Cover Page for Protocol

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Official title of study:	Safety and tolerability of weekly Semaglutide 0.5 mg or 1.0 mg in Chilean subjects with type 2 diabetes
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Protocol

Protocol title: **Safety and tolerability of weekly semaglutide 0.5 mg or 1.0 mg in Chilean subjects with type 2 diabetes**

A 6-months prospective, open-label, non-controlled study in the Chilean public health care system study

***Substance/*Semaglutide**: NN9535

Universal Trial Number: NN9535-4844

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Redacted protocol

Includes redaction of personal identifiable information only.

Study phase: 4

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

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1 Protocol summary

1.1 Synopsis

This is an interventional, single-country, multi-centre, one -arm, open-label, phase 4 study.

Rationale:

In Chile, 85% of the death causes correspond to Chronic Noncommunicable Diseases (NTDs), of which 5% are caused by diabetes.[1]

Semaglutide is the latest GLP-1 RA to be available for the treatment of adults with T2D in Chile, with proven efficacy and safety data, and additional benefits, such as weight loss, and cardiovascular and renal protection.[2]

Currently, there is no locally generated evidence to evaluate safety outcomes) and to replicate the benefits proven in the semaglutide trials[2] (SUSTAIN programme) in local subjects with T2D. Although international data is well received, there is a constant need to assess new drugs in local patients.

Objectives and endpoints:

Primary objective:
To evaluate the short-term safety and tolerability (very common and common treatment-emergent adverse events) of once-weekly subcutaneous semaglutide in subjects with T2D who do not achieve their HbA1c goal added to available standard of the Chilean public health setting.

Secondary objective:
To evaluate the effect on glycaemic control, body weight, and other secondary safety and efficacy laboratory outcomes associated with once-weekly subcutaneous semaglutide in subjects with type 2 diabetes mellitus added to available standard of care in Chilean public health care setting.

Primary endpoints
- Number of treatment-emergent adverse events from day 1 to week 24 of treatment.

Secondary endpoints
- Change from baseline in glycosylated haemoglobin (HbA1c) after 24 weeks of treatment.
- Subject achieving HbA1c < 7,0% after 24 weeks of treatment (yes/no).
- Change from baseline of fasting plasma glucose (FPG) after 24 weeks of treatment.
- Change from baseline of body weight after 24 weeks of treatment.
- Change from baseline of waist circumference after 24 weeks of treatment
- Subjects achieving ≥ 5% and ≥ 10% weight reduction after 24 weeks of treatment (yes/no)
- Change from baseline in laboratory tests after 24 weeks of treatment.
- Subject discontinued due to adverse events (yes/no)
- Number of severe hypoglycaemic episodes per subject
- Number of severe or blood glucose confirmed symptomatic hypoglycaemic episodes per subject
- Number of serious adverse events (SAEs) per subject
- Change from baseline in heart rate (pulse) after 24 weeks of treatment

Overall design:
This is an interventional, single-country, multi-centre, open-label, non-controlled and one-arm, phase 4 study, evaluating the safety and tolerability of once-weekly 0.5 mg or 1.0 mg dosing of subcutaneous semaglutide, according to clinical need, in subjects with type 2 diabetes mellitus added to available standard of care in a Chilean public health care setting

100 subjects will be enrolled according to the inclusion and exclusion criteria to receive 0.5 mg or 1.0 mg subcutaneous once weekly semaglutide according to label.

The study includes a 2-week screening period, followed by a 24-week treatment period and a 5-week follow up period after end of treatment. The maximum individual study duration will be up to 34 weeks.

Study intervention groups and duration:

The study duration for the individual subjects will 24 weeks and up to 34 weeks (see flowchart). The study includes a 2-week screening period, followed by a 24 week treatment period and a 5-week follow up period after end of treatment.

Participants will receive semaglutide in an escalating dose according to label and clinical individual needs for 24 weeks: 0.25 mg (weeks 1 to 4), 0.5 mg (week 5 and onwards). In week 12 control visit, subjects can escalate from 0.5 mg to 1.0 mg according to the investigator criteria if the HbA1c is above the individual target.

The maintenance dose of 0.5 mg will be reached after 4 doses (4 weeks) of 0.25 mg.
The maintenance dose of 1.0 mg will be reached after the week 12 visit (see above) if the participant requires to improve his/her glycaemic control (HbA1c not in target).

Number of participants:

Due to the broad safety objective of this study, no formal sample size calculation was performed. Around 90 subjects are considered appropriate to generate local experience regarding the outcomes for Semaglutide in local subjects. Considering a potential 10% treatment discontinuation, 100 subjects are planned to be included in the treatment period.

Participant characteristics:

Inclusion criteria:
Participants are eligible to be included in the study only if all the following criteria apply:

1. Informed consent obtained before any study-related activities. Study-related activities are any procedures that are carried out as part of the study, including activities to determine suitability for the study.
2. Male or female.
3. Age above or equal to 18 years at the time of signing informed consent.
4. Subjects diagnosed (clinically) with type 2 diabetes ≥ 90 days prior to the screening visit.
5. Stable daily dose of OAD and/or insulin treatment for ≥ 60 days prior to the screening visit.
6. HbA1c 7.5-10% (59-86 mmol/mol) (both inclusive) in V1.
7. Subjects in which Ozempic® is indicated according to approved local label.
8. Fundoscopy/Fundus photography record ≤ 12 months.

Exclusion criteria
Participants are excluded from the study if any of the following criteria apply:

1. Known or suspected hypersensitivity to study intervention(s) or related products.

2. Previous participation in this study. Participation is defined as signed informed consent.
3. Female who is pregnant, breast-feeding or intends to become pregnant or is of childbearing potential and not using adequate contraceptive method, as defined in Appendix 4.
4. Participation in any clinical trial of an approved or non-approved investigational medicinal product within 30 days before the screening visit, except COVID-19 related trials (this is allowed)
5. Treatment with any GLP-1 RA medication prior to the screening visit.
6. Any disorder which in the investigator's opinion might jeopardise subject's safety or compliance with the protocol.
7. Family or personal history of Multiple Endocrine Neoplasia Type 2 or Medullary Thyroid Carcinoma
8. History of pancreatitis (acute or chronic).
9. Renal impairment defined as eGFR below 30 mL/min/1.73 m^2 as per MDRD-4 (Modification of Diet in Renal Disease).
10. Myocardial infarction, stroke or hospitalisation for unstable angina or transient ischaemic attack within the past 180 days prior to the day of screening.
11. Subjects presently classified as being in New York Heart Association (NYHA) Class IV Heart failure.
12. Planned coronary, carotid or peripheral artery revascularisation known on the day of screening
13. Subjects with alanine aminotransferase (ALT) > 2.5 x upper normal limit (UNL).
14. Use of systemic immunosuppressive treatment within 90 days prior to screening.
15. Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria in a period of 90 days before the day of screening. An exception is short-term insulin treatment for acute illness for a total of ≤ 14 days.
16. Known hypoglycaemic unawareness and/or recurrent severe hypoglycaemic episodes as judged by the investigator.
17. Proliferative retinopathy or maculopathy requiring acute treatment. Verified by fundus photography or dilated fundoscopy performed within 12 months prior to screening.
18. History or presence of malignant neoplasms within the last 5 years (except basal and squamous cell skin cancer and carcinoma in situ).

Assessments:

Laboratory tests and investigator controls:

Laboratory tests prior to semaglutide initiation, at week 12 and at week 24:

1. Fasting plasma glucose
2. HbA1c
3. Lipid profile: total cholesterol, low-density lipoprotein cholesterol (LDL cholesterol), high-density lipoprotein cholesterol (HDL cholesterol) and triglycerides
4. Hepatic profile: bilirubin (total and direct), alkaline-phosphatase (ALP), aspartate-aminotransferase (AST), alanine-aminotransferase (ALT), gamma-glutamyl transferase (GGT)
5. Serum creatinine, including eGFR (MDRD)
6. UACR

Safety assessments:

1. Treatment-emergent adverse events registration (described later)
2. Subject discontinued due to adverse events registration

Clinical assessments:

1. Height
2. Body weight
3. Waist circumference
4. Blood pressure
5. Pulse rate

Contacts with subjects (V for face-to-face visits and P for phone visit, either call or video-call):

- V0*: screening visit, week -2
- V1*: treatment period, week 1 ± 10 days
- P2*: treatment period, week 4 ± 10 days
- V3*: treatment period, week 12 ± 10 days
- V4*: end-of-treatment, week 24 ± 10 days
- P5*: follow-up and end-of-treatment, week 29 ± 10 days
- V4A*: anytime, follow-up and end-of-treatment premature discontinuation

* To see details for each visit, see the flowchart.

Subjects will receive a reminder (call or text) by the nurse around 10 days prior to V1, V3, V4 and V4A if applicable, to take laboratory tests samples between 7 and 3 days before those visits.

The local laboratories will report the results to the investigator team directly.

Subjects have optional calls anytime they need (via telephone) with the nurse.

Hypoglycaemia suspicion: subjects are encouraged to take a capillary glucose test, act accordingly to local clinical guidance, and register the result. Semaglutide and other antidiabetic treatments doses can be adjusted at any time according to the subjects' need.

Any medication for acute or chronic disease can be added, adjusted or discontinued according to the subject´s need. This must be registered in the next visit.

Data monitoring committee: No

1.2 Protocol Flowchart

Study I

Study Periods		Screening	Treatment period			End-of-treatment[1]	Follow-up and End-of-Study[1]	Follow-up and End-of-treatment premature discontinuation[2]
Visit (V) or Phone (P) number		V0	V1	P2	V3	V4	P5	V4A
Time of visit	Weeks	-2	1	4	12	24	29	
Visit window	Days		±10	±10	±10	±10	±10	
Informed consent		X						
Laboratory test order		X	X		X			
SUBJECT RELATED INFO/ASSESSMENTS								
Inclusion criteria		X						
Exclusion criteria		X	X					
Concomitant illness and medical history		X						
Concomitant medication and dose adjustment[3]		X	X	X	X	X	X	X
Demography		X						
Diabetes history		X						
History of CV disease		X						
History of gallbladder disease		X						
Smoking habits		X						
Fundoscopy/Fundus photography record ≤ 12 months[4]		X						
Height			X					
SAFETY								
Adverse events			x	x	x	x	x	X
Hypoglycaemic episodes			x	x	x	x	x	X
Physical examination		X	x		x	x		X
Pulse rate			x		x	x		X
Biochemistry (detailed list refer to protocol)			x		x	x		X
Serum human chorionic gonadotropin (hCG)			x					
Creatinine (including eGFR)			x		x	x		X

Protocol Study 1							
Urine Albumin to creatinine ratio		x		x	x		X
EFFICACY (SECONDARY ENDPOINTS)							
Body weight		x		x	x		X
Waist circumference		x		x	x		X
Blood pressure		x		x	x		X
HbA_{1c}		x		x	x		X
Fasting plasma glucose		x		x	x		X
Lipidic profile		x		x	x		X
STUDY MATERIAL							
Drug accountability				x	x		X
Dispensing visit		x		x			
Hand out directions for study product use		x		x			
Instructions to register in the PSP programme (optional for the subject)		x					

Protocol 1 V4 (End-of-Treatment) and P5 (Follow-Up and End-of-Study) are applicable for all study subjects. 2 Subjects discontinuing study product prematurely were to be asked to attend one additional visit to undergo end of study assessments. The visit should include the End-of-Treatment-premature discontinuation (V4A) combined with Follow-up -premature discontinuation visit (V4A). Visit should be scheduled as soon as possible after treatment discontinuation and laboratory tests should be taken and controlled later by the study team. 3 In case of insulin or sulphonylureas, dose adjustment according to protocol 4 Fundoscopy/fundus photography is not part of the study procedure, but it is requested as part of the medical history within 12 months prior to study inclusion. 5 ECG is not part of the study procedure, but it is requested as part of the medical history within 12 months prior to study inclusion. Abbreviations: V: visit, P: phone or videocall visit, CV: cardiovascular, ECG: electrocardiogram, eGFR: estimated glomerular filtration rate, eCRF: electronic case report form							

2 Introduction

2.1 Study rationale

The prevalence of type 2 diabetes mellitus (T2D) in people aged 15 years or older in Chile is estimated to be 12,3%, as of 2017, according to data from the 2016-2017 National Health Survey.[3]

Semaglutide is the latest GLP-1 RAs to be available for the treatment of adult subjects with T2D in Chile. As a family, GLP-1 RAs are recognized as a treatment with an acceptable safety profile.[4,5] Nevertheless, there is a constant need to have local data regarding the safety of this drug family in local subjects. There is previous experience with other GLP-1 RAs, and new efficacy and safety data emerging from recent trials is well incorporated in the medical knowledge, especially the cardiovascular benefit of some GLP-1 RAs, such as liraglutide[6], dulaglutide[7] and semaglutide[2].

