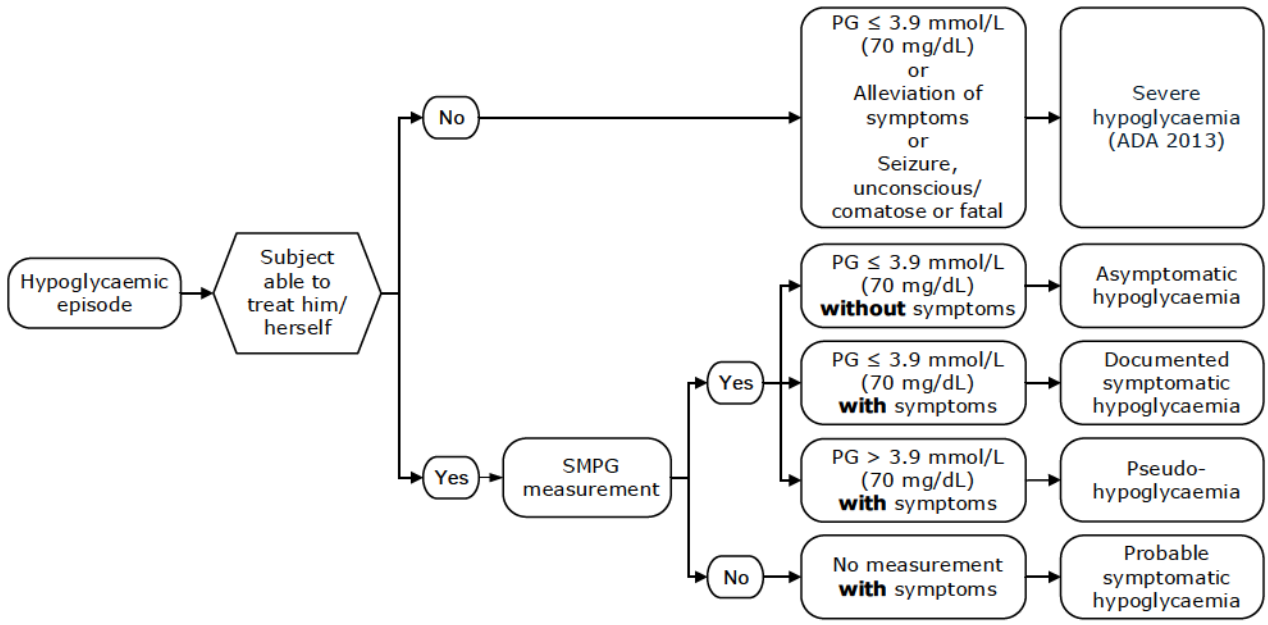
- Severe hypoglycaemia: An episode requiring assistance of another person to actively administer carbohydrate, glucagon or take other corrective actions. PG concentrations may not be available during an event, but neurological recovery following the return of PG to normal is considered sufficient evidence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

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

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

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

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



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

PG: plasma glucose SMPG: Self-measured plasma glucose

Figure 12-2 ADA classification of hypoglycaemia

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

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

Hypoglycaemic episodes are classified according to the Novo Nordisk classification of hypoglycaemia and the ADA classification of hypoglycaemia[34].

In addition, a subset of the episodes conforming ADA definition of severe hypoglycaemic episodes, i.e. episodes of severe hypoglycaemia requiring hospitalisation or documented medical help (e.g. intravenous administration of glucose or administration of glucagon), or episodes that are life

threatening[31] will be analysed as an exploratory endpoint. Life threatening hypoglycaemic episodes relates to hypoglycaemic episodes that are considered serious adverse events which were life threatening or hypoglycaemic episodes where the subject experienced seizure, or was unconscious, or was in coma. This subset is referred to as 'severe hypoglycaemia requiring hospitalisation, documented medical help, or is life threatening'.

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

Upon onset of a hypoglycaemic episode the subject is recommended to measure PG every 15 minutes until the SMPG value is >3.9 mmol/L (70 mg/dL) and/or symptoms have been resolved in accordance with current guidelines[34].

Repeated SMPG measurements and/or symptoms, occurring within a period of 60 minutes after onset of 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 minutes period shall trigger the reporting of a new hypoglycaemia episode.

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 low SMPG value and/or symptom.

