# Cover Page for Protocol

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|---|---|
| Sponsor name: | Novo Nordisk A/S |
| NCT number | NCT04189848 |
| Sponsor trial ID: | NN9535-4648 |
| Official title of study: | A Trial to Compare the Injection Site Pain Experience of Semaglutide 0.25 mg and Dulaglutide 0.75 mg Administered SC |
| Document date: | 06 Oct 2020 |

### 16.1.1 Clinical Study Protocol_22-Nov-2019

# List of contents



*Redacted protocol*
*Includes redaction of personal identifiable information only.*

# CLINICAL STUDY PROTOCOL

## A TRIAL TO COMPARE THE INJECTION SITE PAIN EXPERIENCE OF SEMAGLUTIDE 0.25 MG AND DULAGLUTIDE 0.75 MG ADMINISTERED SC

CONFIDENTIAL

**Sponsor code: NN9535-4648**
**PRA code:[redacted]**
**EudraCT number: 2019-83003844-57**
**Universal Trial Number: U1111-1241-0348**

Comparison of injection site pain experience for semaglutide and dulaglutide sc

| | |
|---|---|
| Investigational product: | Semaglutide and dulaglutide |
| Clinical phase: | Phase 4 trial |
| Indication to be studied: | Not applicable |
| Sponsor: | Novo Nordisk A/S<br>Novo Allé<br>DK-2880 Bagsvaerd<br>Denmark |
| Contract Research Organisation and Clinical Site: | [redacted] |
| Principal Investigator: | [redacted], MD<br>Phone:<br>Fax:<br>E-mail: |

**Version 2.0 – 22 Nov 2019**

**This trial will be performed in compliance with the principles of Good Clinical Practice.**

## SPONSOR AUTHORISATION OF CLINICAL STUDY PROTOCOL

The Sponsor and the Contract Research Organisation agree to conduct the trial as outlined in this clinical study protocol. Any modification of the clinical study protocol must be agreed upon by the Sponsor and the Contract Research Organisation and must be documented in writing.

Name/Position: Date: Signature:

Sponsor: Novo Nordisk A/S

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Sponsor's Contact

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Medical Specialist

# AUTHORISATION OF CLINICAL STUDY PROTOCOL BY CONTRACT RESEARCH ORGANISATION

The Sponsor and the Contract Research Organisation agree to conduct the trial as outlined in this clinical study protocol. Any modification of the clinical study protocol must be agreed upon by the Sponsor and the Contract Research Organisation and must be documented in writing.

Name/Position: Date: Signature:

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**Study Monitor**

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# SYNOPSIS

**Trial Title**
A TRIAL TO COMPARE THE INJECTION SITE PAIN EXPERIENCE OF SEMAGLUTIDE 0.25 MG AND DULAGLUTIDE 0.75 MG ADMINISTERED SC

**Short Trial Title**
Comparison of injection site pain experience for semaglutide and dulaglutide sc

**Trial Codes**
Sponsor code : NN9535-4648
PRA code : [redacted]
EudraCT number : 2019-83003844-57
Universal Trial Number : U1111-1241-0348

**Sponsor**
Novo Nordisk A/S, Novo Allé, DK-2880 Bagsvaerd, Denmark
Sponsor's contact : [redacted], Trial Start-up Manager

**Contract Research Organisation and Clinical Site**
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**Principal Investigator**
[redacted], MD

**Clinical Phase** 4

**Objectives**
The primary objective is to compare, in healthy subjects with overweight or obesity, the injection site pain experience of a single dose of semaglutide 0.25 mg sc using the semaglutide product compared to a single dose of dulaglutide 0.75 mg sc using the dulaglutide product.

**Endpoints**
Primary Endpoint

| Endpoint title | Time frame | Unit |
|---|---|---|
| Intensity of injection site pain | 1 min after each injection (Day 1) | mm on a 100 mm horizontal visual-analogue scale (where 0 mm = no pain, 100 mm = unbearable pain) |

Exploratory Endpoints

| Endpoint title | Time frame | Unit |
|---|---|---|
| Categorical assessment of intensity of injection site pain | Immediately after rating of intensity of injection site pain, i.e. after 1 min plus the time it takes to complete the rating of intensity of injection site pain by visual-analogue scale (Day 1) | 6-point scale (none – very mild – mild – moderate – severe – very severe) |

| Endpoint title | Time frame | Unit |
|---|---|---|
| Moderate or more injection site pain | Dichotomous variable based on *categorical assessment of intensity of injection site pain* (item above) | Yes = moderate, severe, very severe<br>No = none, very mild, mild |
| Quality of pain | Immediately after *categorical assessment of intensity of injection site pain*, i.e. after 1 min plus the time it takes to complete the rating of *intensity of injection site pain* and the *categorical rating of intensity of injection site pain* (Day 1) | Pain quality items on modified SF-MPQ-2 inventory (select all that apply):<br>Throbbing pain ☐<br>Shooting pain ☐<br>Stabbing pain ☐<br>Sharp pain ☐<br>Cramping pain ☐<br>Gnawing pain ☐<br>Hot-burning pain ☐<br>Aching pain ☐<br>Heavy pain☐<br>Tender ☐<br>Splitting pain ☐<br>Tiring-exhausting ☐<br>Sickening ☐<br>Fearful ☐<br>Punishing-cruel ☐<br>Electric-shock pain ☐<br>Cold-freezing pain ☐<br>Piercing ☐ |
| Duration of pain | From time of injection until cessation of pain (Day 1) | min and s |
| Comparative pain experience: | After pain has ended after the last injection (Day 1) | 5-point scale (the last injection hurt much more than the first injection – the last injection hurt more than the first injection – about the same (includes: none of the injections hurt) – the last injection hurt less than the first injection - the last injection hurt much less than the first injection) |
| The semaglutide product hurt less than or about the same as the dulaglutide product | Dichotomous variable based on "*Comparative pain experience*" variable above | Yes = "about the same (includes none of the products hurt)" or "the semaglutide product hurt less than the dulaglutide product" or "the semaglutide product hurt much less than the dulaglutide product"<br>No = "the semaglutide product hurt much more than the dulaglutide product" or "the semaglutide product hurt more than the dulaglutide product" |

**Design and Treatments**

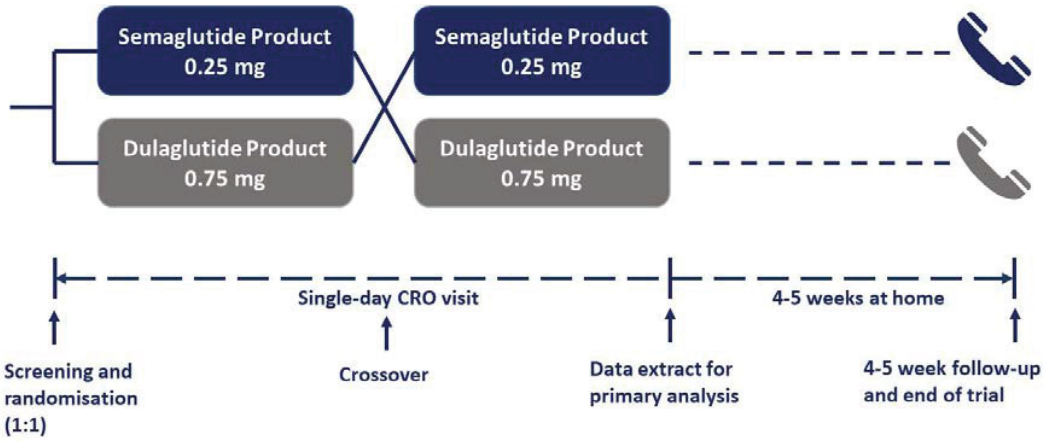
This is a single centre, crossover, randomised, double-blind trial in healthy, overweight or obese, men and women comparing the injection site pain experience of the semaglutide product to the dulaglutide product. Enrolment will be carried out to include no more than 70% of each gender. Subjects will receive 1 dose of semaglutide 0.25 mg and 1 dose of dulaglutide 0.75 mg on the same day. The 2 products will be administered at least 30 minutes apart, in the anterior aspect of the abdominal wall on opposite sides of the midline.

Subjects will be randomised in a 2×2 scheme evenly to 4 sequences of product and injection side as described in the table below:

| Treatment Short Identifier | Treatment Long Identifier | Ratio Required |
|---|---|---|
| **First injection on right side, Second injection on left side** | | |
| A | Semaglutide product (Right) followed by Dulaglutide product (Left) | 1 |
| C | Dulaglutide product (Right) followed by Semaglutide product (Left) | 1 |
| **First injection on left side, Second injection on right side** | | |
| B | Semaglutide product (Left) followed by Dulaglutide product (Right) | 1 |
| D | Dulaglutide product (Left) followed by Semaglutide product (Right) | 1 |

The present trial compares the injection site pain experience after a single use of each product, both given on the same day. To minimise gastrointestinal adverse events inherent to glucagon-like petide-1 (GLP-1) receptor agonist (RA)s the lowest marketed dose of each drug will be used, i.e. semaglutide 0.25 mg and dulaglutide 0.75 mg. Based on pharmacokinetic modelling[1], the single dose of dulaglutide 0.75 mg given on the same day as semaglutide 0.25 mg sc is expected to provide a similar effect to semaglutide 0.5 mg, which is the highest single dose of emaglutide tolerated without dose excatlation due to risk of GI AEs. Also, as per its summary of product characteristics, dulaglutide may be initiated at the 1.5 mg dose.

The length of the crossover interval is set to be as short as possible to minimise the impact of systemic effects of both semaglutide and dulaglutide, especially nausea, between the first and the last injection, while being long enough to minimise residual pain and emotional carry-over from the first injection. See figure below for an overview of the trial design.




CRO=contract research organisation

**Trial Schedule**

Screening : Between Day -21 and Day -1
Confinement period : One day in the clinic: Day 1
Follow-up : A follow-up phone call will take place between 4 and 5 weeks after drug administration on Day 1

**Subjects**
A total of 104 subjects are planned to be randomised to achieve at least 100 completed subjects. The aim is to have an even distribution of male and female subjects in the trial; at least 30% of the same sex should be randomised in the trial.

**Key Inclusion Criteria**
- Male or female, aged 18-75 years (both inclusive) at the time of signing informed consent.
- Body mass index ≥25.0 kg/$m^2$.
- Considered to be generally healthy based on the medical history, physical examination, and the results of vital signs, electrocardiogram and clinical laboratory tests performed during the screening visit, as judged by the Investigator.