Despite this, no hospital or other public entity have semaglutide (or other GLP-1 RAs) in their drug arsenal. Physicians in Chile are constantly asking to have local data generated in local subjects and clinical centres. Having local experiences create opportunities for public subjects to count on new medication options and it is key to inform the national guideline updates to be aligned with the global recommendations and to reduce the gap of local subjects with the international standards.

2.2 Background

GLP-1 RAs are a relatively new therapeutic option for patients with T2D, with proven efficacy and an adequate safety profile. Semaglutide is the latest GLP-1 RA available in Chile. It has a strong clinical programme (SUSTAIN) showing not only a high efficacy in the reduction of HbA1c and weight, but also proven cardiovascular benefits[2]. It has shown an acceptable safety profile, with a similar rate of adverse events compared to the other GLP-1 RAs, being in a majority gastrointestinal adverse events, mostly mild or moderate and with a tendency to improve through the continued weeks of treatment.

There is a proportion of secondary care patients (treated at public hospital out-patient clinics), in need of glycaemic optimization despite the use of different available antidiabetic drugs, including insulins. These patients have limited options to intensify their therapy (DPP-4 inhibitors, SGLT-2 inhibitors and GLP-1 receptor agonists are not part of the public hospital drug arsenal), mainly increasing insulin doses or adding prandial insulin, with secondary hypoglycaemia risk increase. Also, it is well known that a secondary side-effect of insulins is weight gain, in patients that generally already have obesity or overweight as a comorbidity. Considering the safety profile and the potential expected adverse events, we propose the benefits will surpass the risks. Semaglutide has proven not only to have a very high efficacy in reducing HbA1c, but also, it has an important effect in comorbidities, generating weight loss, cardiovascular protection and it has also shown to improve the quality of life.[2]

The indication and use of semaglutide in this study will always be on-label, according to the local regulatory authority approved prescribing information[8,9] and thus will provide valuable data in the relevant setting and within the expected use in clinical practice.

2.3 Benefit-risk assessment

2.3.1 *Risk assessment*

The main benefits and risks related to participating in the study are described in the below sections. More detailed information about the known and expected benefits and risks and reasonably expected adverse events of semaglutide can be found in the summary of product characteristics.

Risks and precautions

The nonclinical safety programme of semaglutide has not revealed any safety issues precluding use in humans.

The sections below describe the important identified and potential risks and precautions associated with semaglutide treatment. These are based on findings in nonclinical studies and clinical trials with semaglutide as well as other GLP-1 RAs. For each of these risks and precautions, mitigating actions have been implemented to minimise the risks for subjects enrolled in this study.

Identified risks:

Gastrointestinal adverse events

Consistent with findings with other GLP-1 RAs, the most frequently reported AEs in clinical trials with semaglutide have been gastrointestinal disorders (nausea, vomiting, diarrhoea, dyspepsia and constipation). Clinical trials have indicated that a low starting dose and gradual dose escalation mitigates the risk of gastrointestinal AEs. Consequently, a low starting dose and dose escalation with 4-week dose-escalation steps have been implemented in the study.

Potential risks

Medullary thyroid cancer

The human relevance of the proliferative C-cell changes found in rodents treated with GLP-1 RAs is unknown, but data suggest that rodents are more sensitive to the mode of action of GLP-1 RAs for induction of C-cell tumours. However, as a precaution, subjects with a family or personal history of MEN 2 or MTC will not be enrolled in the study.

Acute pancreatitis

Acute pancreatitis has been reported in subjects treated with GLP-1 RAs including semaglutide. As a precaution, subjects with a history of acute or chronic pancreatitis will not be enrolled in the study.

Also, subjects will be informed about the symptoms of acute pancreatitis.

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Pancreatic cancer

Subjects with T2D have an increased risk of certain types of cancer such as pancreatic cancer. There is currently no support from nonclinical studies or clinical trials or post marketing data that GLP-1-based therapies increase the risk of pancreatic cancer. However, pancreatic cancer has been included as a separate potential risk due to the scientific debate surrounding a potential association to GLP-1-based therapies and the unknown long-term effects of stimulation of β-cells and suppression of α-cells. Pancreatic cancer has been classified as a potential class risk of GLP-1 RAs by EMA.

Allergic reactions and injection site reaction

As in the case with all protein-based pharmaceuticals, treatment with semaglutide may evoke allergic reactions. These may include localized injection site reactions or generalized reactions, including urticaria, rash, pruritus as well as anaphylactic reactions. As a precaution, subjects with known or suspected hypersensitivity to trial product(s) or related products will not be enrolled in the study. In addition, subjects will be instructed to contact the site staff as soon as possible for further guidance if suspicion of a hypersensitivity reaction to the study product occurs.

Hypoglycaemia

Based on current knowledge about the GLP-1 RA drug class, there is a risk of hypoglycaemic episodes. Hypoglycaemic episodes have mainly been observed when semaglutide is combined with SU or insulin.

Acute renal impairment

In subjects treated with GLP-1 RAs, including semaglutide, gastrointestinal AEs such as nausea, vomiting and diarrhoea may lead to significant dehydration and secondary acute renal impairment. Subjects with gastrointestinal AEs are recommended to drink plenty of fluids to avoid volume depletion. Also, serum creatinine and other markers of kidney function will be monitored throughout the study.

Impaired renal function may increase the risk of metformin associated lactic acidosis when GLP-1 RAs are co-administered with metformin. As a precaution, serum creatinine will be measured regularly. In subjects treated with metformin who experience prolonged or severe nausea and vomiting, the investigator should monitor serum creatinine, and if clinically indicated, withhold metformin until resolution of renal dysfunction. The use of the background medication should be in accordance with the current, approved labels.

Other safety considerations

Teratogenicity (embryo-foetal development toxicity)

Semaglutide caused embryo-foetal malformations in the rat through a GLP-1 receptor mediated effect on the inverted yolk sac placenta leading to impaired nutrient supply to the developing embryo. Primates do not have an inverted yolk sac placenta which makes this mechanism unlikely to be of relevance to humans. However, as a precaution, females who are pregnant, breast-feeding

or intend to become pregnant or are of childbearing potential and not using an adequate contraceptive method will not be enrolled in the study. In addition, pregnancy tests will be performed according to flowchart and at any time during the study if a menstrual period is missed, or as required by local law.

Diabetic retinopathy

A transient worsening of diabetic retinopathy is a recognised complication in selected patients with diabetes after initiation of intensive anti-diabetic treatment. Risk factors for these events include long-standing poor glycaemic control and presence of proliferative retinopathy, and initial large improvements in BG may be an additional aggravating factor. Several studies have, however, documented long-term beneficial effects of intensive glycaemic treatment in reducing retinopathy progression even in intensively treated patients who experienced early worsening. In a cardiovascular outcomes trial with s.c. semaglutide, results indicate an increased risk of events related to diabetic retinopathy in subjects treated with semaglutide compared to placebo. As a precaution in this study, all subjects are required to have a fundus photography or dilated fundoscopy performed 12 months before screening into the study; moreover, subjects with proliferative retinopathy or maculopathy requiring acute treatment will be excluded.

General precautions

All subjects will be included after a thorough evaluation regarding in- and exclusion criteria defined to ensure that subjects are eligible for study enrolment.

There are also strict glycaemic rescue criteria in place to ensure acceptable glycaemic control during the study, see Section 6.7. If rescue medication is required, it should be in accordance with ADA/European Association for the Study of Diabetes (excluding GLP-1 RAs, DPP-4 inhibitors and amylin analogues) and local guidelines.

It is the responsibility of the investigator to ensure the best possible care according to the principles outlined in Diabetes Care 2021 Standards of Medical Care in Diabetes.

Further details with regards to safety of study product are described in the current edition of the professional leaflet.

for semaglutide (NN9535), or any updates thereto.

2.3.2 Benefit assessment

In this study, participants will receive semaglutide as add-on to their current background medication (at least 1 antidiabetic drug: metformin, sulphonylureas, meglitinides, DPP-4 inhibitors, SGLT-2 inhibitors, thiazolidinediones, basal or bolus insulin). Subjects will therefore, for most of the study period, be treated with a regimen anticipated to be better than or equal to the treatment they receive at the time of entry into the study. Based on the results of the phase 3 trials, semaglutide is expected to provide clinically relevant improvements in glycaemic control and body weight, plus the beneficial effect of the drug on cardiovascular outcomes when added to standard of care in subjects with T2D.

In addition, it is expected that all participants will benefit from participation through close contact with the study site, with close follow-up of their T2D and a careful medical examination, all of which will

most likely result in an intensified management of their T2D.

Finally, all subjects in this study will receive study products and auxiliary supplies free of charge.

2.3.3 Overall benefit-risk conclusion

The safety profile for semaglutide generated from the clinical and nonclinical development programme has not revealed any safety issues that would prohibit administration of semaglutide in accordance with the planned clinical study. The phase 3 results indicate that semaglutide will provide an adequate safety profile with clinically relevant improvements in glycaemic control and body weight. Safety and efficacy will be monitored regularly, and acceptable glycaemic control will be reinforced at all times during the study. In conclusion, the potential risk to the subjects in this study is considered low and acceptable in view of the anticipated safety profile and benefits semaglutide will likely provide to subjects with T2D

3 Objectives, and endpoints.

3.1 Primary and secondary objectives

Primary objective:

To evaluate the short-term safety and tolerability (very common and common treatment-emergent adverse events) of once-weekly subcutaneous semaglutide subjects with T2D, added to available standard of care in Chilean public health setting

Secondary objective:

To evaluate the effect on glycaemic control, body weight, and other secondary safety and laboratory outcomes associated with once-weekly subcutaneous semaglutide in subjects with type 2 diabetes (T2D) added to available standard of care in a Chilean public health care setting (which includes medical, nurse and nutritionist care and available drugs in the public system, metformin, SUs and insulins)

3.2 Endpoints

3.2.1 Primary endpoint

Tolerability of semaglutide in GLP-1 naïve subjects in need of treatment optimization, despite available treatments:

Number of adverse events	From baseline to 24 week	Count of subject

3.2.2 Secondary endpoints

Change in glycosylated haemoglobin (HbA1c)	From baseline to 24 week	%-point
Subject achieving HbA1c < 7,0%	From baseline to 24 week	Yes/No
Change of fasting plasma glucose (FPG)	From baseline to 24 week	mg/dL
Change of body weight	From baseline to 24 week	kg
Change of waist circumference	From baseline to 24 week	cm
Subjects achieving ≥ 5% and ≥ 10% weight reduction	From baseline to 24 week	Yes/No
Change in laboratory tests	From baseline to 24 week	Lab test unit correspondent
Subject discontinued due to adverse events (treatment discontinuation)	From baseline to 24 week	Yes/No
Number of severe hypoglycaemic episodes per subject	From baseline to 24 week	Count per subject
Number of severe or blood glucose	From baseline to 24 week	Count per subject

confirmed symptomatic hypoglycaemic episodes per subject		
Number of serious adverse events (SAEs) per subject	From baseline to 24 week	Count per subject
Number of adverse reactions (ARs) per subject	From baseline to 24 week	Count per subject
Number of serious adverse reactions (SARs) per subject	From baseline to 24 week	Count per subject
Number of suspected unexpected serious adverse reactions (SUSARs) per subject	From baseline to 24 week	Count per subject
Change from baseline in heart rate (pulse) after 24 weeks of treatment	From baseline to 24 week	bpm

4 Study design

4.1 Overall design

This is an interventional, single-country, multi-centre, one-arm, open-label, study.