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

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

Investigator must instruct subjects that the answer to the question: "Was the subject able to treat him/herself?" must be answered "No" for an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. PG concentrations may not be available during an event, but neurological recovery following the return of PG to normal is considered sufficient evidence that the event was induced by a low PG concentration[34].

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

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

The investigator must review the diary for low SMPG values not reported as hypoglycaemic episodes. The subject must be questioned whether any of the low values were severe, i.e. whether the subject was able to self-treat or not. If the subject was not able to self-treat, it has to be reported as a severe hypoglycaemic episode.

For low SMPG values for hypoglycaemic episodes where the subject was able to self-treat: If a hypoglycaemic episode form is not completed within 7 calendar days of the SMPG measurement, the episode should be reported on a hypoglycaemic episode form with as much information as possible. Novo Nordisk will not query for additional data except for the start date, SMPG value and whether the subject was able to self-treat due to decreased validity of such data[35, 36].

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

Appendix 8 Titration guideline

Introduction

Titration guidelines have been developed, providing recommended dose adjustments at different PG levels to ensure that subjects receive an optimal treatment. However, it is recognised that treatment should be individualised and the specific titration algorithms may not be applicable in certain clinical situations. Hence, it is important that other information, such as symptoms of hypo/hyperglycaemia, previous response to dose adjustments, other glucose measurements and other indicators of the subject's level of glycaemic control, is taken into consideration when decisions on dosing are made. The investigator is responsible for the treatment of the subjects and can therefore overrule the guidelines to avoid safety hazards.

To optimise and maintain glycaemic control, the investigator should throughout the trial be at least in twice monthly contact with the subjects to assist the subjects in adjusting treatment and to ensure the subject's welfare.

1. Treatment regimens

All subjects in the trial will be treated with IGlar U100 and metformin. At run-in (V2), eligible subjects will be transferred from their previous basal insulin dose to IGlar U100 OD according to Section 3.1, Appendix 8.

During the following 12 weeks the investigator will focus on adjusting the IGlar U100 dose according to Section 3.2, Appendix 8.

At randomisation (V8), eligible subjects will be randomised 1:1 into two parallel treatment groups:

1. metformin + IGlar U100 + semaglutide OW
2. metformin + IGlar U100 + mealtime IAsp TID

During the following 52 weeks treatment period the investigator will focus on adjusting randomised treatment according to Section 3.3, 3.5 and 3.7, Appendix 8.

- 1.1 Injection area
  - IGlar U100 should be injected s.c. into the abdomen, thigh, or upper arm.
  - Semaglutide should be injected s.c. in the abdomen, thigh, or upper arm
  - IAsp should be injected s.c. into the abdomen, thigh, or upper arm.

  Rotation of injection sites within a given region is recommended.

- 1.2 Time of injection
  - IGlar U100 should be administered OD at any time of the day, at the same time every day.

- Semaglutide should be administered OW, at any time of the day irrespective of meals, but on the same day of the week. If a semaglutide dose is missed, it should be administered as soon as noticed, provided the time to the next scheduled dose is at least 2 days (48 hours). If a dose is missed and the next scheduled dose is less than 2 days (48 hours) away, the subject should not administer the missed dose but rather wait for the next scheduled dose. A missed dose should not affect the scheduled dosing day of the week.
- IAsp should be administered TID, with main meals in accordance with local label. Main meals are defined as breakfast, lunch and main evening meal.

2. Initiation and titration

Both self-monitoring of plasma glucose (SMPG) and HbA_{1c} should guide the investigator in the decision to adjust treatments over the course of the trial. Subjects are required to perform SMPG as described in Section 2 and Section 9.1.1.

HbA_{1c} goal should be individualised for each subject within the HbA_{1c} range of 6.5% to 7.5% (48 mmol/mol to 58 mmol/mol) (both inclusive). SMPG targets should be individualised at investigator's discretion within the ranges specified in Table 12-4 ,Table 12-5 and Table 12-6 or in accordance with local guidelines.

2.1 Initiation of IGlar U100 at run-in (Visit 2)

Eligible subjects will discontinue pre-trial basal insulin and the additional OAD (if applicable, including conversion from fixed drug combination medications with metformin and DPP-4i to metformin only).

