# Cover Page for Protocol

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| Sponsor name: | Novo Nordisk A/S |
| NCT number | NCT03687827 |
| Sponsor trial ID: | NN1250-4419 |
| Official title of study: | A randomised, cross-over, open-label, multi-centre trial comparing the effect of insulin degludec and insulin glargine 100U/mL, with or without OADs in subjects with type 2 diabetes using flash glucose monitoring |
| Document date | 04 May 2020 |

### 16.1.1 Protocol and protocol amendments

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

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# Protocol

**Protocol title:** A randomised, cross-over, open-label, multi-centre trial comparing the effect of insulin degludec and insulin glargine 100U/mL, with or without OADs in subjects with type 2 diabetes using flash glucose monitoring

**SWITCH PRO**

**Substance: insulin degludec/insulin glargine 100U/mL**

**Universal Trial Number:** U1111-1203-0580

**EUdraCT Number:** 2017-004047-20

**Trial phase:** 4

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

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# 1 Synopsis

**Rationale:**
The overall purpose of this trial is to investigate how insulin degludec (IDeg) influences glycaemic control compared to insulin glargine 100U/mL (IGlar 100U/mL), using flash glucose monitoring (FGM) in subjects with type 2 diabetes mellitus (T2DM). The accuracy and the widespread integration of FGM in clinical practice of today, provides a rationale for evaluating if the previously shown hypoglycaemia benefits with IDeg, translate into more time in glycaemic range and lower glycaemic variability versus the comparator.

**Objectives and endpoints:**

**Primary objective:**
The primary objective is to compare the effect on glycaemic control of IDeg versus IGlar 100U/mL in a population of T2DM subjects with or without oral anti-diabetic drugs (OADs), using FGM.

**Estimand:**
The primary estimand is the treatment difference between IDeg and glargine with respect to percent time spent in glycaemic target range for all randomised subjects that can use the FGM sensor and adhere to at least 18 weeks of treatment on both insulins. An intercurrent event for the primary estimand is lack of effect from any of the insulins leading to a need for initiation of other diabetes medication(s). As described in section 8.1 in the protocol, treatment intensification may result in trial discontinuation. . The primary estimand will handle these intercurrent events as withdrawals and only use data from completers. The primary estimand is the principle stratum direct effect for the population of completers.
The population level summary statistics is the average percent of time spent in glycaemic target during maintenance for completers. For comparing the two treatments the relevant summary is the difference in the means.

**Primary endpoint:**
Percentage of time spent in glycaemic target range 70-180 mg/dL (3.9–10.0 mmol/L) both inclusive, during the 2-week maintenance period using FGM (Visit 19-21 (week 16-17) and Visit 37-39 (week 34-35)).

**Overall design:**
This is a randomised, cross-over, open-label, multi-centre, multinational, active controlled trial in adult subjects with type 2 diabetes treated with basal insulin with or without OADs with a 2 weeks run-in period to ensure compliance and tolerability of the FGM requirements.

At randomisation (Visit 3), subjects will discontinue pre-trial basal insulin and be randomised in a 1:1 manner to the 2 treatment sequences:

- IDeg once daily ± OADs followed by IGlar 100U/mL once daily ± OADs
- IGlar 100U/mL once daily ± OADs followed by IDeg once daily ± OADs

**Key inclusion criteria:**

- Male or female, age ≥ 18 years at the time of signing informed consent
- Diagnosed with type 2 diabetes mellitus ≥ 180 days prior to the day of screening
- Subjects fulfilling at least one of the below criteria:
    - Experienced at least one severe hypoglycaemic episode within the last year prior to screening (according to the American Diabetes Association definition, January 2018)*
    - Moderate renal impairment defined as estimated glomerular filtration rate (eGFR) value of 30-59 mL/min/1.73 $m^2$ as defined by KDIGO 2012[1] at screening
    - Known hypoglycaemic unawareness as indicated by the investigator according to Clarke's questionnaire question 8[2] at screening
    - Treated with insulin for more than 5 years
    - Episode of hypoglycaemia (defined a glucose alert value of 70 mg/dL (3.9 mmol/L) or less, i.e. Level 1)[3] within the last 12 weeks prior to screening visit
- Treated with any basal insulin ≥ 90 days prior to the day of screening with or without any of the following anti-diabetic drugs :
    - Metformin
    - Dipeptidyl peptidase-4 inhibitor
    - Sodium-glucose co-transporter 2 inhibitor
    - Alpha-glucosidase-inhibitors (acarbose)
    - Thiazolidinediones
    - Marketed oral combination products only including the products listed above
- HbA1c ≤9.5% (80 mmol/mol) at screening confirmed by central laboratory analysis
- BMI ≤ 45 kg/$m^2$

*Hypoglycaemia associated with severe cognitive impairment requiring external assistance for recovery

**Key exclusion criteria:**

- Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria within the past 90 days prior to the day of screening. However, intermittent bolus insulin treatment for periods of no longer than 14 days are permitted prior to the day of screening.
- Anticipated initiation or change in concomitant medications known to affect weight or glucose metabolism (e.g. treatment with orlistat, thyroid hormones, or corticosteroids).
- Uncontrolled and potentially unstable diabetic retinopathy or maculopathy. Verified by a pharmacologically pupil-dilated fundus examination performed by an ophthalmologist or

another suitably qualified health care provider within the past 90 days prior to screening or in the period between screening and run-in

**Randomisation criteria:**

- Subject able and willing to adhere to the protocol including requirements and tolerability in regards to wearing the FreeStyle Libre Pro sensor, based on the investigator's opinion.

**Number of subjects:**
Number of subjects planned to be screened: 674
Number of subjects planned to enter-run-in period: 502
Number of subjects planned to be randomised: 472

**Treatment groups and duration:**
The total duration of the trial will be approximately 41 weeks: 2 weeks screening period, a 2 weeks run-in period, a 36 weeks treatment period and a 1 week follow-up.
This is a cross-over trial and each randomised subject will receive both Investigational Medicinal Products (IMP) for 18 weeks, and both treatment periods will start with a 16 weeks titration period followed by a 2 weeks maintenance period. At cross-over subjects will be switched to the other IMP according to local label.
Subjects using OADs prior to the trial according to inclusion criteria, should continue that treatment throughout the trial with no changes of dose unless for safety reason.

**Trial products:**
Investigational Medicinal Products:

- Test products: Insulin degludec (Tresiba®) 100 U/ml, 3 ml PDS290 pen injector (FlexTouch®)
- Reference therapy: Insulin glargine (Lantus®) 100 U/ml, 3 mL pre-filled pen injector (SoloStar®)

# 2 Flowchart

| | | | Treatment period 1 | | | | | | | | | | Treatment period 2 | | | | | | | | | | End of treatment | Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screening | Run-in | Randomisation | Titration period 1 | | | | | | | Maintenance period 1 | | Titration period 2 | | | | | | | | Maintenance period 2 | | | |
| Visit | V1 | V2 | V3 | P4-P6 | V7 | P8-P10 | V11 | P12-P14 | V15 | P16-P18 | V19 | P20 | V21 | P22-P24 | V25 | P26-P28 | V29 | P30-P32 | V33 | P34-P36 | V37 | P38 | V39 | P40 |
| Timing of Visit (Weeks) | -4 | -2 | 0 | 1-3 | 4 | 5-7 | 8 | 9-11 | 12 | 13-15 | 16 | 17 | 18 | 19-21 | 22 | 23-25 | 26 | 27-29 | 30 | 31-33 | 34 | 35 | 36 | 37 |
| Visit Window (Days) | +10 | -3 | 0 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | +5 |
| SUBJECT RELATED INFORMATION AND ASSESSMENTS | | | | | | | | | | | | | | | | | | | | | | | | |
| Informed consent | X | | | | | | | | | | | | | | | | | | | | | | | |
| Demography[1] | X | | | | | | | | | | | | | | | | | | | | | | | |
| In/exclusion criteria | X | X | | | | | | | | | | | | | | | | | | | | | | |
| Run-in exclusion criteria | | X | X | | | | | | | | | | | | | | | | | | | | | |
| Childbearing potential | X | | | | | | | | | | | | | | | | | | | | | | | |
| Hypoglycaemia Unawareness[2] | X | | | | | | | | | | | | | | | | | | | | | | | |
| Concomitant illness/medical history | X | | | | | | | | | | | | | | | | | | | | | | | |
| Concomitant medication | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Concomitant medication (diabetes) | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Diabetes complications | X | | | | | | | | | | | | | | | | | | | | | | | |
| Diagnosis of diabetes | X | | | | | | | | | | | | | | | | | | | | | | | |
| Body measurements | X | | X | | | | | | | | | | X | | | | | | | | | | X | |

[1] Demography consists of date of birth or year of birth, sex, ethnicity and race (according to local regulation see Appendix 7).