According to the inclusion and exclusion criteria, investigators will select 34, 33 and 33 subjects after screening their local subjects, in each hospital.

The selected 100 subjects will be ≥18 years-old with T2D diagnosed ≥ 90 days prior to the screening visit, in need of treatment optimization with at least 1 antidiabetic drug: metformin, sulphonylureas, meglitinides, DPP-4 inhibitors, SGLT-2 inhibitors, thiazolidinediones, basal or bolus insulin, whose T2D is not well controlled as defined by HbA1C (<7.0%). Subjects using GLP-1 RAs will not be permitted in this study.

Subject eligibility is based on the subjects' medical history, including HbA1c as part of their routine laboratory tests.

The study will be conducted in the secondary care setting (outpatient), in 3 public hospitals in Chile.

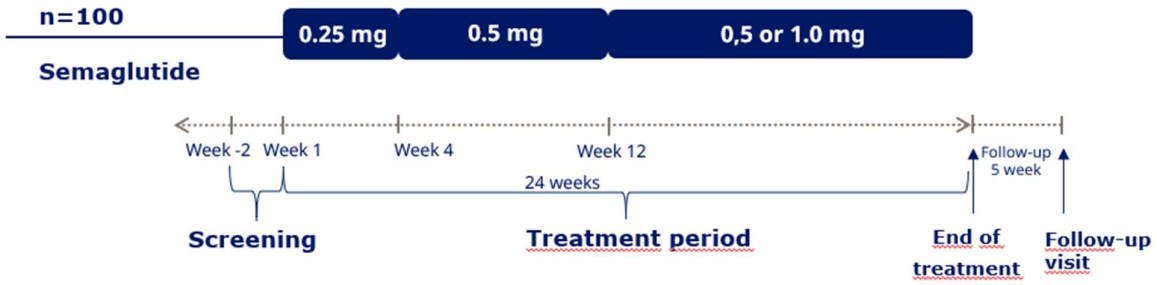
The maximum study duration for the individual subjects will be up to 34 weeks, +/- 10 days (see flowchart).

The study includes an up to 2-week screening period, followed by a 24-week treatment period and a 5-week follow up period after end of treatment.

The interventions will be providing the study treatment (Ozempic® pens) and laboratory tests required by the protocol, on top of standard of care. GLP-1 RAs are not part of the public hospitals´drug arsenal, which is the reason Novo Nordisk is providing the medication.

Please see Figure 1 for a schematic overview of the study

Figure 1 Study design



4.2 Scientific rationale for study design

The study has been designed as a one-arm study. Due to the objectives of this study, 100 subjects is considered to be an acceptable number to start the treatment.

The 24-week treatment duration is considered enough to ensure adequate time to evaluate the safety and tolerability, including dose escalation, of once-weekly dosing of 0.5 mg or 1.0 mg subcutaneous semaglutide in people with T2D added to available standard of care in Chilean public health care.

The 5-week follow-up period is included to find any adverse event associated with the treatment, considering the long medication half-life.

4.2.1 Patient input into design

N/A

4.3 Justification for dose

Semaglutide will be administered once weekly in a subcutaneous (s.c.) injection, as in the indication approved in Chile.

Participants will receive semaglutide in a dosing escalation manner for 24 weeks: 0.25 mg (weeks 1 to 4), 0.5 mg (weeks 5 to 12) and 0.5mg or 1.0 mg (weeks 13 to 24).

The maintenance dose of 0.5 mg will be reached after 4 doses (4 weeks) of 0.25 mg.

After the maintenance dose of 0.5 mg is reached, the dose can be changed to 1.0 mg at V3 (week 12), according to the investigator choice.
Should the subject present AE after dose escalation to 1 mg per week, the investigator may reduce the dose to 0.5 mg at any time.
Both doses are currently approved in Chile.

4.4 End of study definition

The end of the study is defined as the date of the last visit of the last participant in the study in the 3 research centres.

A participant is considered to have completed the study if he/she has completed all periods of the study including the last visit shown in the flowchart.

The primary endpoint is evaluated from visit V1 to V4. The primary completion date (PCD) is defined as the date of visit P5 (week 29) on which the last participant in the clinical study has an assessment for the primary endpoint. If the last participant is withdrawn early, the PCD is considered the date when the last participant would have completed visit V4A.

5 Study population

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

Pre-screening is defined as review of the subject medical records, including handing out participantinformation, as well as database review. Any pre-screening activities must be documented on site by the investigator.

Number of subjects

Number of subjects planned to be enrolled: 100
Number of subjects expected to complete the study (defined as treated with trial product for 24 weeks): 90

5.1 Inclusion criteria

Participants are eligible to be included in the study only if all the following criteria apply:

1. Informed consent obtained before any study-related activities. Study-related activities are any procedures that are carried out as part of the study, including activities to determine suitability for the study.
2. Male or female.
3. Age above or equal to 18 years at the time of signing informed consent.
4. Subjects diagnosed (clinically) with type 2 diabetes ≥ 90 days prior to the screening visit.
5. Stable daily dose of OAD and/or insulin treatment for ≥ 60 days prior to the screening visit.
6. HbA1c 7.5-10% (59-86 mmol/mol) (both inclusive) in V1.
7. Subjects in which Ozempic® is indicated according to approved local label.
8. Fundoscopy/Fundus photography record ≤ 12 months.

5.2 Exclusion criteria

Participants are excluded from the study if any of the following criteria apply:

1. Known or suspected hypersensitivity to study intervention(s) or related products.
2. Previous participation in this study. Participation is defined as signed informed consent.
3. Female who is pregnant, breast-feeding or intends to become pregnant or is of childbearingpotential and not using adequate contraceptive method.

4. Participation in any clinical trial of an approved or non-approved investigational medicinal product within 30 days before the screening visit, except COVID-19 related trials (this is allowed)
5. Treatment with any GLP-1 RA medication prior to the screening visit.
6. Any disorder which in the investigator's opinion might jeopardise subject's safety or compliance with the protocol.
7. Family or personal history of Multiple Endocrine Neoplasia Type 2 or Medullary Thyroid Carcinoma
8. History of pancreatitis (acute or chronic).
9. Renal impairment defined as eGFR below 30 mL/min/1.73 m^2 as per MDRD-4 (Modification of Diet in Renal Disease).
10. Myocardial infarction, stroke or hospitalisation for unstable angina or transient ischaemic attack within the past 180 days prior to the day of screening.
11. Subjects presently classified as being in New York Heart Association (NYHA) Class IV Heart failure.
12. Planned coronary, carotid or peripheral artery revascularisation known on the day of screening
13. Subjects with alanine aminotransferase (ALT) > 2.5 x upper normal limit (UNL).
14. Use of systemic immunosuppressive treatment within 90 days prior to screening.
15. Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria in a period of 90 days before the day of screening. An exception is short-term insulin treatment for acute illness for a total of ≤ 14 days.
16. Known hypoglycaemic unawareness and/or recurrent severe hypoglycaemic episodes as judged by the investigator.
17. Proliferative retinopathy or maculopathy requiring acute treatment. Verified by fundus photography or dilated fundoscopy performed within 12 months prior to screening.
18. History or presence of malignant neoplasms within the last 5 years (except basal and squamous cell skin cancer and carcinoma in situ).

5.3 Lifestyle considerations

No specific restrictions during the study. Subjects should be indicated to follow the local protocol for each clinical centre, regarding lifestyle recommendations.

Lifestyle considerations aligned to the local guidelines, and any specific consideration, in example, related to the management of adverse events will be according to the investigator´s decision.

Subjects can be derived to the local Novo Nordisk patient support programme, according to the investigator´s criteria for nurse, nutritional or physical activity support. This is an available benefit for all the local subjects to whom semaglutide is prescribed.

5.4 Screen failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently eligible for participation according to the inclusion/exclusion criteria. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participantsto meet requirements from regulatory authorities. Minimal information includes informed consent date, demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study *may not* be rescreened, except for completion of missing information.

5.5 Run-in criteria and dosing day criteria

First dose must only be administered after assessments related to primary and/or secondary endpoints are completed.

Re-sampling is not allowed if the subject has failed any of the run-in/dosing day criteria related to laboratory parameters. However, in case of technical issues (e.g. haemolysed or lost), re-sampling is allowed for the affected parameters.

5.5.1 Run-in Criteria

If the subject meets all the clinically available inclusion criteria and has no exclusion criteria and has signed the informed consent, then he/she can be scheduled for V1. During this visit, exclusion criteria will be reconfirmed and study medication will be dispensed.

5.5.2 Dosing day criteria

During V1, the investigator will explain how to start and titrate semaglutide, how to use the device and self-applicate the drug.
Dose adjustment of concomitant medication, in particular s sulphonylureas and insulins will be done to avoid hypoglycaemic risk.

Dose adjusting recommendations (on day 1of trial medication):

- Insulin dose reduction of at least 20% (subjects will be asked to report any hypoglycaemia suspicion that may require further dose adjustment).
- Sulphonylureas: discontinuation or half dose reduction.

6 Study intervention(s) and concomitant therapy

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Trial product comprise investigational medicinal products (IMPs), including placebo and comparators, non-investigational medicinal products (NIMPs) and/or investigational medical devices.

6.1 Study intervention(s) administered

- Semaglutide is to be administered by once weekly s.c. injections.
- Injections may be administered in the thigh, abdomen, or upper arm, at any time of day irrespective of meals. The injections are to be administered on the same day of the week during the study.
- Subjects will follow a fixed dose-escalation. The maintenance dose of the 0.5 mg treatment will be reached after four doses (four weeks) of 0.25 mg.
- Maintenance dosage may be escalated to 1.0 mg treatment according to investigator criteria of diabetes control and tolerability group at V3. If not tolerated, maintenance dose may be reduced back to 0.5 mg.
- Total treatment duration is planned to be 24 weeks.

- If a semaglutide dose is missed, it should be administered as soon as noticed, provided that the time to the next scheduled dose is at least two days ahead. If a dose is missed and the next scheduled dose is less than two days away, the subject should not administer a dose until the next scheduled dose. A missed dose will not affect the scheduled dosing day of the week.

- When discontinuing treatment after the end of the treatment (V4), subjects should be switched to a suitable available product at the discretion of the investigator, according to available standard of care.

- The investigator must document that directions for treatment use are given to the subject verbally and in writing as directions for use (DFU) document, summary of product characteristics (SmPC) at the first dispensing visit as specified in the flowchart.

Investigational medicinal products (IMP)

Commercially available Ozempic ® presentations will be used in this study.

- Ozempic®: solution for injection, 2 mg/ 1,5 mL
- Ozempic®: solution for injection, 4 mg/ 3 mL

Non-investigational medicinal products (NIMP)

Metformin adjustment, Insulin (all kinds) adjustment or addition, iSGLT-2 adjustment, or addition and/or other OADs addition or adjustment.

6.2 Preparation, handling, storage and accountability

Only participants enrolled in the study may use study intervention and only delegated site staff may *supply* study intervention.

Semaglutide preparations (not in-use and in-use) are not to be exposed to excessive heat or direct sunlight and are not to be used if they had been frozen. The IMP is only to be used if it appeared clear and colourless.