Subjects will be transferred from their pre-trial basal insulin treatment (once or twice daily) to OD IGlar U100, provided by Novo Nordisk A/S in accordance with the approved local label of IGlar U100.

2.2 Titration of IGlar U100 during run-in

The IGlar U100 dose can be adjusted in the run-in period in connection with the site visits or telephone contacts. Increases in the IGlar U100 dose should be based on the mean of three pre-breakfast SMPG values obtained on the day of the visit/telephone contact and two days before the contact according to Table 12-4.

If one of the SMPG values is below target (< 4.0 mmol/L or <71 mg/dL), the IGlar U100 dose should be reduced in accordance with Table 12-5.

Table 12-4 Increase of IGlar U100 dose

Mean pre-breakfast SMPG values		Increase of dose
mmol/L	mg/dL	U
4.0-6.9	71-125	No adjustment
7.0-7.8	126-140	2
7.9-8.9	141-160	4
9.0-10.0	161-180	6
>10.0	>180	8

Table 12-5 Reduction of IGlar U100 dose

Lowest pre-breakfast SMPG value		Reduction of dose
mmol/L	mg/dL	U
< 3.1	< 56	4
3.1-3.9	56-70	2

It is important that the decision of IGlar U100 doses is based on all available information, such as symptoms of hypo- and/or hyperglycaemia, previous responses to dose adjustments as well as SMPG measurements other than those required per the trial protocol.

2.3 Titration of IGlar U100 from randomisation (Visit 8)

A reduction in the dose of IGlar U100 upon semaglutide/IAsp treatment initiation should be considered in accordance with the approved local label to reduce the risk of hypoglycaemia. Further dose reductions may be needed during the trial and in particular during dose escalation of semaglutide.

Dose adjustments of IGlar U100 can be done in line with the titration algorithm described in Table 12-4 and Table 12-5 and the individualised target according to investigator's discretion. However, from randomisation (V8), the investigator should primarily focus on adjusting the semaglutide or IAsp dose.

2.4 Initiation of semaglutide at Visit 8

Subjects randomised to semaglutide should initiate treatment with a dose of 0.25 mg

2.5 Dose adjustment of semaglutide from randomisation (Visit 8)

After 4 weeks of treatment with 0.25 mg, the dose should be increased to 0.5 mg. After at least 4 weeks with a dose of 0.5 mg OW, the dose of semaglutide can be increased to 1 mg to further improve glycaemic control, at the investigator’s discretion.

Further dose adjustments including dose reductions of semaglutide are allowed during the trial. Dose reduction from the dose of 1 mg to the dose of 0.5mg of semaglutide is allowed in case of safety concern or unacceptable intolerability. Date and dose need to be recorded in the CRF when trial product dose is initiated and changed, in accordance with the approved local label.

2.6 Initiation of IAsp at Visit 8

Subjects randomised to the IAsp treatment arm should initiate treatment with 4U of IAsp before each main meal, TID.

2.7 Titration of IAsp from randomisation (Visit 8)

IAsp dose adjustments should be considered twice weekly. Dose adjustments should be based on pre-prandial and bedtime SMPG from the preceding 3 days according to Table 12-6 and the individualised goal according to investigator's discretion.

- Pre-breakfast IAsp dose will be adjusted according to the pre-lunch SMPG the previous three days
- Pre-lunch IAsp dose will be adjusted according to the pre-dinner SMPG the previous three days
- Pre-dinner IAsp will be adjusted according to the bedtime SMPG the previous three days

Table 12-6 Dose adjustment of IAsp twice weekly

Preprandial or bedtime SMPG			Dose adjustment
mmol/L	mg/dL		U
< 4.0	< 71	One or more values < 71 (4.0)	-1
4.0 – 6.9	71-125	No values < 71 (4.0) and max one value > 125	0
>6.9	>125	No values < 71 (4.0) and two or more values > 125	+1

It is important that the decision of IAsp doses is based on all available information, such as symptoms of hypo- and/or hyperglycaemia, previous responses to dose adjustments as well as SMPG measurements other than those required per the trial protocol.

2.8 Deviations from the algorithm/dose adjustment recommendation

It is recommended that the algorithm/dose adjustment recommendations are followed. However, it is also important that the decision to adjust insulin/semaglutide doses is based on all relevant information. A reason for deviating from the algorithm/dose adjustment recommendations should be entered into the CRF by the investigator as applicable.