**Key Exclusion Criteria**
- Female who is pregnant, breast-feeding or intends to become pregnant within 4 weeks of Day 1 or is of childbearing potential and not using highly effective contraceptive methods.
- Any disorder which in the Investigator's opinion might jeopardise subject's safety, evaluation of results, or compliance with the protocol.
- Glycosylated haemoglobin (HbA1c) ≥ 6.5 % (48 mmol/mol) at screening.
- Use of prescription medicinal products or non-prescription drugs or herbal products, except routine vitamins, topical medication, contraceptives and occasional use of paracetamol (not allowed within 24 hours prior to drug administration), within 14 days prior to Day 1.
- Average intake of more than 21 units of alcohol per week for male subjects and more than 14 units per week for female subjects: 1 unit of alcohol equals approximately 250 mL of beer, 100 mL of wine, or 35 mL of spirits).
- Positive drug and alcohol screen (opiates, methadone, cocaine, amphetamines [including ecstasy], cannabinoids, barbiturates, benzodiazepines, tricyclic antidepressants, and alcohol) at screening and admission to the clinical research centre.
- Use of tobacco and nicotine products, defined as any of the below:
    - Smoking more than 1 cigarette or the equivalent per day on average.
    - Not able or willing to refrain from smoking and use of nicotine substitute products during the in-house period.
- Subject is not able to understand and read English or Dutch, or subject is not able to understand and comply with the trial requirements.

**Trial Drug**

| Name | Name of Intervention Product |
|---|---|
| Semaglutide 1.34 mg/mL PDS290 pre-filled pen-injector | Semaglutide product |
| Trulicity 0.75 mg solution for injection in pre-filled pen (dulaglutide) | Dulaglutide product |

**Variables**

Safety : Intensity of injection site pain on a visual-analogue scale (VAS), categorical assessment of injection site pain intensity (6-point scale), quality of pain modified short-form McGill Pain Questionnaire 2 (SF-MPQ-2) inventory, duration of pain assessment, comparative pain assessment (5-point scale), adverse events, clinical laboratory (if postdose assessments are deemed relevant by the Investigator), physical examination (if postdose assessments are deemed relevant by the Investigator), 12-lead ECG (if postdose assessments are deemed relevant by the Investigator), and vital signs

**Statistical Methods**

Sample size calculation : The sample size calculation considers both the primary endpoint and the dichotomous endpoints. Considering precision on the proportion of the dichotomous endpoints, a sample size of 100 subjects results in a confidence interval (CI) with a width of 10% on each side, eg, for a proportion of 60%, the CI is 60% (50%-70%).

A standard deviation (SD) of within-pair differences in VAS pain score between 2 SC injections was obtained from Novo Nordisk clinical trial INS-4011. The within-subject variance (adjusting for the effects of speed, volume, and injection region) was estimated to 348, corresponding to an SD of the within-pair difference of $\sqrt{(2 \cdot 348)} = 26$ mm. A prospective study of acute pain found that the minimum clinically important difference (MCID) for worsening of pain, ie, the difference on a VAS associated with the selection of "a little more pain" rather than "about the same", had a mean value of 10 mm.[5]

With 100 subjects, a conservative SD of 30 mm, and 90% power, it is possible to detect a difference smaller than 10 mm. Hence a sample size of 100 subjects is considered sufficient to detect a clinically important difference. Allowing for 4% dropouts or missing data, a total of 104 subjects will need to be randomised.

Analysis of endpoints : The primary endpoint will be analysed by a fixed analysis of variance model with VAS score as the dependent variable, and product, injection side (right side, left side), injection number (first injection, second injection), and subject as fixed effects. From the model, the difference in VAS score between the 2 products will be estimated and presented with a 95% confidence interval (CI) and a p-value. The interpretation of the difference in VAS pain scores will be supported and contextualised by the results of the analyses of the exploratory endpoints. Descriptive statistics only will be applied for other safety parameters and secondary endpoints.

**Table 1 Schedule of Assessments**

| Visit | Screening | Pretreatment | Treatment | Follow-up Phone Call |
|---|---|---|---|---|
| **Trial Day** | **Days -21 to -1** | **Day 1** | | **Day 29 to Day 36** |
| | | **Predose** | **Dosing and After** | |
| Ambulatory | X | X | X | X |
| Admission | | X | | |
| Discharge | | | X | |
| Informed Consent | X | | | |
| Medical History | X | | | |
| Previous Injection Experience[a] | X | | | |
| Demographics | X | | | |
| Hand out of subject ID card | | X | | |
| Physical Examination | X | | X[b] | |
| Body Height, Body Weight, and BMI Calculation | X | | | |
| Serology (HBsAg, anti-HCV, anti-HIV-1 and -2) | X | | | |
| Urine Drug and Alcohol Screen | X | X | | |
| Urine Pregnancy Test (Females of Childbearing Potential Only) | X | X | | X[c] |
| Clinical Laboratory[d] | X | | X[d] | |
| HbA1c | X | | | |
| 12-lead ECG[e] | X | | X[e] | |
| Vital Signs[f] | X | | X | |
| Eligibility Check | X | X[g] | | |
| Randomisation and Stratification[h] | | X | | |
| Trial Drug Administration[h] | | | X | |
| Intensity of Injection Site Pain VAS[i] | | | X | |
| Categorical Assessment of Injection Site Pain Intensity[j] | | | X | |
| Quality of Pain Modified SF-MPQ-2 Inventory[k] | | | X | |
| Duration of Pain[l] | | | X | |
| Comparative Pain Assessment[m] | | | X | |
| Previous and Concomitant Medication | X | X | X | X |
| AE Monitoring | X | X | X | X |
| Technical Complaints[n] | | X | X | |
| Drug Accountability | | | X | |

AE=adverse event; BMI=body mass index; ECG=electrocardiogram; HbA1c=glycosylated haemoglobin; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus; SF-MPQ-2=short-form McGill Pain Questionnaire 2; VAS=visual-analogue scale

[a] Previous injection experience as recalled by the subject to the best of their ability: product used (name, dose, type [vial/syringe, pre-filled syringe, autoinjector, other], indication, frequency of use, injection site pain, chronological period used).

[b] Physical examination: this will be a focused examination only done if deemed relevant by the Investigator.

[c] For the check on pregnancy at the follow-up phone call, female subjects of childbearing potential will be handed out a urine pregnancy test on Day 1. They will have to do the pregnancy test at the earliest in the morning of Day 29 and at the latest in the morning of the follow-up phone call.

[d] Clinical laboratory tests (including clinical chemistry and haematology): at screening (non-fasting).
The same tests may be done after the second trial drug administration on Day 1 prior to discharge, if deemed relevant by the Investigator.

[e] 12-lead ECG: at screening.
12-lead ECG may be done after the second trial drug administration on Day 1 prior to discharge, if deemed relevant by the Investigator.

[f] Vital signs (supine systolic and diastolic blood pressure, and pulse): at screening and after the second trial drug administration on Day 1 prior to discharge.

[g] Eligibility check on Day 1 before dosing concerns the urine pregnancy test (female subjects of childbearing potential only), urine drug and alcohol screen, and concomitant medication only.

[h] Subjects will be randomised in a 2×2 scheme evenly to 4 sequences of product and injection side as in the table below:

| Treatment Short Identifier | Treatment Long Identifier | Ratio Required |
|---|---|---|
| **First injection on right side, Second injection on left side** | | |
| A | Semaglutide product (Right) followed by Dulaglutide product (Left) | 1 |
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| D | Dulaglutide product (Left) followed by Semaglutide product (Right) | 1 |

Subjects will receive 1 single dose of semaglutide 0.25 mg and 1 single dose of dulaglutide 0.75 mg on the same day. The 2 products will be administered at least 30 minutes apart, in the anterior aspect of the abdominal wall on opposite sides of the midline.

[i] One minute after each injection, the VAS to rate the intensity of injection site pain will be administered.

[j] The categorical assessment of injection site pain intensity (6-point scale) will be started after the VAS to rate the intensity of injection site pain has been completed after each injection.

[k] The quality of pain modified SF-MPQ-2 inventory will be started after the categorical assessment of injection site pain intensity (6-point scale) has been completed after each injection.

[l] Subjects have to indicate after each injection when the pain, if any, is gone.

[m] The comparative pain assessment (5-point scale) comparing pain between the 2 injections will be completed after the last injection.

[n] All technical complaints that occur, from the time of receipt of the product at the site until the time of the last usage of the product, must be collected and reported to Novo Nordisk.

# TABLE OF CONTENTS

## TABLE OF TABLES

## TABLE OF FIGURES

# LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | adverse event |
| ALAT (ALT) | alanine aminotransferase |
| ASAT (AST) | aspartate aminotransferase |
| ASCVD | arteriosclerotic cardiovascular disease |
| BMI | body mass index |
| CA | Competent Authority |
| CI | confidence interval |
| CHMP | Committee for Medicinal Products for Human Use (formerly: Committee for Proprietary Medicinal Products [CPMP]) |
| CRF | case report form |
| CSP | clinical study protocol |
| CSR | clinical study report |
| CTD | Clinical Trial Directive |
| DUN | dispensing unit number |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| GCP | Good Clinical Practice |
| GDPR | General Data Protection Regulation |
| GI | gastrointestinal |
| GLP | glucagon-like peptide |
| HbA1c | glycosylated haemoglobin |
| HBsAg | Hepatitis B surface antigen |
| HCV | hepatitis C virus |
| IB | investigator's brochure |
| ICF | informed consent form |
| ICH | International Council for Harmonisation (formerly: International Conference on Harmonisation) |
| IEC | Independent Ethics Committee |
| LSFT | last subject first treatment |
| MCID | minimum clinically important difference |
| PCD | primary completion date |
| PK | pharmacokinetic(s) |
| [redacted] | |
| RA | receptor agonist |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| sc | subcutaneous |
| SD | standard deviation |
| SF-MPQ-2 | Short-form McGill Pain Questionnaire 2 |
| SmPC | summary of product characteristics |
| SOP | standard operating procedure |
| T2DM | type 2 diabetes mellitus |
| TEAE | treatment-emergent adverse event |
| TMM | trial materials manual |
| ULN | upper limit of normal |
| VAS | visual-analogue scale |
| WMA | World Medical Association |
| WMO | Wet medisch-wetenschappelijk onderzoek met mensen (Medical Research Involving Human Subjects Act) |

# 1. INTRODUCTION

## 1.1 Background

Type 2 diabetes mellitus (T2DM) is a debilitating, chronic disease associated with increased morbidity and mortality. According to current treatment guidelines, first-line treatment consists of lifestyle management and metformin. If further glycaemic control is needed, for patients with established arteriosclerotic cardiovascular disease (ASCVD), and for patients with no ASCVD for whom there is a need to minimise hypoglycaemia, and/or compelling need to minimise weight gain or promote weight loss, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are recommended as second in line treatment. Unfortunately, despite their demonstrated clinical efficacy, a barrier to the adoption of injectables may exist, among other factors, in the form of fear of injection site pain.

The purpose of the current trial is to compare the injection site pain experience of 2 subcutaneous GLP-1 RAs for once-weekly administration, approved and widely used, for the treatment of T2DM in major markets: semaglutide (Ozempic®) and dulaglutide (Trulicity®).