[2] Information on hypoglycaemia unawareness will be recorded according to Clarke's questionnaire, question 8[2]. The investigator must ask the subject in the following way: "To what extent can you tell by your symptoms that your blood glucose is low?" Subjects answering 'never, rarely or sometimes' are considered to have impaired awareness of hypoglycaemia

| | | | Treatment period 1 | | | | | | | | | | Treatment period 2 | | | | | | | | | | End of treatment | Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screening | Run-in | Randomisation | Titration period 1 | | | | | | | Maintenance period 1 | | Titration period 2 | | | | | | | | Maintenance period 2 | | | |
| Visit | V1 | V2 | V3 | P4-P6 | V7 | P8-P10 | V11 | P12-P14 | V15 | P16-P18 | V19 | P20 | V21 | P22-P24 | V25 | P26-P28 | V29 | P30-P32 | V33 | P34-P36 | V37 | P38 | V39 | P40 |
| Timing of Visit (Weeks) | -4 | -2 | 0 | 1-3 | 4 | 5-7 | 8 | 9-11 | 12 | 13-15 | 16 | 17 | 18 | 19-21 | 22 | 23-25 | 26 | 27-29 | 30 | 31-33 | 34 | 35 | 36 | 37 |
| Visit Window (Days) | +10 | -3 | 0 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | +5 |
| Randomisation criteria | | | X | | | | | | | | | | | | | | | | | | | | | |
| Discontinuation/Withdrawal criteria | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| EFFICACY | | | | | | | | | | | | | | | | | | | | | | | | |
| Pre-breakfast SMPG (3 days prior to next contact) | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | |
| HbA1c | X | | X | | X | | X | | X | | X | | X | | X | | X | | X | | X | | X | |
| SAFETY | | | | | | | | | | | | | | | | | | | | | | | | |
| Adverse event | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Medication Error | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Technical Complaints | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Biochemistry | X | | | | | | | | | | | | X | | | | | | | | | | X | |
| Pregnancy test | X | | | | | | | | | | | | | | | | | | | | | | | |
| Vital signs | X | | X | | | | | | | | | | X | | | | | | | | | | X | |
| Physical examination | X | | X | | | | | | | | | | X | | | | | | | | | | X | |
| Eye examination | X | | | | | | | | | | | | | | | | | | | | | | | |
| OTHER ASSESSMENTS | | | | | | | | | | | | | | | | | | | | | | | | |
| FGM Sensor Data | | | | | | | | | | | | | | | | | | | | | | | | |
| FGM fitting | | X | | | | | | | | | X | | | | | | | | | | X | | | |

| | | | Treatment period 1 | | | | | | | | | | Treatment period 2 | | | | | | | | | | End of treatment | Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
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| FGM removal[3] | | | X | | | | | | | | | | X | | | | | | | | | | X | |
| PRO questionnaires | | | | | | | | | | | | | | | | | | | | | | | | |
| Diabetes Pen Experience Measure | | X | X | | | | | | | | | | X | | | | | | | | | | X | |
| TRIM-diabetes device | | | X | | | | | | | | | | X | | | | | | | | | | X | |
| Confirmation of unchanged OADs | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| TRIAL MATERIAL | | | | | | | | | | | | | | | | | | | | | | | | |
| Dose of trial insulin | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Dispensing visit | | | X | | X | | X | | X | | X | | X | | X | | X | | X | | X | | | |
| Drug accountability | | | X | | X | | X | | X | | X | | X | | X | | X | | X | | X | | X | |
| REMINDERS | X | | X | | X | | X | | X | | X | | X | | X | | X | | X | | X | | X | X |
| IWRS session | X | | X | | X | | X | | X | | X | | X | | X | | X | | X | | X | | X | |
| Hand out ID card | X | | | | | | | | | | | | | | | | | | | | | | | |
| Hand out and instruct in Pro device | | X | | | | | | | | | X | | | | | | | | | | X | | | |
| Hand out directions for use | | | X | | | | | | | | | | X | | | | | | | | | | | |
| Training in trial product, pen-handling | | | X | | | | | | | | | | X | | | | | | | | | | | |
| Hand out and instruct in BG-meter | | | X | | | | | | | | | | | | | | | | | | | | | |
| Hand out and instruct in diary | | | X | | X | | X | | X | | X | | X | | X | | X | | X | | X | | | |

[3] Confirmation that 14 days data have been collected should be obtained, as described in section 9.1.1.4

| | | | Treatment period 1 | | | | | | | | | | Treatment period 2 | | | | | | | | | | End of treatment | Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
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| Visit Window (Days) | +10 | -3 | 0 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | +5 |
| Collect diary | | | | | X | | X | | X | | X | | X | | X | | X | | X | | X | | X | |
| First date on trial product | | | X | | | | | | | | | | X | | | | | | | | | | | |
| First dose on trial product | | | X | | | | | | | | | | X | | | | | | | | | | | |
| Cross-over | | | | | | | | | | | | | X | | | | | | | | | | | |
| Last date on trial product | | | | | | | | | | | | | X | | | | | | | | | | X | |
| Last dose on trial product | | | | | | | | | | | | | X | | | | | | | | | | X | |
| End of treatment | | | | | | | | | | | | | | | | | | | | | | | X | |
| End of trial | | | | | | | | | | | | | | | | | | | | | | | | X |
| Sign-off case-book | | | | | | | | | | | | | | | | | | | | | | | | X |

# 3 Introduction

## 3.1 Trial rationale

The overall purpose of this trial is to investigate how insulin degludec (IDeg) influences glycaemic control compared to insulin glargine 100U/mL (IGlar 100U/mL), using FGM.
Since significant technical improvements have been made in the precision, accuracy, and usability of modern, continuous or flash, glucose monitoring devices, their relevance in ambulatory diabetes care is increasing. These devices, measuring glucose concentration in interstitial fluid, are widely used in clinical practice, considered an established part of diabetes management and will be increasingly used going forward [4] [5] . Data on IDeg, generated by modern glucose monitoring technique, are therefore repeatedly asked for by key opinion leaders and health care professionals.

Furthermore, as the efficacy and safety of IDeg has been evaluated in an extensive clinical development programme[6]; the purpose of this trial is not to focus on hypoglycaemia risk, evaluated by hypoglycaemia forms, but rather to evaluate if the previously shown hypoglycaemia benefits with IDeg translate into more time in glycaemic target range 70-180 mg/dL (3.9-10.0 mmol/L) less hypoglycaemia and lower glycaemic variability versus the comparator.

Finally as the safety profiles of both investigational medicinal products are well characterised, a selective safety data collection approach will be used[7].

## 3.2 Background

### 3.2.1 Therapeutic area – type 2 diabetes mellitus

T2DM is characterised by insulin resistance, impaired insulin secretion, increased hepatic glucose output due to glucagon dysregulation and thus chronic hyperglycaemia[8]. A number of landmark studies have demonstrated the importance of maintaining tight glycaemic control to reduce the risk of long-term complications associated with diabetes[9].

The current treatment cascade follows a stepwise approach comprising of lifestyle changes in combination with pharmacological intervention. Metformin is recommended as initial pharmacological therapy, followed by combination therapy with other OADs, GLP-1 receptor agonists or insulin as the disease progresses[10].