3. Data surveillance

Novo Nordisk A/S will ensure monitoring of insulin titration and provide feed-back to sites throughout the trial.

It is important that data regarding dose titration is entered into the diary and into the CRF. If delays occur, action cannot be taken in due time before the subject's next site visit/phone contact. The aim is to reduce the time periods in which a subject may receive suboptimal treatment.

Appendix 9 Country-specific requirements

Poland:

Novo Nordisk carries liability for the Trial exclusively in the scope defined by the applicable laws and in particular by the Civil Code and the Pharmaceutical Law dated 6 September 2001 (uniform version Journal of Laws of 2008 No. 45 item 271 with amendments). In order to support potential claims for liability attributable to the Trial, Novo Nordisk and Investigator are covered by the Insurance Policy issued according to applicable Polish law.

Germany:

During the COVID-19 pandemic a set of mitigating actions has been prepared as support to sites on how to handle trial requirements during the pandemic. Adherence to the protocol should be complied with to the extent possible. The outlined actions should be regarded as temporary and should not be used if normal protocol procedure is possible.

The actions are divided into three groups.

Primary endpoint

In order to ensure trial validity without compromising subjects' safety, primary endpoint data will be collected to the extent possible by expanding the visit window for End of Treatment (EoT). The visit window of ± 7 days may be expanded for up to - 4 weeks / + 12 weeks. During the extended visit window subjects will continue to receive trial product until they have completed the EoT visit.

Subjects' self-measured plasma glucose will continue to be supervised by the titration group members on a regular basis and subjects will be in contact with site (phone contact at least bi-weekly).

Changes to visit schedule during trial conduct

Adherence to the clinical trial protocol should continue to the extent possible during the outbreak. In cases where this is not possible due to epidemiological restrictions, changes to the visit schedule may be implemented. Planned physical site visits may be performed outside protocol-defined visit windows or may be converted into phone contacts, at the investigator's discretion.

Following subject specific mandatory assessment may be performed outside of the protocol specific requirements during the COVID-19 outbreak:

- urine pregnancy tests should be provided together with the trial product in case a physical site visit is converted to a phone contact
- eye examination at EoT can be postponed until the follow-up visit

Alternative dispensing of trial product, from site to subject

In case a site visit is converted to a phone contact or a subject is hindered in receiving trial product at site, alternative dispensing methods may be performed. Following options for alternative dispensing methods are allowed if subject is unable to come to site:

- trial product is collected at site by appointed substitute
- trial product is delivered by a site staff member to the subject/substitute off-site

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

Log of Protocols Trial ID: NN9535-4386 UTN: U1111-1200-0164 EUdraCT No.: 2017-003219-20	~~CONFIDENTIAL~~	Date: Version: Status: Page:	16 March 2021 1.0 Final 1 of 1

Novo Nordisk

Log of Protocols

Date	Final, version	Protocol includes the following amendments
09-JAN-2018	1.0 Final 4386-protocol-version-1.0. [redacted]	N/A First version of the protocol.
09-MAY-2018	2.0 Final 4386-protocol-version-2.0 [redacted]	
08-jul-2020	3.0 Final 4386-protocol-version-3.0 [redacted]	Local German amendment due to Covid-19

Protocol Amendment

no 1

to Protocol, version 2.0 dated 09 May 2018

Trial ID: NN9535-4386

Effect of semaglutide once-weekly versus insulin aspart three times daily, both as add on to metformin and optimised insulin glargine (U100) in subjects with type 2 diabetes
A 52-week, multi-centre, multinational, open-label, active-controlled, two armed, parallel-group, randomised trial in subjects with type 2 diabetes

Trial phase: 3b
Applicable to Germany

Table of Contents

1 Introduction including rationale for the protocol amendment

Changes are introduced to fulfil local requirements in Germany.