The investigator should take appropriate action to ensure correct storage of the IMP. The storage conditions for semaglutide are summarised in Table 1

Table 1 Storage conditions of the investigational medicinal product

Trial product	Shipping conditions	Storage conditions Not in-use	Storage condition In-use
Semaglutide	2°C to 8°C	• Store in a refrigerator (2°C to 8°C) • Do not freeze • Protect from light	• Store below 30°C/86°F • Use within 6 weeks) • Do not freeze • Protect from light

- Each site will be supplied with sufficient trial products for the study on an ongoing basis. Trial product will be distributed to the sites according to number of subjects in screening.
- The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all trial products received, and that any discrepancies are reported and resolved before use of the trial products.
- All trial products must be stored in a secure, controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and delegated site staff.
- The investigator must inform Novo Nordisk immediately if any trial product has been stored outside specified conditions (e.g., outside temperature range) and the investigator was to take appropriate action to avoid recurrence of the detected deviation. Storage outside of the indicated temperature range for up to 15 minutes is considered negligible and was not recorded as a

deviation. The trial product must not be dispensed to any subject before it has been evaluated and approved for further use by Novo Nordisk.

- The investigator or designee is responsible for drug accountability and record maintenance (i.e. receipt, accountability and final disposition records).

- The investigator or designee must instruct the subject in what to return at next visit.

- All returned (used or un-used), expired or damaged trial products (for technical complaint samples,see Appendix 5 [Section 10.5]) must be stored separately from non-allocated trial products. No temperature monitoring is required

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

- 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.

6.3 Study intervention compliance

Drug treatment compliance

Throughout the study, the investigator will remind the subjects to follow the study procedures and requirements to encourage subject compliance.

Subject compliance is assessed by monitoring of drug accountability. Prior to visits where drug accountability is performed (V3 and V4) the subject is asked to return all used, partly used, and unused IMP including empty packaging material. The investigator should assess the amount of IMP returned compared to what was dispensed at the last dispensing visit and, in case of discrepancies, to question the subject.

If any suspicion of non-compliance arises, apart from occasionally or missed doses, the site must enter into a dialogue with the subject, re-emphasizing the importance of compliance and uncover barriers to compliance. This dialogue must be documented. Compliance will be assessed by cross checking the following sources and comparing these to the expected use:

- Drug accountability information; counting returned trial product, visual inspection of pens
- Questioning of subjects

Treatment start and stop dates will be recorded in the eCRF.

6.4 Dose modification

Participants will receive once weekly semaglutide s.c. injection in a dose escalation manner for 24 weeks: 0.25 mg (weeks 1 to 4), 0.5 mg (weeks 5 to 12) and 0.5mg or 1.0 mg (weeks 13 to 24).

The maintenance dose of 0.5 mg will be reached after 4 doses (4 weeks) of 0.25 mg.

After the maintenance dose of 0.5 mg is reached, the dose can be changed to 1.0 mg during the week 12 control if there is clinical need for the change according to investigator criteria.

6.5 Continued access to study intervention after end of study

When discontinuing study intervention after the end of treatment (V4), the participants should be transferred to a suitable marketed product at the discretion of the investigator or treating physician.

6.6 Treatment of overdose

Scarce previous experience related to accidental overdose exists from the semaglutide clinical development programme.

Events of nausea, vomiting and headache have been reported in connection with accidental administration of up to 4 mg semaglutide. No symptoms of hypoglycaemia have been reported in connection with overdose of semaglutide.

In the event of overdosage, appropriate supportive treatment must be initiated according to the subject's clinical signs and symptoms.

For more information on overdose, also consult the current version of the Semaglutide investigator's brochure (IB).

6.7 Concomitant therapy

Concomitant medication is defined as any medication, other than the IMP, taken during the study, including the screening and follow-up periods. Details of all concomitant medications will be recorded in the eCRF at study entry (i.e., at V0). The information collected for each concomitant medication included, as a minimum, the trade name or generic name of the concomitant medication, the indication, the start and stop dates.

Any changes in concomitant medications, including rescue medication, will be recorded at each visit as they occurred. If a change is due to an AE, then this must be reported according to Section 8.3.

6.7.1 Rescue medicine

Subjects with unacceptable hyperglycaemia should be evaluated according to standard of care and treatment should be adjusted accordingly (see Appendix 7).

7 Discontinuation of study intervention and participant discontinuation/withdrawal

Discontinuation of specific sites or of the study as a whole is detailed in Appendix 1 (Section 10.1.11).

7.1 Discontinuation of study intervention

Study intervention may be discontinued at any time during the study at the discretion of the participant or at the discretion of the investigator for safety, behavioural, compliance or administrative reasons.

Efforts must be made to have participants attend and complete all scheduled visit procedures, and to have the subjects who discontinue trial product attend premature discontinuation visit (V4A) to collect the required data for the analysis of the primary (and confirmatory secondary) endpoint. Only participants who withdraw consent will be considered as withdrawn from the study. Participants must be educated about the continued scientific importance of their data, even if they discontinue study intervention.

The study intervention must be discontinued, if any of the following applies for the participant:

1. Violation of any of the inclusion or exclusion criteria.
2. Pregnancy.
3. Intention of becoming pregnant.
4. Suspicion of acute pancreatitis.
5. Simultaneous use of an approved or non-approved investigational medicinal product in another clinical study.
6. Withdrawal of informed consent.

Note: Simultaneous participation in a study with the primary objective of evaluating an approved or non-approved investigational medicinal product for prevention or treatment of COVID-19 disease or post-infectious conditions is allowed at the investigator's discretion without discontinuation of study intervention.

Subjects discontinued from trial product should be prescribed alternative therapy at the investigator's discretion.

See the flowchart for data to be collected at the time of premature discontinuation visit and for any further evaluations that need to be completed.

The primary reason for discontinuation of study intervention must be specified in the eCRF, and finaltrial product accountability must be performed.

7.1.1 Handling of missing dose

If any participant missed a dose, they must administer study treatment as soon as possible within 5 days after the missed dose, as on-label. If more than 5 days have passed, they will have to skip the missed dose and administer the next dose on the regularly scheduled day. In each case, subjects can then resume their regular once weekly dosing schedule

7.1.2 Rescue criteria

Refer to Section 6.7.1 for description of rescue medication

7.2 Participant discontinuation/withdrawal from the study

A participant may be discontinued from the study at any time at thediscretion of the investigator for safety, behavioural, compliance or administrative reasons

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

If a participant withdraws consent or is withdrawn by the investigator prior to run-in/receipt of study intervention, he/she will not be asked to have any follow-up assessments performed. The following data must be collected: Demography, eligibility criteria, dateof informed consent, date of screening and the date when participant's participation ended. The end of study form must be completed.

If a participant withdraws consent or is withdrawn by the investigator after run-in/receipt of study intervention, the investigator must ask the participant if he/she iswilling, as soon as possible, to have assessments performed according to visit V4A. See the flowchart for data to be collected.

Final trial product accountability must be performed even if the participant is not able to come to the site.

If the participant withdraws consent, Novo Nordisk may retain and continue to use any data collected before such a withdrawal of consent for the purpose of the study or scientific research.

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

Although a participant 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 participant's rights. Where the reasons are obtained, the primary reason for withdrawal must be specified in the eCRF.

7.3 Lost to follow-up

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

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

- The site must attempt to contact *the participant* and reschedule the missed visit as soon as possible and counsel *the participant* on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with *the participant.* These contact attempts should be documented in the participant's source document.
- Should *the participant* continue to be unreachable, *he/she* will be considered to have withdrawn from the study witha primary reason of 'lost to follow-up'.

8 Study assessments and procedures

The following sections describe the assessments and procedures, while their timing is summarised in the flowchart.

Informed consent must be obtained before any study-related activity, see Appendix 1 (Section 10.1.3).

All screening evaluations must be completed and reviewed to confirm that potential participants meet all inclusion criteria and none of the exclusion criteria.

The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reason for screen failure, as applicable.

At screening, participants will be provided with a card stating that they are participating in a study and giving contact details of relevant site staff that can be contacted in case of emergency.

Adherence to the study design requirements, including those specified in the flowchart, is essential and required for study conduct.

Please refer to Section 6.3 for drug treatment compliance.

Review of laboratory reports must be documented either on the documents or in the subject's source documents.

The maximum amount of blood collected from each participant over the duration of the study will not exceed 80 mL.

Repeat samples may be taken for technical issues and unscheduled samples or assessments may be taken for safety reasons. Please refer to Appendix 2 (Section 10.2) for further details on laboratory samples.

8.1 Efficacy assessments

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

8.1.1 Plasma glucose measurements

Blood samples

Blood samples will be taken according to the flowchart and analysed at the site´s local laboratory to determine levels of the following glycaemia-related parameters:

- HbA1c %
- FPG (mg/dL)

8.1.2 Clinical efficacy laboratory assessments

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

8.2 Safety assessments

1. Treatment-emergent adverse events registration (described later)
2. Subject discontinued due to adverse events registration

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

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

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

In case of an abnormal and clinically significant finding fulfilling the definition of medical history or concomitant illness, the investigator must record the finding on the medical history/concomitant illness form.

Information on hypoglycaemia unawareness will be recorded according to Clarke's questionnaire, question 8.[10] The investigator must ask the participant in the following way: "To what extent can youtell by your symptoms that your blood glucose is low?" Participants answering ‘never, rarely or sometimes’ are considered to have impaired awareness of hypoglycaemia, whereas those answering ‘often or always’ are not.

8.2.1 Physical examinations

A physical examination will be performed by the investigator at the screening visit (V0), V1, V3, V4 and V4A if applicable according to local procedures.

The **physical examination** includes the following items:

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

Review of the physical examination will be documented either on the front page of

the documents or in the subject's medical record.

The physical examinations have to **follow these categories:**

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

In case of an abnormal clinically significant finding pertaining to the screening visit, the investigator have to provide a comment in the subject's medical record and record this on the concomitant illness form in the eCRF. At subsequent visits, any clinically significant changes or new clinically significant findings has to be reported as an AE according to Section 8.3.

Body measurements will also be measured and recorded as specified in the flowchart.

- Body weight will be measured and recorded in the eCRF in kg with one decimal (without shoes and only wearing light clothing).
- Height will be measured without shoes in cm and recorded in the eCRF to nearest ½ cm.
- Waist circumference is defined as the minimal abdominal circumference located midway between the lower rib margin and the iliac crest. Three consecutive measurements of waist circumference will be performed and recorded in the eCRF. The waist circumference will be was measured in cm to the nearest ½ cm using a non-stretchable measuring tape. Waist circumference will be measured while the subject is in a standing position with an empty bladder and wearing light clothing with accessible waist. The subject has to be standing with arms down their side and feet together. The tape has to touch the skin but not compress soft tissue and twists in the tape are to be avoided. The subject will be asked to breathe normally and the measurement will be taken when the subject is breathing out gently.
- Body mass index (BMI) will be calculated in the eCRF using the equation:
  BMI kg/m2 = body weight (kg)/(height (m) x height (m)) or (kg/m2 = [lb/in2 x 703])

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2 Vital signs

- **Blood pressure**

The method for measuring systolic and diastolic blood pressure will follow the standard clinical practice at individual sites, but as a minimum the following guideline has to be adhered to:

- Caffeine, smoking and exercise should be avoided for at least 30 minutes prior to measuring the blood pressure.
- The blood pressure should be measured in a sitting position, with the legs uncrossed and the back and arms supported.

- Subjects should be sitting for at least five minutes before the measurement was taken and the data should be recorded in the eCRF.
- The subject should not talk during the measurement.

- **Pulse rate**

Pulse rate will be measured in connection to the blood pressure measurements. Record the pulse rate for the last 2 blood pressure measurements in the eCRF. The pulse rate is to be recorded as the mean of the last 2 measurements.

8.2.3 Clinical safety laboratory assessments

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

8.2.4 Pregnancy testing

Woman of childbearing potential (WOCBP) should only be included after a negative, highly sensitive serum pregnancy test (refer to Appendix 2).