### 3.2.2 Insulin degludec

IDeg is an insulin analogue with unique pharmacological properties and a long duration of action, beyond 42 hours[11]. IDeg provides similar glycaemic control to comparators with a 14–18% lower risk of confirmed hypoglycaemia and a 23–38% lower risk of nocturnal confirmed hypoglycaemia compared to IGlar 100U/mL in T2DM (phase 3a trials)[12, 13]. Moreover, in the SWITCH 2 trial (T2DM, phase 3b trial) IDeg was associated with a 23% lower risk of overall confirmed

symptomatic hypoglycaemia, a 25% lower risk of nocturnal confirmed symptomatic hypoglycaemia and a 51% lower risk of severe hypoglycaemia compared to IGlar 100U/mL[11]. The hypoglycaemic risk reduction for IDeg compared to glargine 100 U/mL was more pronounced in the maintenance period in all trials[11] [12] [13].

IDeg is developed in two strengths (100 U/mL and 200 U/mL) that are demonstrated to be bio-equivalent in clinical pharmacology trials. IDeg has been approved in more than 90 countries globally and is indicated for treatment of diabetes mellitus as monotherapy, in combination with oral anti-diabetic agents and GLP-1 receptor agonist, and as part of a basal-bolus insulin regimen in adults and children from the age of 1 year (GLP-1 receptor agonist co-usage and paediatric indication <18 years is not an approved indication in all countries with market authorisation). For further details please refer to the current version of the IDeg IB[6] and any updates thereof, and local labelling.

### 3.2.3 Insulin glargine 100U/mL

IGlar 100U/mL is a long-acting insulin analogue, indicated for treatment of diabetes mellitus in combination with oral antidiabetic agents and as part of a basal-bolus insulin regimen[14] [15].

### 3.2.4 Flash Glucose Monitoring

The FreeStyle Libre Pro FGM system will be used in this trial and referred as FGM system.
It is a CGM system, FDA approved and European Union European Conformity (CE) labelled. It is indicated for detecting trends and tracking patterns in persons (age 18 and older) with diabetes (see Operator's manual).

The FGM sensor, applied on the subject's upper back arm, uses wired enzyme technology for tracking glucose concentration in the body's interstitial fluid. The sensor is factory calibrated and will not require calibration by the subjects[16].

The FGM reader will show continuous glucose measurements retrospectively at time of scanning of the sensor, allowing identification of intra and interday glycaemic excursions[17].

## 3.3 Benefit-risk assessment

The main expected benefit for the subjects participating in this trial is the potential improved glycaemic control under an optimised basal treatment. This aim will be achieved with a recommended titration 'basal insulin dose adjusted algorithm' at different plasma glucose levels.

The individual subjects will receive medical care with close contact to the clinical sites (i.e. weekly contacts) and the anticipated treatment regimen is expected to be equal to or better than the previous treatment regimen experienced before trial initiation. However, subjects will have to spend some extra time monitoring and recording data (e.g. SMPG values) every day as well as in connection to visits to the clinic and phone contacts.

The high frequency of contacts between the subject/investigator and the thorough evaluation of SMPG values will provide the opportunity for optimising the titration of basal insulin based on SMPG values and thereby contributing to obtain improved glycaemic control.

The anticipated side effects are associated with the known and established safety profile of the registered trial products (e.g.: hypoglycaemia, hypersensitivity reactions for the basal insulins) and FGM sensor (mild local skin irritation for the FGM sensor's adhesive patch). The side effects will be mitigated by the close supervision of the trial subjects.

The maximum trial duration for each subject is approximately 41 weeks and the treatment duration for a subject is planned to be 36 weeks.

Trial products will be provided by Novo Nordisk free of charge during the subjects' participation in the trial. Subjects will receive IDeg and IGlar 100U/mL in prefilled pens. Subjects will also receive a glucose meter including auxiliaries as well as diaries for reporting of SMPGs and insulin doses.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of IDeg and IGlar 100U/mL may be found respectively in the current version of:

- insulin degludec IB[18]
- insulin glargine 100U/ml SmPC[14], US Prescribing Information[15], or local labelling
- FreeStyle Libre Pro Operator's manual

Based on the above, it can be concluded that the clinical benefits outweigh the potential risks for subjects participating in this trial.

# 4 Objectives and endpoints

## 4.1 Primary, secondary and exploratory objective(s)

The primary objective is to compare the effect on glycaemic control of IDeg versus IGlar 100U/mL in a population of T2DM subjects with or without OADs, using FGM.

**Estimand:**
The primary estimand is the treatment difference between IDeg and IGlar 100U/mL with respect to percent time spent in glycaemic target range for all randomised subjects that can use the FGM sensor and adhere to at least 18 weeks of treatment on both insulins. An intercurrent event for the primary estimand include lack of effect from any of the insulins leading to a need for initiation of other diabetes medication(s). As described in section 8.1 in the protocol, treatment intensification may result in trial discontinuation. . The primary estimand will handle these intercurrent events as withdrawals and only use data from completers. The primary estimand is the principle stratum direct effect for the population of completers.

The population level summary statistics is the average percent of time spent in glycaemic target during maintenance for completers. For comparing the two treatments the relevant summary is the difference in the means.

## 4.2 Primary, secondary and exploratory endpoints

### 4.2.1 Primary endpoint

Percentage of time spent in glycaemic target range 70-180 mg/dL (3.9–10.0 mmol/L) both inclusive, during the 2-week maintenance period using FGM (Visit 19-21 (week 16-17) and Visit 37-39 (week 34-35)).

### 4.2.2 Secondary endpoints

#### 4.2.2.1 Confirmatory secondary endpoints

N/A

#### 4.2.2.2 Supportive secondary endpoints

- Percentage of time spent in tight glycaemic target range 70-140 mg/dL (3.9–7.8 mmol/L) both inclusive, during the 2-week maintenance periods using FGM (Visit 19-21 (week 16-17) and Visit 37-39 (week 34-35)).

- Percentage of time spent in nocturnal glycaemic target range 70-140 mg/dL (3.9-7.8 mmol/L) both inclusive, in the nocturnal period (00:01 am – 05:59 am both inclusive) during the 2-week maintenance periods using FGM (Visit 19-21 (week 16-17) and Visit 37-39 (week 34-35)).

- $HbA_{1c}$ (% and mmol/mol) after two weeks of maintenance periods (Visit 19-21 (week 16-17) and Visit 37-39 (week 34-35)).

- Mean glucose levels (mg/dL and mmol/L) during the 2-week maintenance periods using FGM (Visit 19-21 (week 16-17) and Visit 37-39 (week 34-35)).

### 4.2.3 Exploratory endpoints

- Glycaemic variability calculated as standard deviation (mg/dL and mmol/L) and coefficient of variation (% ) of glucose levels during the 2-week maintenance treatment using FGM (Visit 19-21 (week 16-17) and Visit 37-39 (week 34-35)).

- Mean insulin dose (IU) during the 2-week maintenance treatment period (Visit 19-21 (week 16-17) and Visit 37-39 (week 34-35)).

- Percentage of time spent in the hypoglycaemia alert range (Level 1) 54-69 mg/dL (3.0-3.8 mmol/L) both inclusive, during the 2-week maintenance periods using FGM (Visit 19-21 (week 16-17) and Visit 37-39 (week 34-35)).

- Percentage of time spent in the clinically significant hypoglycaemic range (Level 2) <54mg/dL (<3.0 mmol/L) during the 2-week maintenance periods using FGM (Visit 19-21 (week 16-17) and Visit 37-39 (week 34-35)).

- Number of clinically significant hypoglycaemic episodes (Level 2) <54mg/dL (<3.0 mmol/L) for at least 15 minutes during the 2-week maintenance periods using FGM (Visit 19-21 (week 16-17) and Visit 37-39 (week 34-35)).

- Number of clinically significant hypoglycaemic episodes (Level 2) <54mg/dL (<3.0 mmol/L) for at least 15 minutes in the nocturnal period (00:01-05:59 AM, both inclusive) during the 2-week maintenance periods using FGM (Visit 19-21 (week 16-17) and Visit 37-39 (week 34-35)).

# 5 Trial design

## 5.1 Overall design

This trial is a 41-week, randomised, cross-over, open-label, multi-center, active controlled trial comparing the effect of insulin IDeg versus insulin IGlar 100U/mL, with or without OADs in subjects with type 2 diabetes using flash glucose monitoring.