Both semaglutide and dulaglutide are marketed in a pen-injector. Whereas the dulaglutide pen-injector for single use has an integrated needle, a needle must be attached to the semaglutide pen-injector for multiple use before each injection. The semaglutide pen-injector will be used with the NovoFine Plus® 4 mm x 32 G needle with which it is normally co-packed; together, they will be referred to as the semaglutide product. The pre-filled dulaglutide pen-injector will be referred to as the dulaglutide product.

The present trial compares the injection site pain experience after single use of each product, both given on the same day. Due to the risk of gastrointestinal adverse events such as nausea and vomiting inherent to GLP-1 RAs, the lowest marketed dose of each drug will be used, i.e semaglutide 0.25 mg and dulaglutide 0.75 mg.

Detailed information about semaglutide sc and the 1.5 ml PDS290 pre-filled pen is available in the investigator's brochure (IB)[2]. Detailed information about dulaglutide sc, and the dulaglutide pre-filled pen is available in the summary of product characteristics (SmPC)[3].

## 1.2 Risk-Benefit Assessment and Risk Mitigation

### 1.2.1 Anticipated Clinical Benefits

The subjects will not benefit from the treatment because there are no know benefits to receiving a single dose of semaglutide and a single dose of dulaglutide, regardless of health status.

### 1.2.2 Risks Related to Semaglutide

Subjects enrolled in the present trial do not have T2DM and are only exposed to a single dose of semaglutide and thus, may not have the same risks as the patients included in the clinical development programme. Detailed information about the semaglutide risks, precautions and mitigation actions for patients with T2DM are described in the correct edition of the IB[2] or any updates hereof. The known side effects (adverse drugreactions) associated with semaglutide are mainly gastrointestinal (nausea, diarrhoea, vomiting, abdominal pain, abdominal distension, constipation, dyspepsia, gastritis, gasto-oesophageal reflux disease, eructation, flatulence), but also include cholelithiasis, decreased appetite, dizziness, dysgeusia, fatigue, increased heart rate, increased lipase and amylase, injection site reactions and weight decrease, diabetic retinopathy complications, hypoglycaemia and anaphylactic reactions.

#### 1.2.2.1 Description of selected side effects

***Gastrointestinal disorders***

Consistent with other GLP-1 RAs, the most frequentadverse reactions with semaglutide are gastrointestinal (GI, nausea, diarrhoea, vomiting). In general, these reactions are mild or moderate in severity, of short duration and dose dependent. Clinical trials have shown that a low starting dose and gradual dose escalation mitigates the risk of developing gastrointestinal symptoms.

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

***Hypoglycaemia***

There is a low risk of hypoglycaemic episodes when semaglutide is used as monotherapy.

#### 1.2.2.2 Potential risks

For the risks below there is some basis for suspicion of an association to semaglutide but the association has not been confirmed.

***Allergic reactions***

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

***Acute pancreatitis***

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

As a precaution, subjects with a history of chronic pancreatitis or recent acute pancreatitis will not be enrolled in the trial.

***Pancreatic cancer***

Pancreatic cancer has been classified as a potential class risk for all marketed GLP-1 RAs by regulatory agencies. However, in the clinical development programme, rates of pancreatic cancer were low and do not support a causal association with semaglutide, and no safety concerns related to the pancreas were identified in the nonclinical programme.

***Medullary thyroid cancer***

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

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

#### 1.2.2.3 Other safety considerations

***Drug interactions***

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

***Pregnancy, lactation and fertility***

Studies in animals have shown reproductive toxicity. There are limited data from the use of semaglutide in pregnant women. Therefore, semaglutide should not be used during pregnancy. If a patient wishes to become pregnant, or pregnancy occurs, semaglutide should be discontinued immediately. In lactating rats, semaglutide was excreted in milk. As a risk to a breast-fed child cannot be excluded, semaglutide should not be used during breast-feeding.

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

### 1.2.3 Risks Related to Dulaglutide

Dulaglutide belongs to the same class of drugs as semaglutide and as such they share many of the same efficacy and safety characteristics. As dulaglutide is a marketed drug its characteristics are described in the EU SmPC[3].

### 1.2.4 Risks Associated with Participation in the Clinical Trial

In the current trial, risks related with venous blood sampling are minimal as no pharmacokinetic (PK) samples will be collected; only a few blood samples will be taken for clinical laboratory evaluations.

### 1.2.5 Possible Interactions with Concomitant Medical Treatments

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

### 1.2.6 Risk Mitigation

All subjects in this trial will have a thorough medical check before entering the trial. During the trial, they will be followed closely and carefully by qualified medical staff. This will mitigate the known and potential risks.

### 1.2.7 Risk-Benefit Rationale

The healthy subjects enrolled in the trial will not have immediate health benefits from participating in this trial. Data from this trial might, however, benefit future treatment of subjects with T2DM based on knowledge about the injection experience. The safety profiles of semaglutide and dulaglutide are well documented; AEs were mostly predictable based on the known effects of GLP-1 RAs. Thus, based on the large nonclinical and clinical studies with semaglutide (1.34 mg/mL) and dulaglutide (1.5 mg/mL and 3 mg/mL) and on the usablility evaluation of both dose devices, it is concluded that there are no safety issues that would prohibit administration of semaglutide and dulaglutide in accordance with the planned clinical trial.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of semaglutide and dulaglutide sc, the 1.5 mL PDS290 pre-filled pen, and the dulaglutide pre-filled pen are available in the IB[2] and the SmPC[3].

## 1.3 Trial Rationale

The purpose of the current trial is to compare the injection site pain experience of 2 subcutaneous GLP-1 RAs for once-weekly administration, approved and widely used, for the treatment of T2DM in major markets: semaglutide (Ozempic®) and dulaglutide (Trulicity®).

# 2. OBJECTIVES

The primary objective is to compare, in healthy, overweight or obese subjects, the injection site pain experience of a single dose of semaglutide 0.25 mg sc using the semaglutide product compared to a single dose of dulaglutide 0.75 mg sc using the dulaglutide product.

# 3. ENDPOINTS

**Table 2 Primary Endpoint**

| Endpoint title | Time frame | Unit |
|---|---|---|
| Intensity of injection site pain | 1 min after each injection (Day 1) | mm on a 100 mm horizontal visual-analogue scale (where 0 mm = no pain, 100 mm = unbearable pain) |

**Table 3 Exploratory Endpoints**

| Endpoint title | Time frame | Unit |
|---|---|---|
| Categorical assessment of intensity of injection site pain | Immediately after rating of intensity of injection site pain, i.e. after 1 min plus the time it takes to complete the rating of intensity of injection site pain by visual-analogue scale (Day 1) | 6-point scale (none – very mild – mild – moderate – severe – very severe) |
| Moderate or more injection site pain | Dichotomous variable based on *categorical assessment of intensity of injection site pain* (item above) | Yes = moderate, severe, very severe<br>No = none, very mild, mild |
| Quality of pain | Immediately after *categorical assessment of intensity of injection site pain*, i.e. after 1 min plus the time it takes to complete the rating of *intensity of injection site pain* and the *categorical rating of intensity of injection site pain* (Day 1) | Pain quality items on modified SF-MPQ-2 inventory (select all that apply):<br>Throbbing pain ☐<br>Shooting pain ☐<br>Stabbing pain ☐<br>Sharp pain ☐<br>Cramping pain ☐<br>Gnawing pain ☐<br>Hot-burning pain ☐<br>Aching pain ☐<br>Heavy pain☐<br>Tender ☐<br>Splitting pain ☐<br>Tiring-exhausting ☐<br>Sickening ☐<br>Fearful ☐<br>Punishing-cruel ☐<br>Electric-shock pain ☐<br>Cold-freezing pain ☐<br>Piercing ☐ |

| Endpoint title | Time frame | Unit |
|---|---|---|
| Duration of pain | From time of injection until cessation of pain (Day 1) | min and s |
| Comparative pain experience: | After pain has ended after the last injection (Day 1) | 5-point scale (the last injection hurt much more than the first injection – the last injection hurt more than the first injection – about the same (includes: none of the injections hurt) – the last injection hurt less than the first injection - the last injection hurt much less than the first injection) |
| The semaglutide product hurt less than or about the same as the dulaglutide product | Dichotomous variable based on "*Comparative pain experience*" variable above | Yes = "about the same (includes none of the products hurt)" or "the semaglutide product hurt less than the dulaglutide product" or "the semaglutide product hurt much less than the dulaglutide product"<br>No = "the semaglutide product hurt much more than the dulaglutide product" or "the semaglutide product hurt more than the dulaglutide product" |

# 4. INVESTIGATIONAL PLAN

## 4.1 Overall Trial Design and Plan

### 4.1.1 Type of Trial

This is a single centre, crossover, randomised, double-blind trial in healthy, overweight or obese, men and women comparing the injection site pain experience of the semaglutide product to the dulaglutide product. Enrolment will be carried out to include no more than 70% of each gender. Subjects will receive 1 dose of semaglutide 0.25 mg and 1 dose of dulaglutide 0.75 mg on the same day. The 2 products will be administered at least 30 minutes apart, in the anterior aspect of the abdominal wall on opposite sides of the midline.

Subjects will be randomised in a 2×2 scheme evenly to 4 sequences of product and injection side as described in Table 4:

**Table 4 Product and Side of Injection on Abdomen per Treatment**

| Treatment Short Identifier | Treatment Long Identifier | Ratio Required |
|---|---|---|
| First injection on right side, Second injection on left side | | |
| A | Semaglutide product (Right) followed by Dulaglutide product (Left) | 1 |
| C | Dulaglutide product (Right) followed by Semaglutide product (Left) | 1 |
| First injection on left side, Second injection on right side | | |
| B | Semaglutide product (Left) followed by Dulaglutide product (Right) | 1 |
| D | Dulaglutide product (Left) followed by Semaglutide product (Right) | 1 |

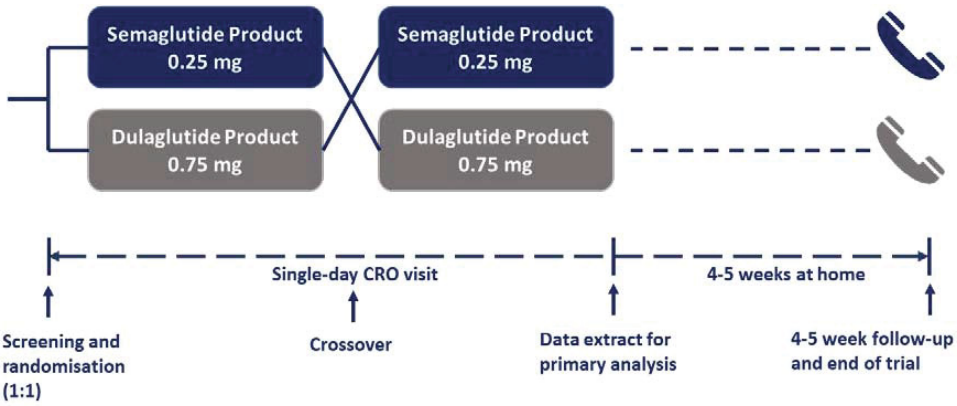
The present trial compares the injection site pain experience after a single use of each product, both given on the same day. To minimise GI AEs inherent to GLP-1 RAs the lowest marketed dose of each drug will be used i.e. semaglutide 0.25 mg and dulaglutide 0.75 mg. Based on pharmacokinetic modelling[1], the single dose dulaglutide 0.75 mg given on the same day as semaglutide 0.25 mg sc is expected to provide a similar effect to semaglutide 0.5 mg, which is the highest single dose of semaglutide tolerated without dose excalation due to risk of GI AEs. Also, as per its SmPC, dulaglutide may be initiated at the 1.5 mg dose.