Pregnancy testing should be performed whenever a menstruation is missed or when pregnancy is otherwise suspected.

8.3 Adverse events and other safety reporting

The investigator is responsible for detecting, documenting, recording and following up on events listed below:

- AEs and SAEs
- AEs leading to discontinuation of study intervention under clinical investigation
- Selected types of AEs requiring additional data collection and other events requiring collection of additional information (Table 5)
- Other events as applicable

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

Some AEs require additional data collection on a specific event form. The relevant event(s) are listed below in **Table 5**, together with other events requiring collection of additional information.

Table 5 AEs requiring additional data collection and other events requiring additional data collection

Event type	*AE requiring additional data collection*	*Other event requiring collection of additional information*
Medication error	*X*	
Misuse and abuse	*X*	
Hypoglycaemic episodes		*X*

Definitions and reporting timelines for the events mentioned in the above table can be found in Appendix 3 (Section 10.3) *and Appendix 6 (Section 10.6) for hypoglycaemic episodes.*

8.3.1 Time period and frequency for collecting AE information

All AEs and SAEs specified in Section 8.3 must be collected and reported. The events must be collected from the first administration of study intervention under clinical investigation and until the follow-up visit/end of study visit, in accordance with the flowchart (1.2) or whenever, within the above time period, the site becomes aware of an AE or SAE.

Conditions present prior to the timepoint from which AEs are collected and anticipated day-to-day fluctuations of these conditions, including those identified during screening or during other study-related procedures performed before exposure to study intervention under clinical investigation, will be recorded as medical history/concomitant illness.

AE and SAE reporting timelines can be found in Appendix 3 (Section 10.3). All SAEs must be recorded and reported to Novo Nordisk within 24 hours, and the investigator must submit any updated SAE data to Novo Nordisk or designee within 24 hours of it beingavailable.

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

8.3.2 Method of detecting AEs

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

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

8.3.3 Follow-up of AEs

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

8.3.4 Regulatory reporting requirements for SAEs

Prompt notification by the investigator to Novo Nordisk of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants andthe safety of a study intervention 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 study intervention under clinical investigation. Novo Nordisk will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators. This also includes suspected unexpected serious adverse reactions (SUSAR)

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

8.3.5 Pregnancy

A blood pregnancy test will be performed at the local laboratory for women of childbearing potential if a menstrual period is missed or if pregnancy is suspected any time during the study.

Pregnancy testing is not required for women not of child bearing potential defined as women who had undergone a hysterectomy, bilateral oophorectomy or bilateral tubal ligation, or who are postmenopausal (e.g., above the age of 45, who had been without menstrual period for at least one year).

Female subjects will be instructed to notify the investigator immediately if they became pregnant during the study.

The trial product will be discontinued in case of pregnancy and will be specified in the eCRF as the primary reason for the discontinuation of treatment.

For subjects who discontinue treatment prematurely, the premature discontinuation visit should be scheduled as soon as possible.

Subjects discontinued from trial product should be prescribed alternative therapy at the investigator's discretion.

See the flowchart for data to be collected at the time of premature discontinuation visit and for any further evaluations that need to be completed.

The investigator must report any pregnancy in subjects who had received trial product.

The investigator must follow the pregnancy until the pregnancy outcome was determined. If the pregnancy resulted in a live birth, the newborn infant will be followed until one month of age.

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

Details of pregnancies in female participants will be collected after first exposure to IMP and until the new-born infant is one month of age. For details regarding collection and reporting of pregnancy information, please refer to Appendix 4 (Section 10.4).

8.3.6 Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs

The following disease-related events (DREs) are common in participants with disease, condition under study and can be serious/life threatening:

- Hyperglycaemic episodes

Hyperglycaemia

Because hyperglycaemic episodes are typically associated with the disease under study, non-serious hyperglycaemic episodes will not be reported according to the standard process for reporting of AEs, even though the episodes meet the definition of an AE.

Definitions, classification and reporting requirements for hyperglycaemic episodes are described in Appendix 7 (Section 10.7).

If the hyperglycaemic episode fulfils the criteria for an SAE, then in addition to the above, an AE form and a safety information form must also be filled in.

8.3.7 Technical complaints

Technical complaints on Ozempic® which occur from the first time of usage until the last time of usage of the product and which is considered related to an SAE must be reported to Novo Nordisk via trial specific technical complaint form in the CRF and according to instructions found in Appendix 5 (Section 10.5).

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

Technical complaints on Ozempic® not related to an SAE, may be reported to Novo Nordisk Affiliate via the spontaneous reporting system.

9 Statistical considerations

This section is a summary of the planned statistical analyses of the endpoints including primary and key secondary endpoints.

9.1 Statistical hypotheses

No confirmatory hypotheses are planned to be tested.

9.2 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.

Participant Analysis Set	Description
Full analysis set	All participants exposed to the study product.

In-trial observation period: This observation period is defined as the period from date of initiation 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 study product. The observation period starts at the date of first dose of study 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 (P5)
- The premature discontinuation follow-up visit (V4A)
- The last date on study product + 42 days for safety and +7 days for efficacy
- 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 study product corresponding to approximately five half-lives of semaglutide s.c.

Data points collected outside an observation period will be treated as missing in the analysis. Baseline (week 1) 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. If subjects or observations are excluded, the reasons

for their exclusion must be documented before database lock and described in the clinical trial report. Any decision to exclude either a subject or single observation from the statistical analysis is the joint responsibility of the members of the Novo Nordisk study group.

9.3 Statistical analyses

If needed, the statistical analysis plan (SAP) will be finalised prior to first participant first visit (FPFV), to provide a more technical and detailed description of the statistical analyses. This section is a summary of the planned statistical analyses.

9.3.1 General considerations

Baseline will be defined at week 1 prior to or at first exposure of treatment.

All the primary and secondary safety endpoint will be summarised as described in the section 9.3.2 and 9.3.3. Secondary efficacy endpoints will be summarised and analysed as described section 9.3.3.

9.3.2 Primary endpoints

The primary endpoint will be evaluated in the full analysis set (FAS) using the on-treatment period.

A treatment-emergent AE is an event that has onset date (or increase in severity) during the on-treatment observation period. These will therefore be referred to as 'on-treatment AEs' hereafter.

TEAEs will be reported in terms of the number of subjects with at least one event (N), the percentage of subjects with at least one event (%), the number of events (E) and the event rate per 100 years (R) for on-treatment period.

9.3.3 Secondary endpoints analysis

Safety endpoints

The safety endpoints will be evaluated based on FAS using the on-treatment observation period and the in-trial observation period unless otherwise stated.

Adverse Events:

All AEs and hypoglycemic episodes are summarised descriptively in terms of the number of subjects with at least one event (N), the percentage of subjects with at least one event (%), the number of events (E) and the event rate per 100 years (R) for on-treatment period. These summaries are replicated by outputs including all 'in-trial' AEs (i.e., AEs with onset date [or increase in severity] during the 'in-trial' observation period). AEs with onset after the end of the 'in-trial' observation period will be reported in a listing.

All AEs will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) coding.

Classification of Hypoglycaemia:

Treatment emergent: Hypoglycaemic episodes will be defined as treatment emergent if the onset is in the on-treatment observation period (see Section 9.2).

Hypoglycaemic episodes are classified based on the newest adapted guidelines approved internally in 2019 (refer to section 10-6).

Efficacy Endpoints:

The secondary efficacy endpoints and assessments at scheduled timepoints will be summarised descriptively based on FAS using the on-treatment observation period and the in-trial observation period. Descriptive statistics (mean, Standard Deviation (SD), median, and range for continuous variables and proportion for categorical variables) will be used.

The following continuous secondary endpoints will be analysed statistically based on FAS and the on-treatment observation period:

- HbA1c (%-point)
- Fasting plasma glucose (mg/dL)
- Body weight (Kg, %)
- Waist circumference (cm)
- Fasting blood lipids (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) (mg/dL)

For this purpose, a mixed model for repeated measurements (MMRM) will use all assessments in the specific observation period. The dependent variable (response) is change from baseline in HbA1c at all scheduled visits. This model will include time (visits) as fixed factor and baseline HbA_{1c} as covariate. Interactions between visit and baseline HbA1c will also be included in the model. An unstructured covariance matrix will be used to describe the variability for the repeated measurements for a patient (if the model will not converge a compound symmetry covariance matrix will be considered as the simpler alternative). Patients without post-baseline measurements for HbA_{1c} will not be included in the analysis. Least-square means estimates for change from baseline in HbA_{1c} at week 24 for an average patient in FAS (i.e. a reference patient with a mean baseline HbA_{1c}) will be reported and include associated 95%CI and p-value that tests the null-hypothesis of no change from baseline at week 24. The MMRM is a well-established method that appropriately accounts for the uncertainty pertaining to missing data. This analysis assumes that missing data are missing at random (i.e. missing values may be dependent on observed, but not unobserved data).

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

9.4 Sample size determination

Due to the broad safety objective of this study, no formal sample size calculation is performed. The sample size of 90 participants are expected to complete the study out of 100 enrolled.
This is considered appropriate to generate appropriate experience regarding the safety primary outcome and efficacy secondary outcomes of semaglutide in local subjects.

10 Supporting documentation and operational considerations

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

10.1.1 Regulatory and ethical considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki[11] and applicable ICH Good Clinical Practice (GCP) Guideline[12]
- 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 study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate safety hazard to study participants.

Before a site is allowed to start screening participants, written notification from Novo Nordisk must be received.

The investigator will be responsible for:

- providing written summaries of the status of the study 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 study at the site and adherence to requirements of ICH guidelines, the IRB/IEC, and all other applicable local regulations
- ensuring submission of the CSR synopsis to the IRB/IEC
- reporting any potential serious breaches to the sponsor immediately after discovery

10.1.2 Financial disclosure

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

10.1.3 Informed consent process

The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study. This includes the use of an impartial witness where required according to local requirements.

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

Participants must be informed that their participation is voluntary. Participants will be required to sign and date a statement of informed consent that meets the requirements of local regulations, ICH GCP[12] guidelines, Declaration of Helsinki,[11] privacy and data protection requirements, where applicable, and the IRB/IEC or site.

The medical record must include a statement that written informed consent was obtained before any study-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 anystudy-related activity.

The responsibility of seeking informed consent must remain with the investigator, but the investigator may delegate the task to a medically qualified person, in accordance with local requirements.

Participants must be re-consented to the most current version of theinformed consent form(s) during their participation in the study.

A copy of the informed consent form(s) must be provided to the participant.

10.1.4 Information to participants during the study

Subjects can be derived to the local Novo Nordisk patient support programme, according to the investigator´s criteria for nurse, nutritional or physical activity support. This is an available benefit for all the local subjects to whom semaglutide is prescribed (see flowchart). It is the subject´s decision to join the programme at any time or not.

10.1.5 Data protection

Participants will be assigned a unique identifier (CL + centre number (1, 2 or 3) + patient number (000 onwards per centre), a subject ID, i.e., CL1001. Any participant records or datasets that are transferred to Novo Nordisk will contain the identifier only. No direct identifiersfrom the participant are transferred to Novo Nordisk.

The participant and any biological material obtained from the participant will be identified by subject ID, visit number and study ID. Appropriate measures such as encryption or leaving out certain identifiers will be enforced to protect the identity of participants as required by local, regional and national requirements.

The participant must be informed about his/her privacy rights, including that his/her personal study-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 participant.

The participant 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.

Personal data may be collected from participants due to process requirements from Novo Nordisk's suppliers. This data is needed to ensure that the relevant data analysis for the study can be performed, but will not be part of the data transferred to Novo Nordisk, the assessment of the study endpoints or the clinical study report. A list of any such data values must be kept as part of the study documentation along with an explanation of why it was required.