The trial includes a screening visit (Visit 1), followed by a 2-week run-in period for eligibility assessment in regards to adherence to FGM requirements. At randomisation (Visit 3), eligible subjects will be randomised 1:1 into one of two treatment periods receiving either IDeg or IGlar 100U/mL. Each treatment period consist of a 16-week titration period followed by a 2-weeks maintenance period where subjects will wear the FreeStyle Libre Pro Sensor.
After the first titration and maintenance period the subject will switch to the other trial product, with dose adjustment according to local label, performing the same assessments as in the first treatment period (16-week titration period followed by a 2-weeks maintenance period).

For details of the dosing of IDeg and IGlar 100U/mL, refer to Appendix 8.

The follow-up period is 1 week.

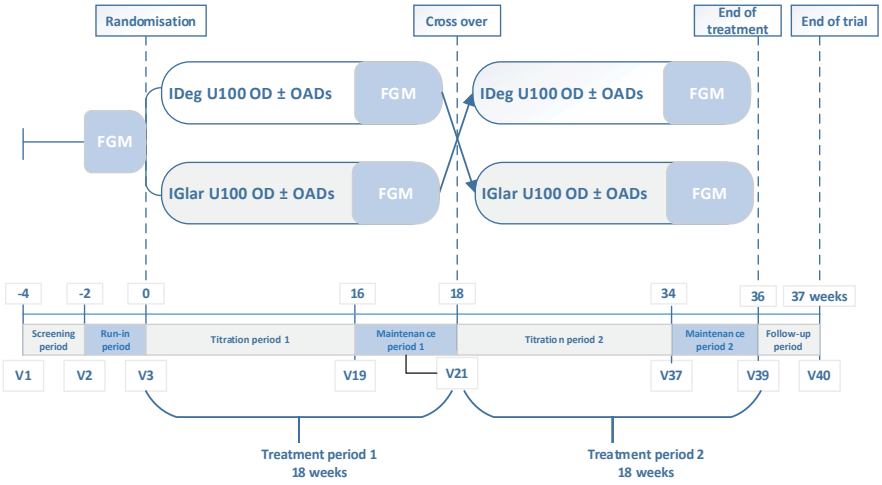


**Figure 1 Trial design**

## 5.2 Subject and trial completion

Approximately 674 subjects will be screened to achieve 472 subjects randomly assigned to trial product.
Approximately 502 subjects are planned to be included in the run-in period.

**Trial period completion for a subject:**
Trial period completion is defined as when the randomised subject has completed the final scheduled visit ('end of trial' according to the flowchart).
'Date of trial completion' is the date the subject completed the final scheduled visit.

**Treatment period completion for a subject:**
Treatment period completion is defined as when the randomised subject has received the required treatment, and attended the 'end of treatment' visit according to the flowchart.

The treatment period 1 starts at Visit 3 and is defined as when the randomised subject has received the required treatment for at least 18 weeks and attended Visit 21 according to the flowchart.

The treatment period 2 starts at Visit 21 and is defined as when the randomised subject has received the required treatment for at least 18 weeks and attended Visit 39 according to the flowchart.

**Required treatment:**
Completion of both treatment periods is required for contribution to the analysis. Only the data from subjects completing 16 weeks of titration and 2 weeks of maintenance wearing the FreeStyle Libre Pro device, with both trial products, will be used in the outcome analyses.

## 5.3 End of trial definition

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

## 5.4 Scientific rationale for trial design

The cross-over design is chosen to reduce the number of subjects needed to obtain sufficient power.

An open labelled trial design is chosen to minimize inconvenience for the subjects as IDeg and IGlar 100U/mL are presented in different pen injector systems. Full blinding would require a double dummy approach or the use of syringes and needles.

The trial population are adult male and female subjects with T2DM with an HbA1c equal or below 9.5% while treated with any basal insulin with or without OADs for at least 90 days, and who recently have experienced hypoglycaemia or have increased risk of severe hypoglycaemia. This population is chosen in order to reflect a general T2DM population, not excluding subjects with a high risk of hypoglycaemia.

Subjects requiring treatment with basal and bolus are not included to avoid the confounding element of bolus insulin.

A 16 weeks titration period is selected as data from previous IDeg trials demonstrate that subjects previously treated with basal insulin ± OADs can achieve improved and stable HbA1c levels within 16 weeks of titration[11].
The treat-to-target approach will be applied in both treatment arms in order to optimise titration and glycaemic control throughout the trial according to Appendix 8. The treat to target trial requires good subject's adherence, thus subjects with an HbA1c above 9.5% have been excluded as poor compliance is a likely cause of elevated HbA1c amongst the T2DM population.

A body mass index (BMI) limit of $\leq 45.0$ kg/m$^2$ includes as broad a population as possible while excluding very obese individuals who might be extremely insulin resistant.

Subjects with unstable proliferative retinopathy requiring acute treatment, hepatic or severe renal impairment or uncontrolled severe hypertension and subjects who with the 26 weeks prior to screening have experienced a cardiovascular event as defined in the exclusion criteria are not eligible for inclusion in this trial due to the treat-to-target approach and their need for more individualised therapy.

## 5.5 Justification for dose

At randomisation (Visit 3) pre-trial insulin treatments will be discontinued and eligible subjects are randomised 1:1 into one of two treatment sequences:

- IDeg OD ± OADs followed by IGlar 100U/mL OD ± OADs
- IGlar 100U/mL OD ± OADs followed by IDeg OD ± OADs

At randomisation and at cross over, subjects will initiate treatment according to local labels, no maximum trial insulin dose is specified.
The dosing time should preferably be kept throughout the entire treatment period.
Both IMPs should be injected subcutaneously into the thigh, upper arm (deltoid area) or the abdomen. The chosen region should be the same throughout the trial for each trial product. Rotation of injection sites within a given region is recommended

Subject treated with one or more allowed OAD(s), see inclusion criteria, Section 6.1, should continue their pre-trial OAD(s) treatment throughout the trial, with no change of dose unless for safety reasons.

# 6 Trial population

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

## 6.1 Inclusion criteria

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

1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial
2. Male or female, age ≥ 18 years at the time of signing informed consent
3. Diagnosed with type 2 diabetes mellitus ≥ 180 days prior to the day of screening
4. Subjects fulfilling at least one of the below criteria:
    a. Experienced at least one severe hypoglycaemic episode within the last year prior to screening (according to the ADA definition, January 2018) *
    b. Moderate renal impairment defined as estimated glomerular filtration rate (eGFR) value of 30-59 mL/min/1.73 $m^2$ as defined by KDIGO 2012[1] at screening
    c. Known hypoglycaemic unawareness as indicated by the investigator according to Clarke's questionnaire question 8[2] at screening
    d. Treated with insulin for more than 5 years
    e. Episode of hypoglycaemia (defined by a glucose alert value of 70 mg/dL (3.9 mmol/L) or less, i.e. Level 1)[3] within the last 12 weeks prior to screening visit
5. Treated with any basal insulin ≥ 90 days prior to the day of screening with or without any of the following anti-diabetic drugs :
    a. Metformin
    b. Dipeptidyl peptidase-4 inhibitor
    c. Sodium-glucose co-transporter 2 inhibitor
    d. Alpha-glucosidase-inhibitors (acarbose)
    e. Thiazolidinediones

f. Marketed oral combination products only including the products listed in criteria 5a-5e

6. HbA1c ≤9.5% (80 mmol/mol) at screening confirmed by central laboratory analysis
7. BMI ≤ 45 kg/m2

*Hypoglycaemia associated with severe cognitive impairment requiring external assistance for recovery