The length of the crossover interval is set to be as short as possible to minimise the impact of systemic effects of both semaglutide and dulaglutide, especially nausea, between the first and the last injection, while being long enough to minimise residual pain and emotional carry-over from the first injection.

An overview of the trial design is given in Figure 1.

The follow-up period is 4-5 weeks (28 days with a +7 days window).

**Figure 1 Overview of the Trial Design**




CRO=contract research organisation

### 4.1.2 Screening Period

Subjects will report to the medical screening facility for the eligibility screening (see Section 4.3 for inclusion and exclusion criteria) within 3 weeks prior to drug administration.

Subjects will sign the trial-specific informed consent form (ICF) prior to any trial-specific screening procedures being performed. The written informed consent will be obtained for all subjects, regardless of their eligibility for the trial; the signed ICFs will be retained and archived at [redacted] and a copy will be provided to the subject.

Eligibility screening will consist of the assessments as presented in the schedule of assessments (Table 1).

### 4.1.3 Treatment Period

Subjects will be in the clinical research centre for 1 day, on Day 1. On this day, the subjects will be admitted, the drug will be administered twice, and the subjects will be discharged after all assessments have been performed. During this day subjects will be provided with a card stating that they are participating in a trial and given contact details of relevant trial site staff.

If the subject admits to bodily pain (eg, headache) at admission (Day 1), then Day 1 should be rescheduled within the visit window as the existing pain could impact the injection site pain assessment.

Assessments during the treatment period will be performed as presented in the schedule of assessments (Table 1).

#### 4.1.4 Follow-up

A follow-up phone call will take place between 4 and 5 weeks after drug administration on Day 1. In this phone call, the females of childbearing potential will be asked if they are pregnant.

## 4.2 Discussion of Trial Design

A total of 104 subjects are planned to be randomised to achieve at least 100 completed subjects. The aim is to have an even distribution of males and females in the trial; at least 30% of the same sex should be randomised in the trial.

Subjects with a body mass index (BMI) ≥25.0 kg/m$^2$ but generally healthy will be included to minimise inter-subject variability due to frequent comorbidities in the target users of semaglutide and dulaglutide (T2DM). It is assumed that the ability to detect differences between the 2 products does not differ between healthy subjects and target users. Only subjects with a BMI ≥ 25 kg/m$^2$ will be included to reduce the risk of intramuscular injection. Both male and female subjects will be included to ensure generalizability to the intended users of both genders. Only individuals 18 years of age or older are eligible because semaglutide sc and dulaglutide sc are only approved for use in adults with T2DM. The upper age limit of 75 years is justified by the cognitive demands of the subjects when completing the inventories used in this trial.

The length of the cross-over interval is set to be as short as possible to minimise systemic effects of semaglutide and dulaglutide, especially nausea, between the first and the last injection, while being long enough to minimise residual pain and emotional carry-over from the first injection.

## 4.3 Selection of Trial Population

#### 4.3.1 Inclusion Criteria

Note: Restrictions that apply to the period after admission are described in Section 4.4.8, except when they concern a statement of willingness.

The following inclusion criteria must be met for a subject to be eligible for inclusion in the trial:

1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial.
2. Male or female, aged 18-75 years (both inclusive) at the time of signing informed consent.
3. Body mass index ≥25.0 kg/m$^2$.
4. Considered to be generally healthy based on the medical history, physical examination, and the results of vital signs, electrocardiogram and clinical laboratory tests performed during the screening visit, as judged by the Investigator.

### 4.3.2 Exclusion Criteria

Note: Restrictions that apply to the period after admission are described in Section 4.4.8, except when they concern a statement of willingness.

A subject who meets any of the following exclusion criteria will not be eligible for inclusion in the trial:

1. Known or suspected hypersensitivity to trial product(s) or related products.
2. Previous participation in trial INS-4603, INS-4582 or NN9535-4648. Participation is defined as having received investigational product.
3. Female who is pregnant, breast-feeding or intends to become pregnant within 4 weeks of Day 1 or is of childbearing potential and not using highly effective contraceptive methods.
4. Participation in a drug study within 60 days prior to drug administration in the current trial OR participation in more than 4 other drug studies in the 12 months prior to drug administration in the current trial.
5. Any disorder which in the Investigator's opinion might jeopardise subject's safety, evaluation of results, or compliance with the protocol.
6. Glycosylated haemoglobin (HbA1c) ≥ 6.5 % (48 mmol/mol) at screening.
7. Supine blood pressure at screening (after resting for ≥ 5 min) outside the range of 90-160 mmHg for systolic or 45-89 mmHg for diastolic.
8. Supine pulse rate (as part of vital signs) outside the range of 40−100 beats/min after resting for ≥ 5 minutes at screening.
9. Use of prescription medicinal products or non-prescription drugs or herbal products, except routine vitamins, topical medication, contraceptives (see Section 4.4.8) and occasional use of paracetamol (not allowed within 24 hours prior to drug administration), within 14 days prior to Day 1.
10. Diagnostic test results positive for HIV-1 or HIV-2 infection.
11. Diagnostic test results positive for active hepatitis B or hepatitis C infection.
12. Mental incapacity, language barriers, or unwillingness to comply with the requirements of the protocol, which may preclude adequate understanding or co-operation during the trial as judged by the Investigator.
13. Average intake of more than 21 units of alcohol per week for male subjects and more than 14 units per week for female subjects: 1 unit of alcohol equals approximately 250 mL of beer, 100 mL of wine, or 35 mL of spirits).
14. Positive drug and alcohol screen (opiates, methadone, cocaine, amphetamines [including ecstasy], cannabinoids, barbiturates, benzodiazepines, tricyclic antidepressants, and alcohol) at screening and admission to the clinical research centre.
15. Use of tobacco and nicotine products, defined as any of the below:
    - Smoking more than 1 cigarette or the equivalent per day on average.
    - Not able or willing to refrain from smoking and use of nicotine substitute products during the in-house period.
16. Blood donation, plasma donation, or blood draw
    - In excess of 400 mL within the past 90 days prior to the day of screening
    - In excess of 50 mL within the past 30 days prior to the day of screening

17. Personal or first-degree relative(s) history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma.
18. Subjects with a history of malignant neoplasms within the past 5 years prior to screening will be excluded from the trial.
19. Presence or history of pancreatitis (acute or chronic; as declared by the subject or reported in the medical records).
20. Subject is not able to understand and read English or Dutch, or subject is not able to understand and comply with the trial requirements.
21. Subject depends on the Sponsor, the Investigator, or the study centre, or subject is the Investigator or any sub-investigator, research assistant, pharmacist, study coordinator, other staff, or relative thereof directly involved in the conduct of the trial.
22. Vulnerable subject (e.g. person kept in detention) who may have an increased likelihood of being wronged or of incurring additional harm.

Please note that subjects should refrain from consumption of any foods containing poppy seeds and alcohol within 48 hours (2 days) prior to screening and admission to the clinical research centre to avoid false-positive drug screen results. In addition, they should refrain from strenuous exercise within 96 hours (4 days) prior to screening and admission as this could result in abnormal clinical laboratory values.

#### 4.3.3 Removal of Subjects from Assessment

Participation in the trial is strictly voluntary. A subject has the right to withdraw from the trial at any time for any reason.

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

If a subject is withdrawn from the trial, the Sponsor will be informed immediately. If there is a medical reason for withdrawal, the subject will remain under the supervision of the Investigator until satisfactory health has returned.

Subjects who drop out or withdraw for any reason without completing all screening evaluations successfully will be considered screening failures.

A subject who is withdrawn or voluntarily withdraws from the trial for any reason, whether related to the trial product or not, after having received a subject number, will be considered an early-termination subject. Early-termination subjects will not be replaced.

[redacted] will make every effort to ensure that early-termination subjects who have received trial drug complete the safety follow-up assessments.

## 4.4 Treatments

### 4.4.1 Treatments Administered

Subjects will be randomised in a 2×2 scheme evenly to 4 sequences of product and injection side as shown in Table 4 in Section 4.1.1. Subjects will receive 1 dose of semaglutide 0.25 mg and 1 dose of dulaglutide 0.75 mg on the same day. The 2 products will be administered at least 30 minutes apart, in the anterior aspect of the abdominal wall on opposite sides of the midline.

Unblinded members of the [redacted] staff not otherwise involved in the trial procedures will be responsible for trial drug administration. In each subject, the 2 injections should be performed by the same staff member.

The [redacted] staff member will be instructed to select an injection site on the assigned side of the midline, that, according to their judgement based on visual inspection and palpation, has the maximal thickness of subcutaneous fat. The injection with the semaglutide product will be performed as described in the 1.5 mL PDS290 pre-filled pen directions for use and the NovoFine® Plus 4 mm x 32 G needle instructions for use. The injection with the dulaglutide product will be performed as described in the dulaglutide pre-filled pen (Trulicity®) instructions for use.

Using a lifed skin fold with either product (the semaglutide product or the dulaglutide product) will not be an option.

The unblinded [redacted] staff will instruct the subject to avoid discussing the administration of the trial drug with other study staff including the Investigator.

### 4.4.2 Identity of Investigational Products

Novo Nordisk A/S Denmark will supply the following products, see Table 5:

**Table 5 Products Supplied by Novo Nordisk A/S**

| Name | Name of Intervention Product |
|---|---|
| Semaglutide 1.34 mg/mL PDS290 pre-filled pen-injector | Semaglutide product |
| Trulicity 0.75 mg solution for injection in pre-filled pen (dulaglutide) | Dulaglutide product |

This NovoFine® Plus 4 mm x 32 G needle will be sourced directly by [redacted].

For details concerning drug storage and drug accountability see Appendix 9.1.

The characteristics of the 2 products are shown in Table 6.