10.1.6 Committees structure

10.1.6.1 Novo Nordisk safety committee

Novo Nordisk will perform ongoing safety surveillance. If new safety signals are identified, these will be evaluated by an internal safety committee.

10.1.7 Dissemination of clinical study data

Study information will be disclosed at clinicaltrials.gov and novonordisk-trials.com and, if applicable, also on other national or regional study registries. It will be disclosed according to applicable requirements, relevant recommendations or regulations, such as the Declaration of Helsinki,[11] the International Committee of Medical Journal Editors (ICMJE),[13] the Food and Drug Administration Amendment Act (FDAAA),[14] European Commission Requirements[15, 16, 17] and in accordance with Novo Nordisk commitment to clinicaltransparency. If a participant requests to be included in the study via the Novo Nordisk e-mail contact at these web sites, Novo Nordisk may disclose the investigator's contact details to the participant. As a result of increasing requirements for transparency, some countries require public disclosure of investigator names and their affiliations.

10.1.8 Data quality assurance

10.1.8.1 Case report forms

Novo Nordisk is responsible for the data management of this study including qualitychecking of the data.

To demonstrate his/her oversight of the collected data, the investigator should sign the CRF on a regular basis during the conduct of the study as well as at the end of the study, asdescribed in the CRF completion guideline.

All participant data relating to the study will be recorded on CRFs unless transmitted electronically to Novo Nordisk (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The following will be provided as paper CRFs and eCRF to be used:

- AE forms
- Pregnancy forms
- Safety information forms
- Technical complaint forms

Corrections to the CRF data may be made by the investigator or the investigator's delegated staff. An audit trail will be maintained in the CRF application containing as a minimum: the old and the new data, identification of the person entering the data, date and time of the entry and reason for the correction. If corrections are made by the investigator's delegated staff after the date when the investigator signed the CRF, the CRF must be signed and dated again by the investigator.

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

10.1.8.2 Monitoring

The investigator must permit study-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 study. If the electronic source data does not have a visible audit trail, the investigator must provide the monitor with signed and dated printouts. In addition, the relevant site staff should be available for discussions at monitoring visits and between monitoring visits (e.g., by telephone).

Study monitors will perform ongoing source data verification of critical data points to confirm that data entered into the CRF by authorised site personnel are accurate, complete and verifiable from source documents. Study monitors will perform ongoing source data review to ensure that the study is being conducted in accordance with the current approved protocol and any other study agreements, ICH GCP[12], and all applicable regulatory requirements, evaluating the adequacy of critical processes at site for the execution of the protocol, collection of study data, to ensure that the safety and rights of participants are being protected.

Monitoring will be conducted using a risk-based approach including risk assessment, monitoring plans, centralised monitoring (remote assessment of data by Novo Nordisk) and visits to sites.

Quality tolerance limits (QTLs) will be predefined in the relevant monitoring plan to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarised in the clinical study report.

10.1.8.3 Protocol compliance

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

Deviations must be documented and explained in a protocol deviation by stating the reason, date, and the action(s) taken.

10.1.9 Source documents

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

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the site. Any source data generated by investigator's subcontractors must be archived and accessible by the site.
Data that is transcribed into the eCRF 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 participant's medical history in source documents, such as participant's medical record.

The investigator must document any attempt to obtain external medical information by noting the date(s) when information was requested, and who was contacted.

Definition of what constitutes source data can be found in a source document agreement at each site. There will only be one source document defined at any time for any data element.

10.1.10 Retention of clinical study documentation

Records and documents, including signed informed consent forms, pertaining to the conduct of this study must be retained by the investigator for 15 years after end of study 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 study documents without involving Novo Nordisk in any way. If applicable, electronic CRF and other participant 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 participant data (in an electronic readable format or as paper copies or prints) must be retained by the site. A copy of all data will be stored by Novo Nordisk.

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

10.1.11 Study and site closure

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

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

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

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

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

10.1.12 Responsibilities

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

A qualified physician, who is an investigator or a sub investigator for the study, must be responsible for all study-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 study and the quality of the data produced) in the investigator trial master file. The documents, including the participant identification code list must be kept in a secure locked facility so that no unauthorised persons can get access to the data.

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

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

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

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

10.1.13 Indemnity statement

Novo Nordisk carries product liability for its products, and liability as assumed under the special laws, acts and/or guidelines for conducting clinical studies 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 study or by persons for whom the said site or investigator are responsible.

10.1.14 Publication policy

The information obtained during the conduct of this study 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 study intervention. All information supplied by Novo Nordisk in connection with this study 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 study.

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

Novo Nordisk may publish on its clinical studies website a redacted CSR for this study.

One investigator will be appointed by Novo Nordisk to review and sign the CSR (signatoryinvestigator) on behalf of all participating investigators.

10.1.14.1 Communication of results

Novo Nordisk commits to communicate and disclose results of studies 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 study 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 CSR 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 study.

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

10.1.14.2 Authorship

Novo Nordisk will work with one or more investigator(s) and other experts who have contributed to the study 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.[18]

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

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

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

For a multicentre clinical study, analyses based on single-site data usually have significant statistical limitations and frequently do not provide meaningful information for healthcare professionals or participants, 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 study.

10.1.14.4 Investigator access to data and review of results

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

Individual investigators will have their own research participants' data.

10.2 Appendix 2: Clinical laboratory tests

The laboratory analyses will be performed by the local laboratories.

Laboratory samples include both urine (first morning urine) and blood samples. The specific clinical laboratory tests performed during the study are summarised in Table 6 and Table 7. For details regarding specific timing of each sample, refer to the study flowchart in section 1.2.

Review of the laboratory reports will be documented either on the front page of the documents or in the subject's medical record. The signed documents will be retained at the site as source documentation.

For laboratory report values outside the reference range, the investigator has to specify whether the value was clinically significant or clinically non-significant. All laboratory printouts has to be signed and dated by the investigator on the day of evaluation. The signed laboratory report will be retained at the site as source documentation.

Table 6 Protocol-required efficacy laboratory assessments

Laboratory assessments	***Parameters***
Glucose metabolism	• *$HbA1_c$* (%) • *Fasting plasma glucose*[a] (mg/dL)
Lipids	• *Cholesterol* (mg/dL) • *High density lipoprotein (HDL) cholesterol* (mg/dL) • *Low density lipoprotein (LDL) cholesterol* (mg/dL) • *Triglycerides* (mg/dL)
NOTES: [a]*An FPG result </≤ 3.9 mmol/L (70 mg/dL) in relation to planned fasting visits should not be reported as a hypoglycaemic episode but as an AE at the discretion of the investigator (Appendix 3, Section 10.3).* *A FPG result >16.7 mmol/L (300 mg/dL) should not be reported as a hyperglycaemic episode but as an AE at the discretion of the investigator (Appendix 3, Section 10.3).*	

Table 7 Protocol-required safety laboratory assessments

Laboratory assessments	***Parameters***
Biochemistry[a]	• *Alanine Aminotransferase/ALT (U/L)* • *Alkaline phosphatase/AP(U/L)* • *Aspartate Aminotransferase/AST (U/L)* • *Gamma Glutamyl Transferase/GGT (U/L)* • *Bilirubin (mg/dL)* • *Calcium* (mg/dL) • *Urea* (mg/dL) • *Albumin (g/dL)* • *Total protein (g/dL)*

Pregnancy Testing[c]	• *Highly sensitive serum human chorionic gonadotropin (hCG) pregnancy test*
Other tests	• *Creatinine* (mg/dL) (including eGFR using MDRD formula) • *Urine Albumin to creatinine ratio (mg/g)*
Notes: [a]*Details of required actions and follow-up assessments for increased liver parameters including any discontinuation criteria are given in Appendix 3 (Section 10.3) (Hy's Law) and Section 7.1.* [c]*For women of childbearing potential, as needed, serum testing is required.*	

10.3 Appendix 3: Adverse Events and Serious Adverse Events: Definitions and procedures for recording, evaluating, follow-up, and reporting

10.3.1 Definition of AE

An AE is any untoward medical occurrence in a clinical study participant that is temporally associated with the use of IMP, whether or not considered related to the IMP.

An AE can thereforebe any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease (new or exacerbated) temporally associated with the use of a IMP.

Events to be reported as AEs:

- Any abnormal laboratory test results or safety assessments considered clinically significant in the medical and scientific judgment of the investigator, including events that have worsened from prior to the time point from which AEs are collected
- Conditions detected or diagnosed after IMP administration even though it may have been present prior to the time point from which AEs are collected
- Exacerbation/worsening of a chronic or intermittent condition including either an increase in frequency and/or intensity of the condition
- Signs, symptoms or the clinical sequelae of a suspected drug-drug interaction
- Signs, symptoms or the clinical sequelae of a suspected overdose of IMP regardless of intent
- A ‘lack of efficacy’or ‘failure of expected pharmacological action’ 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 to be reported as AEs:

- Conditions present prior to the time point from which AEs are collected and anticipated day-to-day fluctuations of these conditions. This includes those conditions identified during screening or identified during other study procedures performed before exposure to IMP.
  Note: Conditions present or occurring prior to the time point from which AEs are collected should be recorded as concomitant illness/medical history.

- Medical or surgical procedures (e.g., endoscopy, appendectomy). The condition that leads to the procedure is the AE.
- Medical or surgical procedures not preceded by an AE or worsening of a known condition.

10.3.2 Definition of an SAE

An SAE is any untoward medical occurrence that fulfils at least one of the following criteria:

- **Results in death**
- **Is life-threatening**
  - The term 'life-threatening' refers to an event in which the participant 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 participant has been admitted at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other seriousness criteria, the event is serious. When in doubt as to whether 'hospitalisation' occurred or was necessary, the AE should be considered serious.
  - Hospitalisation for elective treatment (e.g., elective medical or surgical procedures) of a condition that was present prior to the time point from which AEs are collected, and that did not worsen, is not considered an AE.

    Note: Hospitalisations for administrative, study-related, social and convenience reasons do not constitute AEs and should therefore not be reported as AEs or SAEs. Hospital admissions for medical or surgical procedures, planned before study inclusion, are not considered AEs or SAEs
- **Results in persistent or significant disability/incapacity**
  - The term 'disability' means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experience of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g., sprained ankle), that 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 by the investigator 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 participant 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 must be reported as an SAE using the important medical event criterion if no other seriousness criteria are applicable:
    - Suspicion of transmission of infectious agents via IMP
    - Risk of liver injury defined as alanine aminotransferase (ALT) or asparate aminotransferase (AST) >3x UNL and total bilirubin >2x UNL where no alternative aetiology exists (Hy's law)

10.3.3 Description of AEs requiring additional data collection *and other events requiring collection of additional information*

Adverse events requiring additional data collection

An AE requiring additional data collection is an AE where Novo Nordisk has evaluated that additional data is needed in the evaluation of safety.

Medication error:

- A medication error is an unintended failure in the IMP treatment process that leads to, or has the potential to lead to, harm to the participant, such as:
  - administration of wrong drug
  - wrong route of administration, such as intramuscular instead of subcutaneous
  - 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 study participant were likely to happen as judged by the investigator, although they did not necessarily occur.

Misuse and abuse:

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

Note: Medication error, misuse and abuse must always be reported on an AE form and a specific event form must be completed. The AE diagnosis on the AE form must reflect what occurred (e.g.,

accidental overdose, intentional overdose or other). If the medication error and/or misuse and abuse resulted in a clinical consequence, this must be reported on an additional AE form.

Other events requiring collection of additional information

Hypoglycaemic episodes

All hypoglycaemic episodes must be recorded on a hypoglycaemic episode form. If the hypoglycaemic episode fulfills the criteria for an SAE, then in addition to the hypoglycaemic episode form, an AE form and a safety information form must be filled in. One AE form and safety information form can cover several hypoglycaemic episode forms, if the participant has not recovered between the episodes.

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

10.3.4.1 AE and SAE recording

The investigator will record all relevant AE/SAE information in the CRF.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory and diagnostics reports) related to the event.