### 6.2 Exclusion criteria

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

**1.** Known or suspected hypersensitivity to trial product(s) or related products.
**2.** Previous participation in this trial. Participation is defined as signed informed consent.
**3.** Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using adequate contraceptive methods (adequate contraceptive measures as required by local regulation or practice).
**4.** Receipt of any investigational medicinal product within 4 weeks before screening.
**5.** Any disorder which in the investigator's opinion might jeopardise subject's safety or compliance with the protocol.
**6.** Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria within the past 90 days prior to the day of screening. However, intermittent bolus insulin treatment for periods of no longer than 14 days are permitted prior to the day of screening.
**7.** Anticipated initiation or change in concomitant medications known to affect weight or glucose metabolism (e.g. treatment with orlistat, thyroid hormones, or corticosteroids).
**8.** Uncontrolled and potentially unstable diabetic retinopathy or maculopathy. Verified by a pharmacologically pupil-dilated fundus examination performed by an ophthalmologist or another suitably qualified health care provider within the past 90 days prior to screening or in the period between screening and run-in
**9.** Presence or history of malignant neoplasms within the past 5 years prior to the day of screening. Basal and squamous cell skin cancer and any carcinoma in-situ are allowed.
**10.** Any of the following: myocardial infarction, stroke, hospitalisation for unstable angina pectoris or transient ischaemic attack within the past 180 days prior to the day of screening
**11.** Inadequately treated blood pressure defined as Grade 3 hypertension or higher (Systolic ≥180 mmHg or diastolic ≥100 mmHg) at screening.
**12.** Impaired liver function defined as Alanine Aminotransferase (ALT) ≥2.5 times or Bilirubin >1.5 times upper normal limit at screening.
**13.** Renal impairment defined as estimated glomerular filtration rate (eGFR) value of eGFR <30 mL/min/1.73m$^2$ as defined by KDIGO 2012[1] at screening
**14.** Anticipated change in lifestyle affecting glucose control.
**15.** Currently using real time CGM or FGM system

## 6.3 Lifestyle restrictions

Change in lifestyle affecting glucose control must be avoided throughout the trial.

While wearing the FGM sensor, subjects will be asked to comply with requirements described in Section 9.1.1.4.

## 6.4 Screen failures

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

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

## 6.5 Run in exclusion criteria

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

1. Included in the trial in violation of the inclusion and/or exclusion criteria
2. Pregnancy
3. Intention of becoming pregnant
4. Simultaneous participation in another clinical trial of an approved or non-approved investigational medicinal product
5. Initiating use of real time CGM or FGM other than use specified by protocol

## 6.6 Run in failures

Run-in failures are defined as subjects who are not eligible to be randomised (i.e. has met one of the run-in exclusion criteria or has not met the randomisation criteria).
A screen failure session must be made in the IWRS and the screening failure form must be completed in the eCRF together with the reason for not continuing in the trial.

No follow-up visit should take place and no additional assessments are needed. SAEs from run-in failures must be recorded by the investigator in the eCRF. Follow-up of SAEs must be carried out according to Appendix 4

### 6.7 Randomisation criteria

To be randomised, the following randomisation criteria must be answered "yes":

1. Subject able and willing to adhere to the protocol including requirements and tolerability in regards to wearing the FreeStyle Libre Pro sensor, based on the investigator's opinion.

# 7 Treatments

## 7.1 Treatments administered

### 7.1.1 Investigational medicinal products

- Trial products must only be used, if it appears clear and colourless.
- Only needles provided or approved by Novo Nordisk must be used for administration of trial product.
- The investigator must document that directions for use are given to the subject orally and in writing at the first dispensing visit.

**Table 1 Trial products provided by Novo Nordisk A/S**

| **Trial product name:** | Insulin degludec (Tresiba®) 100 U/mL (IMP, test product) | Insulin glargine (Lantus®) 100 U/ml (IMP, reference therapy) |
|---|---|---|
| **Dosage form:** | Solution for injection | Solution for injection |
| **Route of administration:** | Subcutaneous | Subcutaneous |
| **Recommended initial dose/Unit dose strength(s)/ Dosage level(s):** | Initial dose according to local label. Changes of dose according to Appendix 8. | Initial dose according to local label. Changes of dose according to Appendix 8 |
| **Dosing instructions:** | Once daily | Once daily |
| **Packaging** | 3 ml PDS290 pen injector (FlexTouch®) | 3 mL pre-filled pen injector (SoloStar®) |

### 7.1.2 Non-investigational medicinal products

The following Non-Investigational Medicinal Products (NIMPs) will not be supplied by Novo Nordisk. However, they will be reimbursed if required according to local regulations.

- Metformin, tablets for oral use
- DPP-4i, tablets for oral use
- SGLT2i, tablets for oral use
- Thiazolidinedione, tablets for oral use
- Alpha-glucosidase-inhibitor, tablets for oral use
- Tablets for oral use of marketed combination products only including the products listed above.

For Slovakia-please see Appendix 7 for Country-specific requirements

## 7.2 Medical devices

Non-investigational medical device(s):

- Novo Nordisk needles for pen injectors (not longer than 6mm)
- Blood glucose (BG) meter and auxiliaries
- FGM devices (FreeStyle Libre Pro sensor and reader) and auxiliaries

Complaints related to the needles should be reported to local Novo Nordisk affiliate with a reference to trial ID (see Appendix 6).

For complaints related to the BG meter or the FGM devices, the investigator must contact the device manufacturer's technical support according to operator's manual provided with the devices (see Appendix 4).

**Training in BG meter**:
At randomisation (Visit 3) subjects will be provided with a BG meter including auxiliaries and instructions for use. The subjects will be instructed in how to use the devices as indicated in the flowchart.

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

**Training in FGM devices**:
Novo Nordisk will ensure that trial site staffs receive appropriate training in regards to the use of the FGM devices. Furthermore site staff should familiarise themselves with the FGM operator's manual before using the FGM devices.

Before each FGM period, subjects must be instructed according to Section 9.1.1.4 as indicated in the flowchart (Section 2).

## 7.3 Dose modification

The dosing time should preferably be kept throughout the entire treatment period.

Local labelling requirements will be used at randomisation and cross over to initiate treatment.
No maximum trial insulin dose is specified.
Insulin doses are adjusted according to blood/plasma glucose values as described in Appendix 8.
Surveillance of insulin titration will be performed by Novo Nordisk.

Diaries will be handed out at all clinics visits as indicated in the flowchart (Section 2) to report SMPG measurements and insulin doses as described in Sections 9.1.2 and 9.5. The recommended insulin doses will be individually calculated in the eCRF based on the SMPG measurements and the doses taken in accordance with the titration guideline described in Appendix 8.

### 7.4 Method of treatment assignment

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

### 7.5 Blinding

This is an open-label trial and the specific treatment for a subject will be assigned using an IWRS. The site will access the IWRS before the start of trial product administration for each subject.

### 7.6 Preparation/Handling/Storage/Accountability

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

- Each trial site will be supplied with sufficient trial products for the trial on an on-going basis controlled by the IWRS. Trial product will be distributed to the trial sites according to screening and randomisation.
- The investigator must confirm that appropriate temperature conditions have been maintained during transit for all trial products received and any discrepancies are reported and resolved before use of the trial products.
- All trial products must be stored in a secure, controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.
- The investigator must inform Novo Nordisk immediately if any trial product has been stored outside specified conditions. Additional details regarding handling of temperature deviations can be found in the TMM.
- Trial product that has been stored improperly must not be dispensed to any subject before it has been evaluated and approved for further use by Novo Nordisk.
- The investigator is responsible for drug accountability and record maintenance (i.e. receipt, accountability and final disposition records).
- Drug accountability should be performed at pen level per DUN.
- Destruction of trial products can be performed on an ongoing basis and will be done according to local procedures after accountability is finalised by the site and reconciled by the monitor.
- Destruction of trial products must be documented in the IWRS.

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

- The FGM sensors distributed to the sites will have to be stored according to Table 2 and temperature monitoring is required.

**Table 2 FreeStyle Libre Pro sensor storage conditions**

| Device name | Storage conditions (not-in-use) | In-use conditions | In-use time[b] |
|---|---|---|---|
| Freestyle Libre Pro sensor | Store (4°C – 25°C / 39°F - 77°F)<br>Do not freeze | - | Up to 14 days |

[b] In-use time starts when sensor has been fitted

## 7.7 Treatment compliance

Throughout the trial, the investigator will remind the subjects to follow the trial procedures and requirements to ensure subject compliance. Furthermore, the investigator will at each visit assess the subject's compliance by evaluating the glycaemic control, adherence to the visit schedule and completion of the subject's diaries. If a subject is found to be non-compliant the investigator will remind the subject of the importance of following the instructions given including taking the trial products as prescribed.