In this protocol amendment:

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

2 Changes to Appendix 9 Country specific requirement

Germany:

- *Contraceptive measures considered adequate are only highly effective contraceptive methods as listed in Table 12-3 'Highly effective contraceptive methods' in Appendix 5. The option to use double-barrier methods in females with known intolerance or contraindications to the highly effective methods or where the risk of initiating treatment with a specific highly effective method outweighs the benefit for the female is not applicable for Germany.*

Protocol Amendment

no 2

to Protocol, version 2.0 dated 09 May 2018

Trial ID: NN9535-4386

Effect of semaglutide once-weekly versus insulin aspart three times daily, both as add on to metformin and optimised insulin glargine (U100) in subjects with type 2 diabetes
A 52-week, multi-centre, multinational, open-label, active-controlled, two armed, parallel-group, randomised trial in subjects with type 2 diabetes

Trial phase: 3b
Applicable to Romania

Table of Contents

1 Introduction including rationale for the protocol amendment

Changes are introduced to fulfil local requirements in Romania.

In this protocol amendment:

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

2 Changes to Appendix 9 Country specific requirement

Romania:

- *Contraceptive measures considered adequate are only highly effective contraceptive methods as listed in Table 12-3 'Highly effective contraceptive methods' in Appendix 5. The option to use double-barrier methods in females with known intolerance or contraindications to the highly effective methods or where the risk of initiating treatment with a specific highly effective method outweighs the benefit for the female is not applicable for Romania.*

Date and Signature:

_____

[redacted]

International Trial Manager

Date and Signature:

_____

[redacted]

[redacted]

Log of Protocol Amendments

Protocol amendment no	Date (DD Month YYYY)	Final, Version	Country(ies) and/or trial site(s) affected	Brief content
1	14-Aug-2018	1.0	Germany	Changes are introduced to fulfil local requirements in Germany.
2	20-May-2019	1.0	Romania	Changes are introduced to fulfil local requirements in Romania.

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Memo

To: **Investigators, Study Coordinators, and Site Staff involved in NN9535-4386 (SUSTAIN 11)**

From: **SUSTAIN 11 Trial Management team**

17 April 2020

NN9535-4386 (SUSTAIN 11)

Dear Investigators, Study Coordinators, and Site Staff,

The COVID-19 pandemic we are currently facing is unprecedented and it is putting severe constraints on both work and family life all over the world. We are grateful for your diligence and the difference you make for your subjects. [illegible]

The purpose of this MEMO is to inform you of the mitigations to ensure subject safety during the COVID-19 pandemic and to help maintain the trial validity by collecting critical End of Treatment data.

The importance of Self-Measured Plasma Glucose during the Covid-19 pandemic

[illegible]

Ensure completion of End of Treatment Visit (V36)

[illegible]

[illegible] [redacted] yu

[illegible]

Guidance for visits 8 until visit 36

[illegible]

- [illegible]
  - [illegible]
- [illegible]

- [illegible]

- [illegible]

- [illegible]

- [illegible]

[illegible]

Home visits

[illegible]

[illegible]

[illegible]

[illegible] [redacted] [illegible]

PRO questionnaires

We allow site staff to fill in a paper version of the PRO questionnaires during interview with the subject during a phone visits, and then transfer the responses to the EDC, which will ensure we have a paper version as source data.
Site staff need to add onto the questionnaires a note, that this was filled in during an interview with the subject on the date of the phone visit and save this in the medical records. And then the site staff can transfer the data to the EDC.

Data entry in EDC (InForm)

We acknowledge that despite all your efforts, it is likely that we will have missing data in the next weeks/months due to the COVID-19 pandemic. In addition to documenting all actions in the medical records, it is important to also capture relevant information in EDC.

Below please see the information regarding the preferred way of data entry:
If a visit is converted into a phone visit OR is performed out of the protocol-specified visit window OR is Not Done due to the COVID-19 pandemic, then site must record a FORM LEVEL COMMENT on the DATE of VISIT FORM.

Guidance to enter Form level comment if a site visit is OUT OF WINDOW or Visit is converted to PHONE VISIT in EDC

Step 1: Go to [illegible] and enter the date of visit and contact type.

[redacted]

Step 2: After submitting this data, click on the form level comment icon at top right hand side of the form, (see the red box)

[redacted]

Step 3: Once the below screen appears please provide the reason on the comment [illegible]

[redacted]

Step 4: Once the comment is updated the form appears as below:

[redacted]

Guidance to enter Form level comment if a visit is NOT DONE

Step 1: Go to Date of visit form and click on the form level comment icon at top right hand side of the form, (see the red box)

[redacted]

Step 2: Once the below screen appears please provide the reason on the comment [illegible] Reason incomplete box [illegible]

[redacted]

[redacted]