There may be instances when copies of source documents (e.g., medical records) for certain cases are requested by Novo Nordisk. In such cases, all participant identifiers, with the exception of the subject ID, must be redacted on the copies of the source documents before submission to Novo Nordisk.

For all non-serious AEs, the applicable forms should be signed when the event is resolved or at the end of the study at the latest. For sign-off of SAE-related forms, refer to “AE and SAE reporting via paper CRF” later in this section.

Novo Nordisk products used as concomitant medication: if an AE is considered to have acausal relationship with a Novo Nordisk marketed product used as concomitant medication in the study, it is important that the suspected relationship isreported 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

10.3.4.2 Assessment of severity

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

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

10.3.4.3 Assessment of causality

The investigator is obligated to assess the relationship between IMP and the occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.

Relationship between an AE/SAE and the relevant IMP should be assessed as:

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

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

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

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

The investigator may change his/her opinion of causality, in light of follow-up information, and update the causality assessment in the CRF.

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

10.3.4.4 Final outcome

The investigator will select the most appropriate outcome:

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

10.3.4.5 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, Hy's law). This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a participant dies during participation in the study or during a recognised follow-up period, the investigator should, upon request, provide Novo Nordisk with a copy of the autopsy report including histopathology.

In case an autopsy was not performed, the investigator should provide Novo Nordisk with a death certificate instead

New or updated information should be recorded in the CRF.

10.3.5 Reporting of SAEs

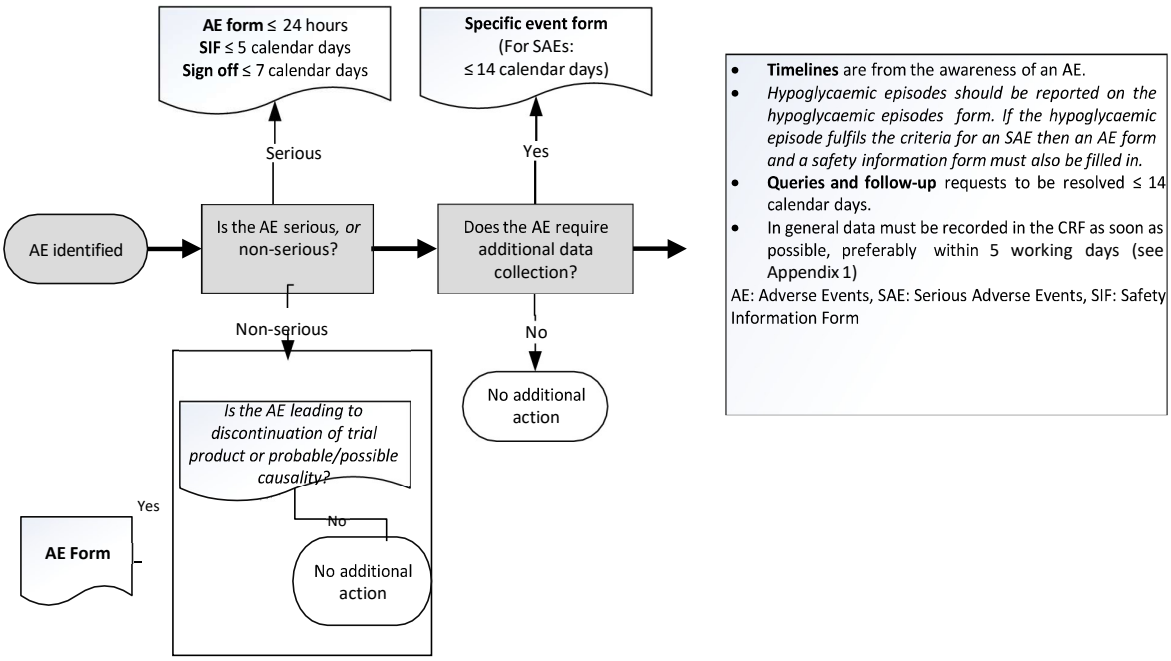
AE and SAE reporting via CRF

Relevant forms must be completed in the eCRF and paper forms.

The relevant CRF forms (AE and safety information forms) must be forwarded to Novo Nordisk or to the corresponding CRO in accordance with Section 10.1.5.

After the study is completed, the study database will be locked, and the CRF will be decommissioned to prevent the entry of new data or changes to existing data. If a site receives a report of a new SAE from a participant or receives updated information on a previously reported SAE after CRF decommission, the site can report this information on a paper AE and safety information form (see below).

Figure 2 Decision tree for determining the event type and the respective forms to complete with associated timelines



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

10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information

10.4.1 *Definitions*

Woman of childbearing potential (WOCBP)

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

Females in the following categories are not considered WOCBP

1. *Premenarcheal*
2. *Females with one or more of the following:*
   - *Documented total hysterectomy*
   - *Documented bilateral salpingectomy*
   - *Documented bilateral oophorectomy*

   For females with permanent infertility due to an alternate medical cause other than the above (e.g., Müllerian agenesis, androgen insensitivity), investigator discretion should be applied in determining study enrolment.
3. *Postmenopausal female:*
   - *A postmenopausal state is defined as amenorrhoea for at least 12 months without an alternative medical cause in a female > 45 years of age. Alternative medical causes for amenorrhoea include, but are not limited to, hormonal contraception or hormonal replacement therapy.*
   - *Females ≥ 60 years of age can be considered postmenopausal.*

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

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

10.4.2 *Contraceptive guidance*

Male participants

No contraception measures are needed for male participants.

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use methods of contraception consistently and correctly. Table 8 lists the highly effective methods of contraception allowed.

Highly effective contraception should be utilised for a least 30 days after last dose of IMP (corresponding to time during treatment and until the end of relevant systemic exposure).

Table 8 Highly effective contraceptive methods allowed[19]

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

NOTES a. Contraceptive use by men or women should comply with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

The following methods are not acceptable methods of contraception: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM).

10.4.3 Collection of pregnancy information

Female participants who become pregnant

Investigator will collect pregnancy information on any female participant who becomes pregnantwhile participating in this study.

Information will be recorded on the appropriate form and submitted to Novo Nordisk within 14calendar days of learning of a participant's pregnancy (see Table 7).

The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on participant and neonate which will be forwarded to Novo Nordiskwithin 14 calendar days. Generally, follow-up will not be required for longer than 1 month beyondthe delivery date.

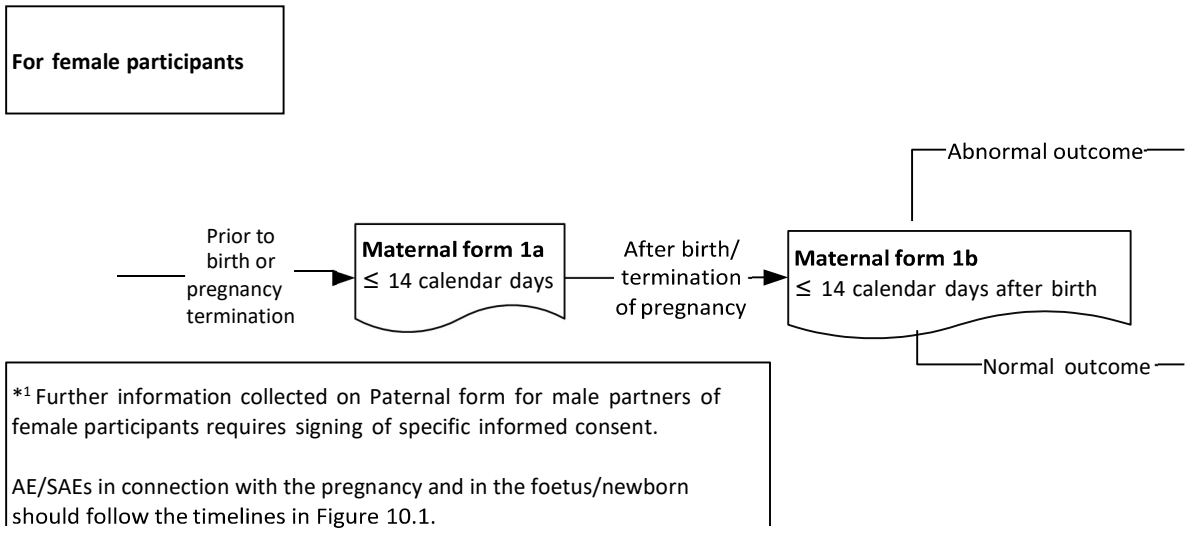
Any termination of pregnancy will be reported, regardless of foetal status (presence or absence ofanomalies) or indication for procedure.

While pregnancy itself is not considered to be an AE or SAE, any adverse event in connection with pregnancy or elective termination of a pregnancy for medical reasons will be reported as an AE orSAE. If relevant, consider adding 'gestational', 'pregnancy-related' or a similar term when reporting the AE/SAE.

Pregnancy outcome should be documented in the participant's medical record. Abnormal pregnancy outcome (e.g., spontaneous abortion, foetal death, stillbirth, congenital anomalies and ectopic pregnancy) is considered an SAE. In case of abnormal pregnancy outcome, paternal information should be recorded in the appropriate form after obtaining the necessary signed paternal informed consent.

If the investigator learns of an SAE occurring as a result of a post-study pregnancy which is considered related to the IMP by the investigator, the SAE should be reported to Novo Nordisk asdescribed in Appendix 3 (Section 10.3.)

Figure 3 Decision tree for determining the forms to complete for collection of pregnancyinformation and timelines for reporting – For female participants



Any female participant who becomes pregnant while participating in the study will discontinuestudy intervention.

Generally, follow-up will be 1 month following the delivery date.

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

10.5.1 Definition of technical complaint

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 study interventions (e.g., discoloration, particles, or contamination)
- Problems with packaging material including labelling
- Problems related to devices (e.g., to the injection mechanism, dose setting mechanism, push button or interface between the pen-injector and the needle)

Time period for detecting technical complaints

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

10.5.2 Recording and follow-up of technical complaints

Reporting of technical complaints to Novo Nordisk

Please refer to instruction page for technical complaint form.

Timelines for reporting technical complaints to Novo Nordisk

The investigator must complete the technical complaint form in the CRF within:

- 24 hours if related to an SAE

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 will collect the technical complaint sample and all associated parts available and notify the monitor within five calendar days of obtaining the sample at trial site. Novo Nordisk Chile affiliate will ensure that the sample is sent to Customer Complaint Center, Novo Nordisk A/S as soon as possible. A copy of the technical complaint form has to be sent with the sample for identification purpose.

If the technical complaint sample is unobtainable, the investigator has to specify on the technical complaint form why it was unobtainable.

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

10.6 Appendix 6: Hypoglycaemic episodes

Table 9 Classification of hypoglycaemia

Classification of hypoglycaemia		
Level	*Glycaemic criteria*	*Description*
Hypoglycaemia alert value (level 1)	*< 3.9 mmol/L (70 mg/dL) and ≥ 3.0 mmol/L (54 mg/dL)*	*Sufficiently low for treatment with fast-acting carbohydrate and dose adjustment of glucose-lowering therapy*
Clinically significant hypoglycaemia (level 2)	*< 3.0 mmol/L (54 mg/dL)*	*Sufficiently low to indicate serious, clinically important hypoglycaemia*
Severe hypoglycaemia (level 3)[1]	*No specific glucose threshold*	*[1]Hypoglycaemia associated with severe cognitive impairment requiring external assistance for recovery*
Notes: The Novo Nordisk terms are adapted from IHSG,[20] ADA,[21] type 1 diabetes outcomes program,[22] ATTD.[23] Severe hypoglycaemia as defined by Seaquist[24] .		

Severe hypoglycaemia

Severe hypoglycaemia is an event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.[24]

Nocturnal hypoglycaemia

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

Reporting of hypoglycaemic episodes

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

Reporting of hypoglycaemic episodes by BG meters:
Plasma glucose (PG) should always be recorded in the eCRF when a hypoglycaemic episode is suspected.