## 7.8 Concomitant medication

Any medication other than the trial products that the subject is receiving at the time of the first visit or receives during the trial must be recorded along with:

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

Changes in concomitant medication must be recorded at each visit; this includes changes of dose for subjects treated with OADs. If a change is due to an AE/SAE then this must be reported according to Section 9.2.

## 7.9 Treatment after the end of the trial

When discontinuing trial products the subject should be transferred to a suitable marketed product at the discretion of the investigator.

# 8 Discontinuation/Withdrawal criteria

The subject may be discontinued at any time during the trial at the discretion of the investigator for safety, behavioural, compliance or administrative reasons.
A subject may also withdraw consent at any time at his/her own request.

If a subject is discontinued or withdraws consent, the investigator must ask the subject if he/she is willing, as soon as possible, to have assessment performed according to Visit 39 and phone contact P40. See the flowchart Section 2 for data to be collected.

## 8.1 Discontinuation from trial

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

1. Included in the trial in violation of the inclusion/exclusion/run-in exclusion criteria or randomised in violation of the randomisation criteria
2. Pregnancy
3. Intention of becoming pregnant
4. Simultaneous participation in another clinical trial of an approved or non-approved investigational medicinal product.
5. Initiation of bolus insulin treatment, GLP-1 receptor agonists or other diabetes medication(s) for more than 14 continuous days.
6. Initiating use of real time CGM or FGM other than use specified by protocol

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

## 8.2 Withdrawal from the trial

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

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

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

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

### 8.2.1 Replacement of subjects

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

### 8.3 Lost to follow-up

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

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

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the trial.
- Before a subject is deemed lost to follow-up, the investigator must make every effort to regain contact with the subject (where possible, at least three telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's source document.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the trial with a primary reason of lost to 'follow -up' and discontinued in IWRS.

# 9 Trial assessments and procedures

- Trial procedures and their timing are summarised in the flowchart.
- Informed consent must be obtained before any trial related activity, see Appendix 3.
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria.
- The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reason for screen failure, as applicable.
- At screening, subjects will be provided with a card stating that they are participating in a trial and giving contact details of relevant trial site staff.
- Adherence to the trial design requirements, including those specified in the flowchart, is essential and required for trial conduct.
- Compliance with the FGM requirement should be evaluated at Visit 3 after the run-in period and after each maintenance period to ensure collection of data to perform analysis of the primary endpoint.
- Review of completed diaries, PRO questionnaires and laboratory reports must be documented either on the documents or in the subject's source documents. If clarification of entries or discrepancies in the diaries or PRO questionnaires is needed, the subject must be questioned and a conclusion made in the subject's source documents. Care must be taken not to bias the subject.

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

## 9.1 Efficacy assessments

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

### 9.1.1 FGM

As indicated in the flow chart in Section 2, all subjects will have FGM profiles generated 3 times during the trial.

The FGM system used in this trial will be the FreeStyle Libre Pro system which consists of two parts:

- the sensor, applied on the back of the subjects' upper arm
- the reader, a hand held device kept at site and used to download data stored on the sensor

The sensor is pre-calibrated during manufacturing and requires no fingerstick calibration during use. The sensor measurements performed in the interstitial fluid are automatically calibrated to plasma equivalent glucose values, which will be shown on the display of the reader upon download of sensor data.

The FGM readings will be blinded to the subject as the reader will be kept at site. Upon download of FGM data at site, the investigator or delegated staff should review the FGM data for safety considerations taking into account all information detailed in the Operator's manual.

The FGM values generated should not be used for insulin dose titration.

#### 9.1.1.1 FGM Reader setting

Each site will receive 2 readers; one to activate all subjects' sensors and download of their data and one as backup.

The FGM reader must be set up before use. The set up includes:

- date and time setting
- entry of the target glucose range. The range 70-180 mg/dL (3.9–10.0 mmol/L) should be used.

Time and date as well as level of battery should be verified each time the reader is used.

#### 9.1.1.2 Fitting and removal of the FGM sensor

Before the first fitting visit (Visit 2), subjects' eligibility must be confirmed.
The sensor must be applied on the back of the upper arm of the subjects, using the sensor applicator as described in the Operator's manual. When applied, a thin, flexible and sterile fibre is inserted just under the skin of the subjects, allowing the measurement of glucose concentration in the interstitial fluid.

The sensor must be activated by holding the site reader within 4cm (1.5inch) of the sensor. Successful start of the sensor must be checked as described in the Operator's manual.

The sensor will store the subject's glucose readings every 15 minutes for up to 14 days.

For further information on preparing, fitting, and removal of the FGM system, please refer to the Operator's manual.

If a subject withdraws consent during one of the FGM periods, a site visit must be scheduled in order to remove the sensor and download data to the reader.

#### 9.1.1.3 Duration of FGM periods

The sensor has an in-use period of 14 days and will automatically stop recording data 14 days after insertion and activation.
As the data accuracy may vary during the first 24 hours after sensor fitting, the FGM data from the 1st day (24h) of each sensor period will be excluded from analysis.

**Subjects must aim to use the sensor for 14 days in-use period**.
**In cases where the sensor is dislodged prematurely, the subject must be fitted with a new sensor as soon as possible. The cumulative number of day's data collected by the sensors must be a minimum of 14 days**.

Additional fitting visit at site will not be considered an unscheduled visit.

*For example: if the first sensor falls off 8 days after fitting, the subject then must be fitted with a second sensor to be worn for at least 6 days to obtain a total of 14 days of data.*

**At Visit 21 and Visit 39, it must be confirmed that a total of 14 days of data have been recorded, before subjects are switched to the other IMP or end treatment**.

#### 9.1.1.4 Wearing of the FGM sensor

Before each FGM periods, subjects must be instructed to follow the recommendations and limitations described in the Operator's manual and user guide while wearing the FGM sensor.

Subjects must be instructed to remove the FGM sensor prior to any X-ray, Computerised Tomography (CT) scan, high-frequency electrical heat (diathermy) treatment or magnetic resonance imaging (MRI).

The FGM periods should be conducted on days representing the subject's normal daily life.
Before each FGM period, investigator or site staff should evaluate with subjects if planned activities would require the FGM assessments to be postponed (e.g. vacations, unusual strenuous exercise, overseas travel etc.).

**FGM periods should not be planned across local daylight saving clock shifts to avoid major impact on time related endpoints, and subjects must be instructed to avoid overnight travel across time zones while wearing the FGM.**

#### 9.1.1.5 Transfer of FGM data

Data stored on the sensor must be downloaded at the site by holding the reader within 4cm (1.5inch) of the sensor. Data on the reader device must then be uploaded to the provided FGM Software program that allows upload of the FGM data from the reader, following the instructions from the user guide provided to sites.
The upload will be documented by the system directly.

The following information must be recorded and transferred into the eCRF for every FGM period:

- Serial number of the FGM sensor
- Sensor activation date and time
- Sensor removal date and time

The investigator or delegated staff must ensure that at least 14 days of data have been recorded according to Section 9.1.1.3. This can be done either on the reader or after upload of FGM data.
The FGM data can be shared with the subject after each FGM period. In case several sensors are used within each FGM period, the data should only be shared once when all needed data have been downloaded from the reader, according to Section 9.1.1.3.

### 9.1.2 Self-measured plasma glucose

Subjects must be instructed to perform pre-breakfast SMPG on the two days prior to, and on the day of the visit/contacts, from Visit 3 to Visit 39.
The BG meter provided by Novo Nordisk must be used for the measurements required in the protocol.

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

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

### 9.1.3 Clinical efficacy laboratory assessments

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

## 9.2 Adverse events

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

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

As the safety profile of the investigational medicinal products are well characterized, in this trial the selective safety data collection[7] will be limited to:

- SAEs
- AEs leading to permanent discontinuation of the IMP
- Medication errors related to trial products
- Pregnancies

The investigator must ensure that the above will be recorded in the CRF in a timely manner.

### 9.2.1 Time period and frequency for collecting AE and SAE information

All events meeting the definition of an SAE (see Appendix 4), AEs leading to permanent discontinuation of the IMP, pregnancies and medication errors related to trial products must be collected and reported.