**Table 6 Visual Appearance and Function of the semaglutide product and the dulaglutide product**

| | Semaglutide product | Dulaglutide product |
|---|---|---|
| |  |  |
| **Uses** | Multiple | Single |
| **Dose volume** | Selectable: 0.19 mL for 0.25 mg dose | 0.5 mL for 0.75 mg dose |
| **Needle** | Must be attached before injection: NovoFine® Plus 4 mm x 32 G | Integrated and hidden, 5 mm, 29 G |

All dose administrations will be performed by trained, unblinded staff at the study site.

Directions for use of all products provided by Novo Nordisk are provided in the Trial Materials Manual (TMM) also provided by Novo Nordisk.

### 4.4.3 Method of Assigning Subjects to Treatment Groups

After obtaining informed consent, subjects will be screened according to the inclusion and exclusion criteria. Subjects who have met all eligibility criteria will receive a subject number upon inclusion in the trial. They will receive the subject number just prior to dosing. The subject number will ensure identification throughout the trial.

The subject number will be the same as the randomisation number given on the randomisation list provided by Novo Nordisk. The randomisation list will be transferred to the [redacted] Pharmacy and kept in a restricted area to which only the [redacted] Pharmacy has access.

Subjects will receive a randomisation number based on the randomisation list provided to the site. The randomisation number encodes the assignment to one of the 4 sequences as described in Section 4.1.1.

Subjects who drop out or withdraw for any reason without completing all screening evaluations successfully will be considered screening failures. Such subjects, and also subjects who are eligible for inclusion in the trial but do not receive the trial drug, will not receive a subject number, and only applicable data will be entered in the electronic case report forms (eCRFs).

### 4.4.4 Selection of Doses in the Trial

Due to the risk of gastrointestinal adverse events such as nausea and vomiting inherent to GLP-1 RAs, the lowest marketed dose of each drug will be used, i.e. semaglutide 0.25 mg and dulaglutide 0.75 mg. Based on pharmacokinetic modelling[1] the single dose of dulaglutide 0.75 mg given on the same day as semaglutide 0.25 mg sc is expected to provide similar effect to semaglutide 0.5 mg, which is the highest single dose of semaglutide tolerated withou dose escalation due to risk of GI AEs. Also, as per its SmPC, dulaglutide may be initiated at the 1.5 mg dose.

### 4.4.5 Timing of Doses in the Trial

The first dose will be administered as follows. An unblinded [redacted] staff member who is present in the study room will start a timer when the other unblinded staff member starts the injection. The timer will be placed such that it is not visible to the subject. The subject will be instructed by an unblinded staff member to indicate when all pain is gone. If no pain is experienced, “00 min, 00 s (sec)” will be recorded. The blinded staff member will not be present in the room when the dosing is given. As soon as possible after dosing and before the 1 minute after injection timepoint, the blinded staff member takes over.

One minute after the injection, the blinded staff member will administer the visual-analogue scale (VAS) to rate the intensity of injection site pain (not the momentary pain at the time of VAS completion) (see Section 4.5.1.1.1).

When the subject has completed the intensity of injection site pain VAS after the first injection of the trial drug, the subject will complete a categorical assessment of injection site pain intensity (6-point scale) (see Section 4.5.1.1.2) and then a quality of pain modified short-form McGill Pain Questionnaire 2 (SF-MPQ-2) inventory (see Section 4.5.1.1.3).

Because the completion of the inventories may distract the subject, they will be reminded at regular intervals to indicate when the pain, if any, is gone, if they have not already done so.

At least 30 minutes after the first injection, after confirmation from the subject that the pain is entirely gone (to not contaminate the rating of the last injection), the timer will be reset, and the last injection will be given. If the pain is not gone at 30 minutes, another attempt will be made at 60 minutes. If pain is still present at that time, no further attempts will be made.

Following the last injection, the same measurements will be performed as after the first injection, as described above. Subjects will not be allowed to consult their own prior ratings. After confirmation from the subject that the pain is entirely gone, the subjects will complete a comparative pain assessment (5-point scale) comparing pain between injections (see Section 4.5.1.1.4).

During the 30 minutes after each administration of the trial drug the subjects should stay in bed or should be seated in a chair, and not walk around.

### 4.4.6 Meals During the Trial

There are no requirements with regard to fed or fasting conditions prior to or after trial drug administration. Further, no fasting is required before obtaining clinical laboratory samples.

With the exception of the restrictions with respect to the use of alcohol, methylxanthine-containing beverages or food, as described in Section 4.4.8, there are no special

requirements related to food and beverage intake. Meals and snacks (such as decaffeinated coffee, herbal tea, fruit, biscuits) will be provided according to [redacted] standard operating procedures (SOPs).

### 4.4.7 Blinding

This is a double-blind trial.

Investigators will remain blinded to each subject's assigned product throughout the course of the trial. Also, all [redacted] staff not participating in unblinded tasks will be blinded to treatment. To maintain this blind, qualified, unblinded members of the [redacted] staff not otherwise involved in the trial procedures will be responsible for trial drug administration according to the randomisation list. Technical complaints will also be collected by unblinded site staff. The unblinded [redacted] staff will not be involved in any other assessments or safety reporting.

Subjects will be blinded to treatment as well. To maintain blinding of subjects, a visual blind will be in place during dose administration.

Individual code break envelopes will be provided for all subjects by Novo Nordisk. Each sealed envelope containing the sequence will be kept in a medication storage room, which is locked with restricted access. To manage the subject's condition in case of a medical emergency, the Investigator is allowed to break the code to know which sequence of product and injection side the subject was randomised to. The date when and reason why the blind was broken must be recorded in the source documentation. The Sponsor (Global Safety department) and unblinded monitor will be informed in case of unblinding.

### 4.4.8 Concomitant Medication and Other Restrictions During the Trial

Note: Restrictions that apply to the period before admission are described in Section 4.3.1 and Section 4.3.2.

The use of all prescription medicinal products or non-prescription drugs or herbal products is not allowed from admission to the clinical research centre until discharge. An exception is made for routine vitamins, topical medication, and contraceptives, which are allowed throughout the trial. During the stay in the clinical research centre, the Investigator may permit a limited amount of paracetamol for the treatment of headache or any other pain, but this is only allowed after all pain assessments have been completed. Other medication to treat AEs during the stay in the clinical research centre may only be prescribed if deemed necessary by the Investigator. If medication is used during the stay in the clinical research centre, the name of the drug, the dose, and dosage regimen will be recorded in the eCRF. Any medication taken between discharge and the follow-up phone call will be documented in a similar fashion.

The use of alcohol, methylxanthine-containing beverages or food (coffee, tea, cola, chocolate, energy drinks), grapefruit (juice), and tobacco products is not allowed during the stay in the clinical research centre.

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

Female subjects of childbearing potential who have a fertile male sexual partner must agree to use highly effective contraception from screening up to 4 weeks after drug administration. Highly effective contraception is defined as:

- Use of combined (oestrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal [patch]), or
- Use of progestogen-only hormonal contraception associated with inhibition of ovulation (oral or injectable).

The above requirements on contraception do not apply if:

- The male partner of the female subject is vasectomised and has a confirmed post-vasectomy semen analysis.
- The female subject practises sexual abstinence during the period mentioned above.

#### 4.4.9 Treatment Compliance

Each of the single doses will be administered by trained unblinded staff at the clinical research centre. The exact times of trial drug administration will be recorded in the eCRF.

## 4.5 Safety Measurements and Variables

Only safety parameters will be assessed in this trial; the trial does not comprise efficacy, PK, or pharmacodynamic measurements.

### 4.5.1 Safety Measurements Assessed and Schedule of Assessments

A schedule of assessments is presented in Table 1.

#### 4.5.1.1 Safety and Tolerability Measurements

Safety and tolerability assessments will consist of intensity of injection site pain VAS, categorical assessment of injection site pain intensity (6-point scale), quality of pain modified SF-MPQ-2 inventory, duration of pain assessment, comparative pain assessment (5-point scale), AEs, clinical laboratory, vital signs, 12-lead ECG, and physical examination. In addition, some assessments will only be performed at screening or predose for the assessment of eligibility and are also described in this section.

All assessments will be performed in accordance with the schedule of assessments (Table 1).

#### 4.5.1.1.1 Intensity of Injection Site Pain Visual-Analogue Scale

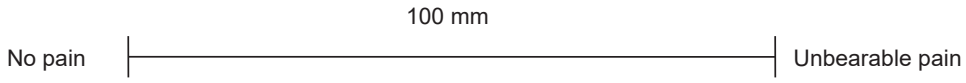
The intensity of injection site pain VAS will be filled in by the subjects starting 1 minute after each injection of the trial drug to report the pain intensity experienced in the first minute after the injection.

Subjects will be instructed to make a vertical line on the VAS (100 mm); the endpoints are “no pain” and “unbearable pain.” The distance (mm) between the endpoint “no pain” and the vertical line on the VAS will be recorded in the eCRF.

First injection

English version:

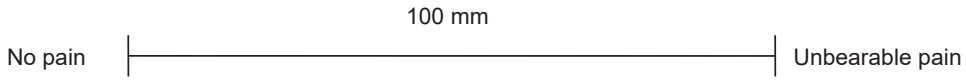
Indicate the intensity of pain you felt during the injection. For this, make a vertical line somewhere through the line below, where the endpoints are “no pain” and “unbearable pain”.




Last injection

English version:

Indicate the intensity of pain you felt during the last injection only. For this, make a vertical line somewhere through the line below, where the endpoints are “no pain” and “unbearable pain”.




#### 4.5.1.1.2 Categorical Assessment of Injection Site Pain Intensity

The categorical assessment of injection site pain intensity is a 6-point scale in which the pain intensity is rated by the subjects as follows:

Please tick one box describing the pain intensity during the injection:

| | |
|---|---|
| none | □ |
| very mild | □ |
| mild | □ |
| moderate | □ |
| severe | □ |
| very severe | □ |

Please tick one box describing the pain intensity during the last injection only:

| | |
|---|---|
| none | □ |
| very mild | □ |
| mild | □ |
| moderate | □ |
| severe | □ |
| very severe | □ |

#### 4.5.1.1.3 Quality of Pain Modified SF-MPQ-2 Inventory

The quality of pain will be assessed using the modified SF-MPQ-2 inventory[4], to be filled in by the subjects as follows:

This questionnaire provides you with a list of words that describe some of the different qualities of pain and related symptoms. Please put an X in all boxes that apply:

| | |
|---|---|
| Throbbing pain | □ |
| Shooting pain | □ |
| Stabbing pain | □ |
| Sharp pain | □ |
| Cramping pain | □ |
| Gnawing pain | □ |
| Hot-burning pain | □ |
| Aching pain | □ |
| Heavy pain | □ |
| Tender | □ |
| Splitting pain | □ |
| Tiring-exhausting | □ |
| Sickening | □ |
| Fearful | □ |
| Punishing-cruel | □ |
| Electric-shock pain | □ |
| Cold-freezing pain | □ |
| Piercing | □ |

#### 4.5.1.1.4 Duration of Pain

The duration of pain as indicated by the subject will be recorded from time of injection until cessation of pain in minutes and seconds.