When a participant experiences a hypoglycaemic episode, the participant should record the

general information in relation to the hypoglycaemia (timing, PG measurements, symptoms, etc.) in the diary (paper notebook delivered to each participant for registers). The investigator should ensure correct reporting of the hypoglycaemic episode and report the hypoglycaemic episode to the CRF. In case a participant is not able to fill in the diary (e.g., in case of hospitalisation), the investigator should still report the hypoglycaemic episode on the hypoglycaemic episodes form.

Upon onset of a hypoglycaemic episode the participant is recommended to measure PG every 15 minutes until the PG value is ≥3.9 mmol/L (70 mg/dL) and/or symptoms have been resolved in accordance with current guidelines.[24]

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

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

Regarding the question: "To feel better, did you need help to get a sugary drink, food, or medicine?" the investigator must instruct the participants to answer "Yes", if the episode was an event that required assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. PG concentrations may not be available during an event, but neurological recovery following the return of PG to normal is considered sufficient evidence that the event was induced by a low PG concentration.[24]

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

Diary review

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

For low PG values for hypoglycaemic episodes with incomplete reporting information:
1. If a hypoglycaemic episode form in the diary is not completed by the participant within 7 calendar days of the PG measurement, the episode should be described in the source documents and reported by the investigator on a hypoglycaemic episode eCRF with as much information as possible. If the participant did not need help to get a sugary drink, food, or medicine, Novo Nordisk will only ask for start date due to recall bias.[25, 26]

Re-training of participants

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

10.7 Appendix 7: Hyperglycaemic episodes

Plasma glucose (PG) should always be measured and recorded when a hyperglycaemic episode is suspected.

A hyperglycaemic episode is defined as PG values >16.7 mmol/L (300 mg/dL).
All hyperglycaemic episodes should be reported according to instruction below. When a participant experiences a hyperglycaemic episode, participant/investigator should record the general information in relation to the hyperglycaemia (timing, PG measurements, symptoms, etc.). In case a participant is not able to fill in the diary (e.g., in case of hospitalisation or at the 'follow-up phone contact'), then investigator should report the hyperglycaemic episode in the CRF.

Repeated PG measurements occurring within a period of 24 hours after onset of a hyperglycaemic episode will per default be considered as one hyperglycaemic episode until a succeeding PG value is ≤16.7 mmol/L (300 mg/dL) and should be reported on one hyperglycaemic episode form. PG measurements >16.7 mmol/L (300 mg/dL) after the 24 hours period shall trigger reporting of a new hyperglycaemia episode. One AE form and safety information form can cover several hyperglycaemic episode forms if the participant has not recovered between the episodes.

In case of several high PG values within the 24 hours interval, the highest value for PG is the one that will be reported as the PG value for the hyperglycaemic episode; but the start time of the episode will remain as the time for the first high PG value.

The investigator must review the diary data for correct reporting of hyperglycaemic episodes. High PG values not having a hyperglycaemic episode form completed within 7 calendar days since the PG measurement should be reported on a hyperglycaemic episode form with as much information as possible. Novo Nordisk will not query for additional data, except for the date and PG value due to decreased validity of such data.[25, 26]

The participant must be re-trained in how to report hyperglycaemic episodes if the investigator identifies high PG and/or ketone values not reported as part of a hyperglycaemic episode.

10.8 Appendix 8: Mitigations to ensure participant safety and data integrity during an emergency situation

10.8.1 *Definition and scope of appendix*

A major emergency is defined as a situation that causes substantial restrictions to study site access for participants and/or sponsor representatives.

In case local restrictions due to a major emergency lead to lock-down of a site, the site must contact Novo Nordisk to allow for implementation of mitigations mentioned in this appendix based on mutual agreement.

According to local regulation, health authorities and independent ethics committees should be notified in case elements of the emergency appendix are activated.

Sites should always try to follow the assessments outlined in the original flowchart (Section 1.2) to the extent possible. Implementation of specific mitigations should be based on assessment of feasibility at the individual site.

Sites should comply with local regulations, requirements and/or guidelines if they are issued.

10.8.2 *Visits*

Screening (V0) should always be performed as on-site visits. If a site is unable to perform these visits on-site, screening of new participants at that site should be on hold until on-site visits are possible.

Visits 0,1,3,4 and 4A should be performed as on-site visits, if in any way possible.
If the end of intervention visit cannot be performed on-site, the visit window for the assessment can be extended for up to 3 months.

At each visit, the investigator must indicate in the CRF how the visit was performed and specify the reason for the preferred assessment method.

10.8.3 *Assessments*

Assessments used for safety or the confirmatory endpoints should be prioritised. The preferred method of assessment is on-site or phone depending on the visit.

Local laboratories or diagnostic facilities can be used for laboratory assesments at the investigator's discretion if on-site visits are not possible or in case of temporary lockdown of the central laboratory. Only findings meeting the definition for an AE (refer to Appendix 3 [Section 10.3]) should be reported in the CRF.

10.8.4 *Study intervention*

Alternative dispensing methods of study intervention may be implemented, and details will be communicated and documented. The dispensing options will be provided by Novo Nordisk A/S and will be based on options and requirements at country level and if permitted by local regulations.

10.9 Appendix 9: Detailed instructions for Adverse Events (AEs) and Technical complaints reporting

Serious adverse events (SAE)

All SAEs must be collected and reported from first administration of Ozempic® until follow-up visit/end of study visit, or whenever, within the mentioned time period the site becomes aware of the SAE.

Sites will fill "NN9535-4844 Adverse Event Form Final" within 24 hours (and any updated SAE data within 24 hours of it being available - on the AE or SIF) and send it to soclin@novonordisk.com (SOCLIN) – with cc io-balat-sas-safety@novonordisk.com (Affiliate Pharmacovigilance). Sent the paper form in an encrypted manner (via email using WinZip). The encryption password will be distributed to the sites.

Within 5 calendar days of the initial aware date of the event, complete "NN9535-4844 SIF - Safety Information Form Final" and send it to soclin@novonordisk.com (SOCLIN) – with cc io-balat-sas-safety@novonordisk.com (Affiliate Pharmacovigilance). Sent the paper form in an encrypted manner (via email using WinZip).

Both forms (AE form and SIF Form) must be signed within 7 calendar days after first knowledge by the investigator and send it to soclin@novonordisk.com (SOCLIN) – with cc io-balat-sas-safety@novonordisk.com (Affiliate Pharmacovigilance), encrypted using WinZip.

Enter the information of the paper form in the eCRF as soon as possible.

If the SAE fulfils the criteria of events which require additional data collection fill eCRF forms for Medication error/Misuse and Abuse or Hypoglycaemic episodes within 14 calendar days after first knowledge.

Non Serious adverse events

For all non serious adverse events in which it has been evaluated by the investigator that there is a probable or possible causality between the event and the Investigational medicinal product, fill "NN9535-4844 Adverse Event Form Final" and sent it within 5 calendar days after first knowledge, to io-balat-sas-safety@novonordisk.com (Affiliate Pharmacovigilance). Sent the paper form in an encrypted manner (via email using WinZip).

Enter the information of the paper form in the eCRF as soon as possible.

For all non serious adverse events in which it has been evaluated by the investigator that there is an unlikely causality between the event and the Investigational medicinal product complete Adverse event form directly in the eCRF.

If the non serious adverse event fulfils the criteria of events which require additional data collection fill eCRF forms for Medication error/Misuse and Abuse or Hypoglycaemic episodes within 14 calendar days after first knowledge.

[redacted] will send monthly reports of the non-serious adverse events coded to Novo Nordisk SafetySurveillance.

Pregnancy information (female participants who become pregnant):

Fill "NN9535-4844 Pregnancy Form Final" within 14 calendar days after first knowledge and sent it to soclin@novonordisk.com (SOCLIN) – with cc io-balat-sas-safety@novonordisk.com (Affiliate Pharmacovigilance). Sent the paper form in an encrypted manner (via email using WinZip).

Technical complaints

Technical complaints on Ozempic® which occur from the first time of usage until the last time of usage of the product and which is considered related to an SAE must be reported to Novo Nordisk specific technical complaint form (NN9535-4844 Technical Complaints Form Final)

Fill "NN9535-4844 Technical Complaints Form Final" and sent it to CCC-clinicaltrials@novonordisk.com with cc io-balat-sas-safety@novonordisk.com (Affiliate Pharmacovigilance) within 24 hours after first knowledge. Sent the paper form in an encrypted manner

(via email using WinZip).
Enter the information of the paper form in the eCRF as soon as possible.

Technical complaints on Ozempic® not related to an SAE, need to be reported to Novo Nordisk Affiliate via the spontaneous reporting system within 5 calendar days after first knowledge. Send a mail to io-balat-sas-safety@novonordisk.com (Affiliate Pharmacovigilance) with the description of the complaint, patient ID, product name and batch number.
Separate the complaint´s sample from the other products and identify it with the code that the Novo Nordisk affiliate will give.
Novo Nordisk affiliate will recollect and send complaints samples to Customer Complaint center.

Signatures

On behalf of Investigator´s Site	On behalf of NOVO NORDISK FARMACEUTICA LTDA.:
Date:	Date:
By: Title: Site:	By: Title:

10.10 Appendix 10: Abbreviations

ADA	*American Diabetes Association*
ADE	*adverse device effect*
AE	*adverse event*
AESI	*adverse event of special interest*
ALT	*alanine aminotransferase*
AST	*aspartate aminotransferase*
ATTD	*Advanced Technologies & Treatments for Diabetes*
BG	*blood glucose*
COA	*clinical outcome assessment*
CRF	*case report form*
CRO	*contract research organisation*
CSR	*clinical study report*
CTFG	*clinical trial facilitation group*
CVOT	*cardiovascular outcome trial*
DFU	*directions for use*
DMC	*Data Monitoring Committee*
DNA	*deoxyribonucleic acid*
DPS	*data points set*
DRE	*disease related event*
DUN	*dispensing unit number*
EAC	*Event Adjudication Committee*
EAS	*event adjudication system*
ECG	*electrocardiogram*
eCRF	*electronic case report form*
FAS	*full analysis set*
FDA	*U.S. Food and Drug Administration*

FDAAA	*FDA Amendments Act*
FPG	*fasting plasma glucose*
FSH	*follicle-stimulating hormone*
GCP	*Good Clinical Practice*
$HbA1_c$	*glycated haemoglobin*
HIV	*Human Immunodeficiency Virus*
HRT	*hormone replacement therapy*
IB	*investigator's brochure*
ICE	*intercurrent event*
ICH	*International Council for Harmonisation*
IEC	*independent ethics committee*
IHSG	*The International Hypoglycaemia Study Group*
IMP	*investigational medicinal product*
IND	*investigational new drug*
IRB	*institutional review board*
ISO	*International Organization for Harmonization*
ISPAD	*International Society for Pediatric and Adolescent Diabetes*
IWRS	*interactive web response system*
LAR	*legally acceptable representative*
LDL	*low-density lipoprotein*
MDR	*Medical Device Regulation*
NIMP	*non-investigational medicinal product*
PAS	*participant analysis set*
PCD	*primary completion date*
PG	*plasma glucose*
PRO	*patient reported outcome*
RNA	*ribonucleic acid*
SADE	*serious adverse device effect*
SAE	*serious adverse event*
SAP	*Statistical Analysis Plan*
SMPG	*self-measured plasma glucose*
SUSAR	*suspected unexpected serious adverse reaction*
TMM	*Trial Materials Manual*
USADE	*Unanticipated serious adverse device effect*
WOCBP	*woman of childbearing potential*

10.11 Appendix 11: Protocol amendment history

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

Protocol version X, including version(s) Y and Z: (date), global/country

This amendment is considered to be substantial/non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union, for non-substantial amendments, include: because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall rationale for preparing protocol version X

Section # and name	*Description of change*	*Brief rationale*

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