These events will be collected from the first trial-related activity after obtaining informed consent and until the end of trial visit, at the time points specified in the flowchart. All SAEs will be recorded and reported to Novo Nordisk or designee within 24 hours of investigator's knowledge of the SAE, as indicated in Appendix 4. The investigator must submit any updated SAE data to Novo Nordisk within 24 hours of it being available.

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

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

Medications errors related to trial products require additional data collection via a specific event form.

Timelines for reporting of AEs are listed in Figure 2.

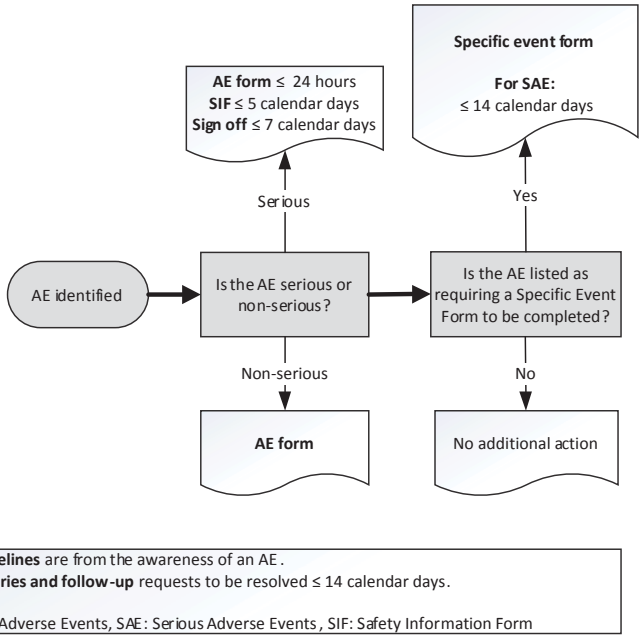


**Figure 2 Decision tree for determining the event type and the respective forms to complete with associated timelines**

### 9.2.2 Method of detecting AEs and SAEs

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

### 9.2.3 Follow-up on AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, or if the event is otherwise explained (e.g. chronic condition) or the subject is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 4.

### 9.2.4 Regulatory reporting requirements for SAEs

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

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

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Novo Nordisk policy and forwarded to investigators as necessary.

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

### 9.2.5 Cardiovascular and death events

Not applicable.

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

Not applicable.

### 9.2.7 Pregnancies and associated adverse events

Details of pregnancies in female subjects will be collected after the first-trial-related activity after obtaining informed consent and until pregnancy's outcome and the new-born infant is one month of age.

If a pregnancy is reported in female subjects, the investigator should inform Novo Nordisk within 14 calendar days of learning of the pregnancy and should follow the procedures outlined in and Figure 3 and Appendix 5.

Pregnancy outcome should be documented in the subject's medical record. Abnormal pregnancy outcome (e.g. spontaneous abortion, foetal death, stillbirth, congenital anomalies and ectopic pregnancy) is considered an SAE.

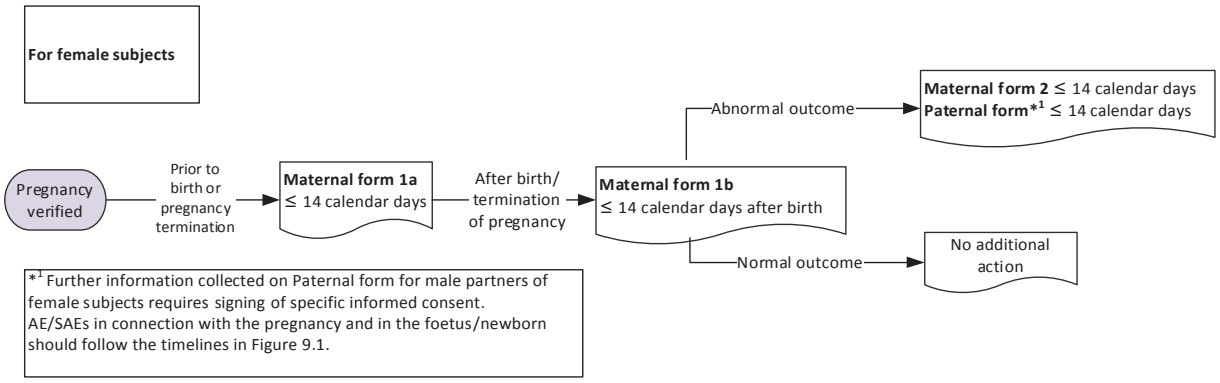


**Figure 3 Decision tree for determining the forms to complete with associated timelines for pregnancy**

### 9.2.8 Medical device incidents (including malfunctions)

Not applicable.

### 9.2.9 Technical complaints

Technical complaints will be collected for all trial products listed on the technical complaint form..

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

## 9.3 Treatment of overdose

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

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

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

For more information on overdose, also consult the current version of the IDeg investigator's brochure[18] and SmPC of Insulin IGlar 100U/mL (Lantus®)[14].

## 9.4 Safety assessments

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

A **concomitant illness** is any illness that is present at the start of the trial or found as a result of a screening procedure or other trial procedures performed before exposure to trial product.
**Medical history** is a medical event that the subject has experienced in the past.

Diabetes history and related complications should be reported separately in the diabetes history/complication form.

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

### 9.4.1 Physical examinations

- A physical examination will include assessments of:
  - Head, Ears, Eyes, Nose, Throat and Neck
  - Respiratory System
  - Cardiovascular System
  - Musculoskeletal System
  - Central and Peripheral Nervous System
  - Skin
- Body measurements will also be measured and recorded as specified in the flowchart.
  - Body weight should be measured in kilogram (kg) or pounds (lb) without coat and shoes wearing only light clothing. Body weight will be recorded to one decimal.
  - Height should be assessed without shoes. Height is measured in inches or centimetres at Visit 1 and recorded to the nearest whole number
  - From the body weight and height the BMI will be calculated in the eCRF.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

### 9.4.2 Vital signs

- Pulse rate as well as diastolic and systolic blood pressure will be assessed.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the subject in a quiet setting without distractions (e.g. television, cell phones).
- Blood pressure at screening will consist of 3 diastolic and systolic blood pressure measurements with intervals of at least 1 minute. All three readings must be entered in the eCRF and the average of the 3 blood pressure readings will be calculated in the eCRF. At the subsequent visits, the blood pressure should only be measured once.
- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

### 9.4.3 Clinical safety laboratory assessments

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

### 9.4.4 Eye Examination

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

Results of an eye examination performed by an ophthalmologist, or another suitably qualified health care provider must be available and evaluated by the investigator before run-in (Visit 2) to assess eligibility. The eye examination should be performed as a fundus photography (e.g. 2-field 60 degree or better, colour or red-free) or by slit-lamp biomicroscopy examination (e.g. using a pre-corneal or corneal contact lens examination) and performed with pharmacologically dilated pupils.

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

### 9.4.5 Pharmacokinetics

Not applicable.

### 9.4.6 Pharmacodynamics

Not applicable.

### 9.4.7 Genetics

Not applicable.

### 9.4.8 Biomarkers

Not applicable.

## 9.5 Insulin dose

During the trial, starting at the randomisation visit (Visit 3), subjects must be instructed to report date and dose of basal insulin in the diaries on the two days prior to, and on the day of the visit/contacts, from Visit 3 to Visit 39.
The recommended insulin doses will be calculated based on recommendations from the Titration Guideline (see Appendix 8) as described in Section 7.3. The investigator must record the following in the eCRF, for each treatment period:

- First date, dose and injection time of trial product
- Last date, dose and injection time of trial product

### 9.6 Health economics – PRO questionnaires

The Patient Reported Outcome (PRO) questionnaires are to be completed by the subject without assistance of the site personnel. Review of the PRO questionnaires must be documented either on the document and/or in the subject's medical record. If clarification of entries is needed, the subject must be questioned and a conclusion made in the subject's medical record. Care must be taken not to bias the subject.

Following PRO questionnaires must be completed according to the flowchart (see Section 2):

- Treatment related impact measure for diabetes device (TRIM-DD)
- Diabetes Pen Experience Measure (DPEM)

Data will be summarized by item and visit by pooling the two treatment arms.
The rationale for the PRO assessment is to collect data for psychometric validation of the newly developed DPEM questionnaire. The psychometric analyses will examine reliability, responsiveness, and validity of the DPEM questionnaire. Data from the TRIM-D questionnaire data will be used in the psychometric analysis, to show that data from the DPEM questionnaire correlates as hypothesized. All results will be published and reported in the DPEM questionnaire development dossier.