#### 4.5.1.1.5 Comparative Pain Assessment (5-point Scale)

The comparative pain assessment is a 5-point scale in which the subjects will compare the pain between the 2 injections.

<u>The subjects will be asked to answer the following question:</u>
Please choose the statement below that best describes your experience:

- The last injection hurt much more than the first injection.
- The last injection hurt more than the first injection.

- They hurt about the same (includes: neither of the injections hurt).
- The last injection hurt less than the first injection.
- The last injection hurt much less than the first injection.

#### 4.5.1.1.6 Adverse Events

The definitions of AEs and serious AEs (SAEs) can be found in Appendix 9.2.

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

Time period and frequency for collecting AE and SAE information

All AEs will be collected from the first trial-related activity after obtaining informed consent and until the follow-up visit at the time points specified in the schedule of assessments (Table 1).

All SAEs will be recorded and reported to Novo Nordisk or designee within 24 hours, as indicated in Figure 2 and Appendix 9.2. The Investigator must submit any updated SAE data to Novo Nordisk within 24 hours of it being available.

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

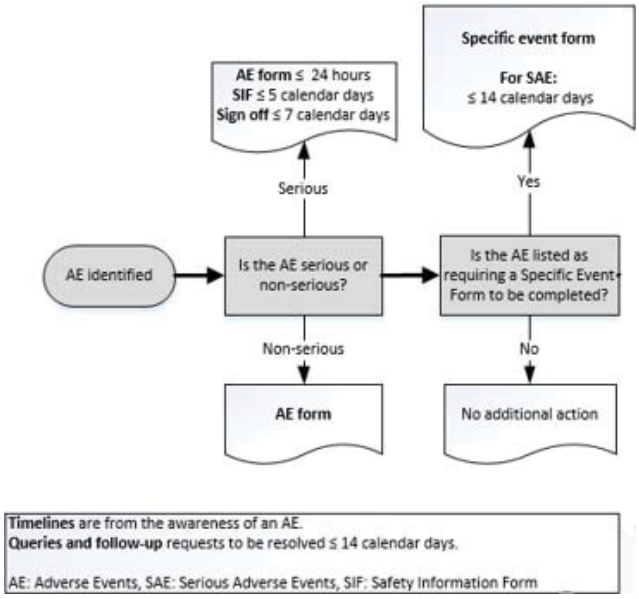
The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 9.2.

Medication error AEs require additional data collection via a specific event form. For definition of medication errors, see Appendix 9.2.

In order for Novo Nordisk to perform a complete investigation of reported SAEs, Novo Nordisk might ask the Investigator to complete a technical complaint form. For reporting of technical complaints, see Section 4.5.1.1.7.

The reporting timelines are specified in Figure 2.

**Figure 2 Decision Tree for Determining the Event Type and the Respective Forms to Complete with Associated Timelines**




Method of detecting AEs and SAEs

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

Follow-up on AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs will be followed until resolution, stabilisation, or if the event is otherwise explained (eg, chronic condition), or the subject is lost to follow-up. Further information on follow-up procedures is given in Appendix 9.2.

Regulatory reporting requirements for SAEs

Prompt notification by the Investigator to Novo Nordisk of an SAE (according to Figure 2 and Appendix 9.2) is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a trial product under clinical investigation are met.

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

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Novo Nordisk policy and forwarded to regulatory authorities, the IEC, and investigators as locally required.

An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from Novo Nordisk will review and then file it along with the IB and will notify the IEC, if appropriate, according to local requirements.

Pregnancies and associated adverse events

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

If a pregnancy is reported in a female subject, the Investigator should inform Novo Nordisk within 14 calendar days of learning of the pregnancy and should follow the procedures outlined below:

- The Investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this trial.
- Information will be recorded on the appropriate form and submitted to Novo Nordisk within 14 calendar days of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the subject and neonate, which will be forwarded to Novo Nordisk. Generally, follow-up will not be required for longer than 1 month beyond the delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- Although pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-trial pregnancy that is considered possibly/probably related to the trial product by the Investigator will be reported to Novo Nordisk as described in Appendix 9.2. Although the Investigator is not obligated to actively seek this information in former subjects, he or she may learn of an SAE through spontaneous reporting.

Pregnancy outcome should be documented in the subject's medical record. An abnormal pregnancy outcome (eg, spontaneous abortion, fetal death, stillbirth, congenital anomaly, and ectopic pregnancy) is considered an SAE.

#### 4.5.1.1.7 Technical Complaints

The unblinded [redacted] staff are responsible for the detection and documentation of technical complaints that occur when using the pen-injectors used in this trial.
Definition of technical complaint:

- A technical complaint is any written, electronic, or oral communication that alleges medical product defects and device product defects. The technical complaint may be associated with an AE, but does not concern the AE itself.

Examples of technical complaints are as follows:

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

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

Time period for detecting technical complaints
All technical complaints that occur from the time of receipt of the product at [redacted] until the time of the last usage of the product must be collected for products predefined on the technical complaint form.

Reporting of technical complaints to Novo Nordisk
Technical complaints must be reported on a separate technical complaint form:

- One technical complaint form must be completed for each affected dispensing unit number (DUN).
- If a DUN is not available, a technical complaint form for each batch, code, or lot number must be completed.

Timelines for reporting of technical complaints to Novo Nordisk
The Investigator must complete as much information on the form as possible and hand it over to the unblinded [redacted] staff. The unblinded [redacted] staff must fill in the unblinded information on the form (such as the DUN and batch, code, or lot number) and forward the technical complaint form to the Customer Complaint Center, Novo Nordisk, within the timelines specified below:

- Technical complaints related to SAEs, within 24 hours
- All other technical complaints, within 5 calendar days

The technical complaint form must be kept inaccessible to blinded site staff.

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

Collection, storage, and shipment of technical complaint samples

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

Reporting of technical complaints for Novo Nordisk products not included in technical complaint form

Technical complaints about Novo Nordisk products not included in the technical complaint form should be reported to local Novo Nordisk affiliate with a reference to trial ID.

#### 4.5.1.1.8 Clinical Laboratory

Blood and urine samples for clinical laboratory assessments will be collected according to [redacted] SOPs. No fasting is required prior to collecting these samples.
The following parameters will be measured:

- Clinical chemistry (serum quantitatively):
  total bilirubin, alkaline phosphatase, aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), creatinine, albumin, sodium, potassium, and calcium.
- Haematology (blood quantitatively):
  leukocytes, haemoglobin, and thrombocytes.
  HbA1c at screening only.
- Serology:
  hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV), and anti HIV-1 and -2.
- Drug and alcohol screen:
  opiates, methadone, cocaine, amphetamines (including ecstasy), cannabinoids, barbiturates, benzodiazepines, tricyclic antidepressants, and alcohol in urine.
- Hormones (serum quantitatively):
  thyroid-stimulating hormone.
- Pregnancy test (female subjects of childbearing potential only):
  β-human chorionic gonadotropin in urine.

In case of unexplained or unexpected clinical laboratory test values, the tests will be repeated as soon as possible and followed up until the results have returned to the normal range and/or an adequate explanation for the abnormality is found. The clinical

laboratory will clearly mark all laboratory test values that are outside the normal range, and the Investigator will indicate which of these deviations are clinically significant. Clinically significant laboratory result deviations after trial drug administration will be recorded as AEs, and the relationship to the treatment will be indicated (see also Appendix 9.2). Clinically significant laboratory results at screening will not be reported as AE as this is considered part of medical history.

#### 4.5.1.1.9 Vital Signs

Systolic and diastolic blood pressure and pulse will be recorded after the subject has been resting for at least 5 minutes in the supine position. These assessments will be made using an automated device.

#### 4.5.1.1.10 Electrocardiogram

A standard 12-lead ECG will be recorded after the subject has been resting for at least 5 minutes in the supine position. The ECG will be recorded using an ECG machine equipped with computer-based interval measurements. The following ECG parameters will be recorded: heart rate, PR-interval, QRS-duration, QT-interval, QTc-interval (Fridericia's), and the interpretation of the ECG profile by the Investigator.

#### 4.5.1.1.11 Physical Examination

Physical examination will be performed according to [redacted] SOPs. In addition, body weight and height will be measured according to [redacted] SOPs.

### 4.5.1.2 Total Blood Volume

Table 7 presents the number and volume of blood samples and the total volume of blood that will be collected throughout the trial per subject.

If deemed necessary by the Investigator or the Sponsor, the number and/or volume of blood samples per assessment may be increased as long as the total volume of blood drawn for a subject does not surpass 500 mL.

**Table 7 Number and Volume of Blood Samples and Total Blood Volume Collected per Subject**

| Assessment | Maximum # Samples | Volume of Blood per Sample (mL) | Total Volume of Blood (mL) |
|---|---|---|---|
| Clinical Chemistry | 2 | 3.5 | 7 |
| Haematology | 2 | 3 | 6 |
| Serology | 1 | 5 | 5 |
| Total Volume of Blood Drawn | | | 18 |

### 4.5.2 Appropriateness of Measurements

The assessments that will be made in this trial are standard and generally recognised as reliable, accurate, and relevant.

#### 4.5.3 Safety Variables

The safety variables to be measured include but are not limited to the variables as given below. A complete list of safety variables will be provided in the statistical analysis plan (SAP).

- Intensity of injection site pain VAS
- Categorical assessment of injection site pain intensity (6-point scale)
- Quality of pain modified SF-MPQ-2 inventory
- Duration of pain
- Comparative pain assessment (5-point scale)
- AEs
- Clinical laboratory (if postdose assessments are deemed relevant by the Investigator)
- Vital signs
- ECG (if postdose assessments are deemed relevant by the Investigator)
- Physical examination (if postdose assessments are deemed relevant by the Investigator)

### 4.6 Statistical Procedures and Determination of Sample Size

#### 4.6.1 Analysis Sets

##### 4.6.1.1 Safety Set

All subjects who have received at least 1 injection of semaglutide or dulaglutide (includes any skin contact with trial product, whether the injection was completed or not).

##### 4.6.1.2 Full Analysis Set

All randomised subjects who have received at least 1 injection of semaglutide or dulaglutide (includes any skin contact with trial product, whether the injection was completed or not). In exceptional cases, subjects from the full analysis set may be excluded. In such cases the exclusion will be justified and documented.

##### 4.6.1.3 Per-Protocol Set

All subjects who have received both injections of semaglutide and dulaglutide and have completed both intensity of injection site pain assessments.

#### 4.6.2 Statistical and Analytical Plan for Safety Evaluation

A SAP will be generated by the Biostatistics Department of [redacted]; the SAP will be finalised prior to database lock. Full details of the analysis to be performed will be included in the SAP.

Any deviation from the SAP will be reported in the section “Changes in Planned Analysis” in the clinical study report (CSR).

#### 4.6.2.1 Evaluation of Safety and Tolerability

Safety and tolerability will be assessed through intensity of injection site pain VAS, categorical assessment of injection site pain intensity, quality of pain modified SF-MPQ-2 inventory, duration of pain assessment, comparative pain assessment, AEs, clinical laboratory, vital signs, ECGs, and physical examination findings (if results are available after dosing), and any other parameter that is relevant for safety assessment.

##### 4.6.2.1.1 Intensity of Injection Site Pain Visual-Analogue Scale

The primary endpoint is given in Table 8.

**Table 8 Primary Endpoint**

| Endpoint title | Time frame | Unit |
|---|---|---|
| Intensity of injection site pain | 1 min after each injection (Day 1) | mm on a 100 mm horizontal visual-analogue scale (where 0 mm = no pain, 100 mm = unbearable pain) |

The primary endpoint will be analysed by a fixed analysis of variance model with VAS score as the dependent variable, and product, injection side (right side, left side), injection number (first injection, second injection), and subject as fixed effects. From the model, the difference in VAS score between the 2 products will be estimated and presented with a 95% confidence interval (CI) and a p-value. The interpretation of the difference in VAS pain scores will be supported and contextualised by the results of the analyses of the exploratory endpoints.

##### 4.6.2.1.2 Categorical Assessment of Injection Site Pain Intensity, Quality of Pain Modified SF-MPQ-2 Inventory, Duration of Pain, and Comparative Pain Assessment

The exploratory endpoints are given in Table 9.

**Table 9 Exploratory Endpoints**

| Endpoint title | Time frame | Unit |
|---|---|---|
| Categorical assessment of intensity of injection site pain | Immediately after rating of intensity of injection site pain, i.e. after 1 min plus the time it takes to complete the rating of intensity of injection site pain by visual-analogue scale (Day 1) | 6-point scale (none – very mild – mild – moderate – severe – very severe) |
| Moderate or more injection site pain | Dichotomous variable based on *categorical assessment of intensity of injection site pain* (item above) | Yes = moderate, severe, very severe<br>No = none, very mild, mild |
| Quality of pain | Immediately after *categorical assessment of intensity of injection site pain*, i.e. after 1 min plus the time it takes to complete the rating of *intensity of injection site pain* and the *categorical rating of intensity of injection site pain* (Day 1) | Pain quality items on modified SF-MPQ-2 inventory (select all that apply):<br>Throbbing pain ☐<br>Shooting pain ☐<br>Stabbing pain ☐<br>Sharp pain ☐ |

| Endpoint title | Time frame | Unit |
|---|---|---|
| | | Cramping pain ☐<br>Gnawing pain ☐<br>Hot-burning pain ☐<br>Aching pain ☐<br>Heavy pain☐<br>Tender ☐<br>Splitting pain ☐<br>Tiring-exhausting ☐<br>Sickening ☐<br>Fearful ☐<br>Punishing-cruel ☐<br>Electric-shock pain ☐<br>Cold-freezing pain ☐<br>Piercing ☐ |
| Duration of pain | From time of injection until cessation of pain (Day 1) | min and s |
| Comparative pain experience: | After pain has ended after the last injection (Day 1) | 5-point scale (the last injection hurt much more than the first injection – the last injection hurt more than the first injection – about the same (includes: none of the injections hurt) – the last injection hurt less than the first injection - the last injection hurt much less than the first injection) |
| The semaglutide product hurt less than or about the same as the dulaglutide product | Dichotomous variable based on "*Comparative pain experience*" variable above | Yes = "about the same (includes none of the products hurt)" or "the semaglutide product hurt less than the dulaglutide product" or "the semaglutide product hurt much less than the dulaglutide product"<br>No = "the semaglutide product hurt much more than the dulaglutide product" or "the semaglutide product hurt more than the dulaglutide product" |

The results will be listed, and they will be presented descriptively, where applicable.

#### 4.6.2.1.3 Adverse Events

A listing of all individual AEs will be provided. Summary tables of treatment-emergent adverse events (TEAEs) will be presented by system organ class based on the Medical Dictionary for Regulatory Activities terminology list (preferred terms): one containing the number of TEAEs (frequency of occurrence, number of subjects experiencing the event) by treatment and one containing the number of drug-related TEAEs (frequency of occurrence, number of subjects experiencing the event) per treatment. Additional tables of total counts by treatment and relationship and by treatment and severity will be given.

#### 4.6.2.1.4 Technical Complaints

A listing of all technical complaints will be provided.

#### 4.6.2.1.5 Clinical Laboratory

Clinical laboratory data will be listed accompanied by an indication if the parameter is outside the reference range. A summary of all data outside the reference range of the clinical laboratory will be provided. Clinical laboratory data will be presented descriptively, where applicable.

#### 4.6.2.1.6 Vital Signs and Electrocardiograms

Vital signs and ECG parameters will be listed, and they will be presented descriptively, where applicable.

#### 4.6.2.1.7 Physical Examination

Changes from baseline for physical examination (if available after dosing) will be described and listed.

### 4.6.3 Determination of Sample Size

The sample size calculation considers both the primary endpoint and the dichotomous endpoints.

Considering precision on the proportion of the dichotomous endpoints, a sample size of 100 subjects results in a confidence interval (CI) with a width of 10% on each side, eg, for a proportion of 60%, the CI is 60% (50%-70%).

A standard deviation (SD) of within-pair differences in VAS pain score between 2 SC injections was obtained from Novo Nordisk clinical trial INS-4011. The within-subject variance (adjusting for the effects of speed, volume, and injection region) was estimated to 348, corresponding to an SD of the within-pair difference of $\sqrt{(2 \cdot 348)} = 26$ mm. A prospective study of acute pain found that the minimum clinically important difference (MCID) for worsening of pain, ie, the difference on a VAS associated with the selection of “a little more pain” rather than “about the same”, had a mean value of 10 mm.[5]

With 100 subjects, a conservative SD of 30 mm, and 90% power, it is possible to detect a difference smaller than 10 mm (Table 10). Hence a sample size of 100 subjects is considered sufficient to detect a clinically important difference. Allowing for 4% dropouts or missing data, a total of 104 subjects will need to be randomised.

**Table 10 Detectable Difference with a Sample Size of 100 Subjects for Different Combinations of Power, and Standard Deviation**

| Number of Subjects | Power | Standard Deviation | Difference |
|---|---|---|---|
| 100 | 0.8 | 25 mm | 7.1 mm |
| 100 | 0.8 | 30 mm | 8.5 mm |
| 100 | 0.9 | 25 mm | 8.2 mm |
| 100 | 0.9 | 30 mm | 9.8 mm |

### 4.6.4 Interim Analysis

After the last subject has completed Day 1, all data collected will be released unblinded for analysis notwithstanding that the subjects have not completed the safety follow-up phone call.

## 4.7 Data Quality Assurance

The trial may be audited by the Quality Assurance Department at [redacted] to assess adherence to the clinical study protocol (CSP) and Quality System. During the conduct of the trial, process-related audits may be performed. An audit certificate will be provided in the appendices of the final CSR outlining any audits and other related activities performed.

The clinical research site will be monitored by the study blinded monitor and unblinded monitor to ensure correct performance of the trial procedures and assure that the trial is conducted according to the relevant regulatory requirements. The eCRF entries will be verified with the source documentation, if applicable (in some cases there are no source pages, therefore verification is not necessary).

Regulatory authorities, the IEC, and/or the Sponsor's clinical quality assurance group may request access to all source documents, eCRFs, and other trial documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities.

Quality control principles will be applied throughout the performance of this trial. Review procedures will be followed at [redacted] for all documents that are generated in relation to the trial.

An explanation will be given for all missing, unused, and spurious data in the relevant sections of the CSR.

# 5. ETHICS

## 5.1 Independent Ethics Committee

The CSP and the ICFs will be submitted for review and approval by the IEC of the foundation "Beoordeling Ethiek Biomedisch Onderzoek" (English translation: "Evaluation of Ethics in Biomedical Research") (Dr. [redacted]) prior to the eligibility screening. The composition of the IEC is in accordance with the recommendations of the World Health Organization, the International Council for Harmonisation (ICH) E6 Guideline for Good Clinical Practice (GCP) (EMA/Committee for Medicinal Products for Human Use [CHMP]/ICH/135/1995)[6], and the EU Clinical Trial Directive (CTD) (Directive 2001/20/EC)[7].

[redacted] will keep the IEC informed about the progress of the trial. All changes in research activities and all unanticipated problems involving risks to human subjects will be immediately reported to the IEC. In accordance with Section 10, Subsection 1, of the Dutch law on Medical Research in Human Subjects (WMO, revised December 2015)[8], [redacted] will inform the subjects and the IEC if anything occurs on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal, or if further recruitment of subjects in the trial has been put on hold for that reason, whichever occurs first. The trial may be suspended pending further review by the IEC, except insofar as suspension would jeopardise the subjects' health. [redacted] will take care that all subjects are kept informed.

No changes will be made in the trial without IEC approval, except when required to eliminate apparent immediate hazards to human subjects.

Notification of the end of the trial will be sent by [redacted] to the Competent Authority (CA) in The Netherlands and to the IEC within 90 days after completion of follow-up for the last subject. In case a trial is temporarily halted, [redacted] will notify the IEC immediately, including the reason for this. In case a trial is ended prematurely, [redacted] will notify the IEC and the CA in The Netherlands within 15 days, including the reasons for the premature termination. A summary of the results of the trial will be sent by [redacted] to the CA and the IEC within 1 year after the end of the trial.

## 5.2 Ethical Conduct of the Trial

This trial will be conducted in accordance with the ethical principles that have their origin in the World Medical Association (WMA) Declaration of Helsinki, adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and subsequent amendments.[9]

This trial is also designed to comply with ICH E6 Guideline for GCP (EMA/Committee for Medicinal Products for Human Use [CHMP]/ICH/135/1995)[6] and the EU CTD Directive 2001/20/EC[7], as incorporated into Dutch Law.[8]

Guidelines adopted by the ICH and other relevant international guidelines, recommendations, and requirements will be taken into account as comprehensively as possible, as long as they do not violate local law.

Whenever the term “Investigator” is noted in the CSP text, it may refer to either the Investigator at the site or an appropriately qualified, trained, and delegated individual of the investigational site.

## 5.3 Subject Information and Consent

All subjects will be informed verbally and in writing regarding the objectives, procedures, and risks of trial participation. The subjects will have to sign the Dutch or English version of the ICF before any trial-related procedures are started. The ICF contains information about the objectives of the trial, the procedures followed during the trial, and the risks and restrictions of the trial, with special reference to possible side effects of the medication and potential interactions. In addition, insurance coverage provided during the trial is explained. The elements addressed in the ICF are according to the ICH E6 Guideline for GCP (EMA/CHMP/ICH/135/1995).[6]

## 5.4 Privacy

All personal details will be treated as confidential by the Investigator and staff at [redacted], and the handling of personal data will be in compliance with the EU General Data Protection Regulation (GDPR).[10]

# 6. TRIAL ADMINISTRATIVE STRUCTURE

## 6.1 Distribution of Activities

Supply of Trial Drug

Novo Nordisk A/S Denmark will supply the semaglutide products and the dulaglutide products for use in the trial.

Laboratory Assessments

The analysis of clinical laboratory samples will be performed at the [redacted] Clinical Laboratory.

eCRF Design

The eCRF design will be performed with the computer program [redacted] by the Database Programming Department of [redacted].

Data Management

Data management will be performed with the computer programs [redacted], a technology subsidiary of [redacted]) by the Data Management Department of [redacted].

Statistics

A SAP will be generated by the Biostatistics Department of [redacted]. The safety analysis will be conducted by the Biostatistics Department of [redacted]. Statistical analysis will be performed with the computer program [redacted].

CSR Writing

The CSR, structured in accordance with the guideline "Structure and Content of Clinical Study Reports - ICH E3",[11] will be written by [redacted].

## 6.2 Documentation

### 6.2.1 Archiving

All documents concerning the trial will be kept on file in the Central Archives of [redacted] for at least 15 years after conduct of the trial. The Sponsor will receive the completed eCRFs (upon request, as PDF file).

### 6.2.2 Recording of Data in Source Documents and eCRFs

Wherever possible, all data will be entered directly into the eCRFs. Source documents will be used in some cases.

A data management plan will be written by the Data Management Department of [redacted] which will be finalised prior to performing any data validation. An appendix to the data management plan (Origin of Source Data List for Data Entry) will identify any data to be recorded directly in the eCRF (ie, no prior written or electronic record of data) and which data should be considered source data.

# 7. CONFIDENTIALITY AND PUBLICATION POLICY

By signing this CSP, the Investigator reaffirms to the Sponsor that he will maintain in confidence all information furnished to him or resulting from this trial. The Investigator will only divulge such information as may be necessary to the IEC, the members of the staff, and the subjects who are involved in this trial.

The primary completion date (PCD) is the last assessment of the primary endpoint, and is for this trial Last Subject First Treatment (LSFT) corresponding to Day 1. If the last subject is withdrawn early, the PCD is considered the date when the last subject would have completed Day 1. The PCD determines the deadline for results disclosure at clinicaltrials.gov according to the Food and Drug Administration Amendments Act.

## 7.1 Publication Policy

Novo Nordisk commits to communicate and disclose results of trials regardless of outcome. Disclosure includes publication of a manuscript in a peer-reviewed scientific journal, abstract submission with a poster or oral presentation at a scientific meeting, or disclosure by other means. The results of this trial will be subject to public disclosure on external web-sites according to international and national regulations. Novo Nordisk reserves the right to defer the release of data until specified milestones are reached, for example when the clinical trial report is available. This includes the right not to release the results of interim analyses, because the release of such information may influence the results of the entire trial. At the end of the trial, one or more scientific publications may be prepared collaboratively by the Investigator(s) and Novo Nordisk. Novo Nordisk reserves the right to postpone publication and/or communication for up to 60 days to protect intellectual property. In all cases the trial results will be reported in an objective, accurate, balanced, and complete manner, with a discussion of the strengths and limitations. In the event of any disagreement on the content of any publication, both the investigators' and Novo Nordisk opinions will be fairly and sufficiently represented in the publication.

## 7.2 Dissemination of Clinical Trial Data

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

# 8. REFERENCES

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4. Dworkin RH, Turk DC, Revicki DA, et al. Development and initial validation of an expanded and revised version of the Short-form McGill Pain Questionnaire (SF-MPQ-2). Pain. 2009;144:35-42.
5. Todd KH, Funk KG, Funk JP, et al. Clinical significance of reported changes in pain severity. Ann Emerg Med.1996;27:485-89.
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7. Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.
8. Medical Research Involving Human Subjects Act (WMO, Wet Medisch-Wetenschappelijk Onderzoek met Mensen), revision December 2015.
9. WMA Declaration of Helsinki (18th WMA General Assembly 1964), revised at 64th World Medical Association General Assembly, Fortaleza, Brazil, October 2013.
10. The General Data Protection Regulation (GDPR). Regulation (EU) 2016/679 of the European Parliament and the Council of the European Union, 27 April 2016.
11. International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline, E3: Structure and Content of Clinical Study Reports (CPMP/ICH/137/95), November 1995.

# 9. APPENDICES

## 9.1 Drug Accountability

- Trial product storage, in-use conditions, and in-use time will be available on the label and in the TMM. The Investigator must confirm that appropriate temperature conditions have been maintained during transit for all trial products received and any discrepancies are reported and resolved before use of the trial products.
- All trial products must be stored in a secure, controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the pharmacist and pharmacy assistant.
- The Investigator must inform Novo Nordisk immediately if any trial product has been stored outside specified conditions. Additional details regarding handling of temperature deviations can be found in the TMM.
- Trial product that has been stored improperly must not be dispensed to any subject before it has been evaluated and approved for further use by Novo Nordisk.
- The Investigator is responsible for drug accountability and record maintenance (ie, receipt, accountability, and final disposition records).
- For trial products packed unblinded in a blinded trial: Drug accountability will be performed by an unblinded person who will ensure that unblinding information such as batch numbers is not revealed to personnel that should remain blinded).
- Drug accountability should be performed at dose level unless this is not possible (eg, products in pen-injectors), then describe and explain the actual level of accountability.

## 9.2 Adverse Events: Definitions and Procedures for Recording, Evaluation, Follow-up, and Reporting to Sponsor

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

| **Events <u>meeting</u> the AE definition** |
|---|
| • Any abnormal laboratory test results or safety assessments, including those that worsen from baseline, considered clinically significant in the medical and scientific judgement of the Investigator.<br>• Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.<br>• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.<br>• Signs, symptoms, or the clinical sequelae of a suspected overdose of trial product regardless of intent. |
| **Events <u>NOT</u> meeting the AE definition** |
| • Pre-existing conditions, anticipated day-to-day fluctuations of pre-existing conditions, including those identified during screening or other trial procedures performed before exposure to trial product.<br>Note: Pre-existing conditions should be recorded as medical history/concomitant illness. |

- Pre-planned procedures, unless the condition for which the procedure was planned has worsened from the first trial-related activity after the subject has signed the informed consent.
- Pain: Non-serious pain will be collected on specific pain-rating schemes. If the event of pain fulfils the criteria for a serious adverse event then in addition to the above, an adverse event form and a safety information form must also be filled in. All other injection site reactions besides pain will be reported as an adverse event (Table 1) and Section 4.5.
  If the event of pain 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.

**Definition of an SAE**

**An SAE is an AE that fulfils at least one of the following criteria:**

- **Results in death**
- **Is life-threatening**

The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death, if it were more severe

- **Requires inpatient hospitalization or prolongation of existing hospitalization**
  - Hospitalization signifies that the subject has been detained at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
  - Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

  Note:
  - Hospitalizations for administrative, trial-related, and social purposes do not constitute AEs and should therefore not be reported as AEs or SAEs.
  - Hospital admissions for surgical procedures, planned before trial inclusion, are not considered AEs or SAEs.
- **Results in persistent disability/incapacity**
  - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
  - This definition is not intended to include experience of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (eg, sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- **Is a congenital anomaly/birth defect**
  - Including events leading to fetal distress or fetal death
- **Important medical event:**
  - Medical or scientific judgement should be exercised in deciding whether SAE reporting is appropriate in other situations. This includes important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious and reported as SAEs using the important medical event criterion.
  - The following AEs must always be reported as SAEs using the important medical event criterion, if no other seriousness criteria are applicable:
    - suspicion of transmission of infectious agents via the trial product.
    - risk of liver injury defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 x the upper limit of normal (ULN) and total bilirubin >2 x ULN, where no alternative aetiology exists (Hy's law).

These are handled under the SAE reporting system.

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

**Medication error:**

A medication error concerning trial products is defined as:

- Administration of wrong drug or use of wrong device.
  Note: Use of wrong dispensing unit number (DUN) is not considered a medication error unless it results in a confirmed administration of wrong drug.
- Wrong route of administration, such as intramuscular instead of sc.
- Accidental administration of a lower or higher dose than intended. The administered dose must deviate from the intended dose to an extent where clinical consequences for the trial subject were likely to happen as judged by the Investigator, although they did not necessarily occur.

**AE and SAE recording**

- The Investigator will record all relevant AE information in the eCRF and SAE information on paper forms.
- 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 (eg, hospital progress notes, laboratory and diagnostics reports) related to the event.
- For all non-serious AEs the applicable forms should be signed when the event is resolved or at the end of the trial at the latest. For sign-off of SAE-related forms, refer to “SAE reporting via paper CRF” later in this section.
- Novo Nordisk products used as concomitant medication: if an AE is considered to have a causal relationship with a Novo Nordisk marketed product used as concomitant medication in the trial, it is important that the suspected relationship is reported to Novo Nordisk, eg, in the alternative etiology section on the safety information form. Novo Nordisk may need to report this AE to relevant regulatory authorities.

**Assessment of severity**

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

- **Mild**: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- **Moderate**: An event that causes sufficient discomfort and interferes with normal everyday activities.
- **Severe**: An event that prevents normal everyday activities.
  Note: Severe is a category used for rating the intensity of an event; and both an AE and SAE can be assessed as severe. An event is defined as ‘serious’ when it meets at least one of the outcomes described in the definition of an SAE and not when it is rated as severe.

**Assessment of causality**

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

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

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

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

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

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

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

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

**Final outcome**

The Investigator will select the most appropriate outcome:

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

**Follow-up of AE and SAE**

The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Novo Nordisk to elucidate the nature and/or causality of the AE or SAE as fully as possible (eg, severe hypersensitivity reactions). This may include additional laboratory tests (eg, skin prick test) or investigations, histopathological examinations, or consultation with other health care professionals.

If a subject dies during participation in the trial or during a recognised follow-up period, the Investigator should provide Novo Nordisk with a copy of autopsy report including histopathology.

New or updated information will be recorded in the case report form (CRF).

**SAE reporting via paper CRF**

- Relevant CRF forms (AE safety information and specific event forms) must be forwarded to Novo Nordisk.
- The Investigator needs to complete the AE and safety information form within the designated reporting time frames (as illustrated in Figure 2).
- If the eCRF is unavailable for more than 24 hours, then the site will use the paper AE form.

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