## 10 Statistical considerations

### 10.1 Sample size determination

The sample size calculation is based on the primary objective for the primary estimand and the primary endpoint of the trial, and is performed as a paired-sample calculation in terms of the mean and standard deviation of the within pair difference within the PP using the paired t-test. Only one previous Novo Nordisk trial using CGM has had a similar design: NN1250-3874 comparing IDeg and IGlar 100U/mL in 24 T1DM subjects using a cross-over design. Regarding time in glycaemic target range (70-180 mg/dL) during the full 24 hours of the day, the within pair difference between IDeg and IGlar 100U/mL had a mean of 0.39 hours and a standard deviation of 2.3. Two previous Novo Nordisk studies have used CGM in T2DM subjects in parallel arm designs, NN1250-3579 and NN1250-3668. However, CGM technology used in those two T2DM trials is outdated compared to the devices used in the current trial, and they are therefore deemed irrelevant as to guidance on expected difference between the two treatments in this trial. The results from the NN1250-3874 trial are used for sample size calculation despite the differences from the present trial, i.e. indication and length of maintenance treatment. A conservative standard deviation of 2.6 is used. To detect a mean difference of 0.39 with 85% power with a standard deviation of 2.6 based on a paired t-test and 1:1 randomisation requires 401 subjects included in the PP. See Table 3 for

sample sizes based on a range of standard deviation and for mean differences of 0.39 and 0.5 respectively.

In the SWITCH 2 trial (NN1250-3998), which had a similar cross-over trial design, 72.1% (721/1000) of the screened subjects were randomised and 80% (580/721) completed treatment in both periods. Part of the drop-out in SWITCH 2 was due to the inconvenience caused by the blinded vial and syringes which is not an issue in the present trial. Also, SWITCH 2 was considerably longer than the current trial with 16 weeks long maintenance periods. Furthermore, the current trial has a run-in period ensuring familiarity with and acceptance of the FGM device. We therefore assume that only 15% will not complete both periods on treatment and, thus, that 85% will end in PP. Hence, we will randomise 1:1 a total of 401/0.85=472 subjects (236 in each sequence) and we expect to screen app. 472/0.7=674 subjects. According to the ADA criteria, 70% of readings, equivalent to 10 days, should be available for a subject to be included in the analysis. We expect that nearly all completers will live up to this and therefore do not adjust the number of subjects needed to account for this.

**Table 3 Sample size and power for various standard deviations and effects**

| | Effect | |
|---|---|---|
| **SD** | 0.39 | 0.50 |
| 2.0 | 239 | 146 |
| 2.3 | 315 | 192 |
| 2.6 | 401 | 245 |

Sample size is computed for 1:1 randomisation and 85% power. SD: standard deviation.

### 10.2 Definition of analysis sets

The full analysis set is all subjects randomised at Visit 3. The safety analysis set is all subjects that are randomised and treated with at least one dose of trial drug after randomisation. The PP analysis set consists of subjects that stay on assigned treatment until and complete FGM assessment at visits 21 and 39 respectively.

### 10.3 Statistical analyses

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

#### 10.3.1 Primary endpoint

The primary endpoint is the percentage of time spent in glycaemic target range (70-180 mg/dL (3.9-10.0 mmol/L), both inclusive) during the 2-week maintenance period. The FreeStyle Libre Pro device stores four measurements per hour and a subject with complete data will contribute with 14*24*4=1344 measurements from each 2-week period. The analysis will discard data from the

first 24 hours as per communication with the vendor and so subjects with complete data will contribute with 13*24*4=1248 glucose recordings. The number of recorded measurements may be smaller for various reasons for subjects in the PP analysis set. Following ADA criteria we will demand that at least 70% of two weeks FGM measurements, corresponding to 10 days of FGM data, must be available for subjects to be included in the analysis. The percentage of time spent in glycaemic target range will be calculated as the number of recorded measurements in glycaemic target range (70-180 mg/dL (3.9-10.0 mmol/L), both inclusive) divided by the total number of recorded measurements.

The primary estimand will be estimated by the primary endpoint analysed in a linear mixed model with treatment and period as fixed effects, subject as a random effect and with an unstructured residual variance matrix.

Using the unblinded data and before DBL, visual tools will be used to determine whether the data, including the primary endpoint, are normally distributed. If it is then found that the data are not normal, an appropriate transformation will be performed and this will be documented in a SAP or the DBL minutes.

Superiority of IDeg OD compared to IGlar 100U/mL OD with respect to percentage of time spent in glycaemic target range will be considered confirmed if non-inferiority is confirmed and the lower limit of the two-sided 95% confidence interval of the difference (IDeg OD - IGlar 100U/mL OD) is entirely above zero or equivalently if the p-value for the one-sided test of

H0: $D \leq 0\%$ against HA: $D > 0\%$

is smaller than 2.5%, where D is the estimated mean difference of time spent in glycaemic target range (IDeg OD - IGlar 100U/mL OD). As such, a fixed hierarchical testing procedure will be applied, which will effectively adjust for multiple testing.

Non-inferiority will be evaluated by comparing the lower limit of the t wo-sided 95% confidence interval for the difference between IDeg and IGlar 100U/mL to a non-inferiority margin of 0.2h/24h (0.83%). If the lower CI limit is above -0.83%, non-inferiority will be considered established.

Missing data due to intercurrent events such as trial discontinuation are not relevant since the primary estimand is based on the PP analysis set.

A sensitivity analysis will be performed to account for heteroscedasticity due to a varying number of FGM readings within the 70% demand. The primary endpoint will be transformed using inverse variance weighting. Specifically, the primary endpoint will be multiplied by a weight calculated as the inverse of the square root of the total number of FGM readings.

An additional sensitivity analysis will be performed where all subjects who have FGM readings for at least seven consecutive days will be included. Inverse variance weighting will be performed as described previously.

### 10.3.2 Secondary endpoints

Supportive secondary endpoints

Percentage of time spent in tight glycaemic target range (70-140 mg/dL (3.9-7.8 mmol/L), both inclusive is calculated in the same way as the primary endpoint using the relevant ranges. A sensitivity analysis using the inverse of the square root of the number of FGM readings as inverse variance weights to account for heteroscedasticity due to a varying number of FGM readings will be performed.

Percentage of time spent in nocturnal glycaemic target range 70-140 mg/dL (3.9-7.8 mmol/L) both inclusive, in the nocturnal period (00:01 am–05:59 am both inclusive) will be calculated in the same way as the primary endpoint but only using readings with a time stamp in the relevant time period. A sensitivity analysis using the inverse of the square root of the number of FGM readings in the relevant time period as inverse variance weights to account for heteroscedasticity due to a varying number of FGM readings will be performed.

All the supportive secondary endpoints regarding time spent in target range are analysed and tested in the same model as the primary endpoint, i. e. one sided tests of the mean difference favouring IDeg must be statistically significantly different from zero at the 0.025 level to support superiority.

As stated in Section 9.1.1.4, sites are instructed not to initiate FGM monitoring periods that will contain daylight saving clock shifts. During data analysis it will be checked if this rule is obeyed, and the length of both the entire day in question in general, and the nocturnal period in question in particular will be adjusted equivalently when it is not. For example, if a subject is under FGM monitoring in the US on 11-MAR-2018 the nocturnal period will start at 00:01AM and end at 04:59 (nominal sensor time) instead of 05:59. In the data analysis one hour will be added to the recorded time points from 02:00 and onwards. In practise then, 11-MAR-2018 will consist of no more than 23h of FGM readings, and the nocturnal period of no more than 4h and 58 minutes of FGM readings. If on the other hand a subject is under FGM monitoring on 04-NOV-2018 in the US one hour will be deducted from the time recorded time points. This will then consist of no more than 25 hours of FGM readings, and the nocturnal period of no more than 6h and 58 minutes of FGM readings. The hour between 01:00-02:00 on 04-NOV will be represented twice in the data, and to separate them an auxiliary variable stating if a time reading is in the daylight saving period or not will be added to all FGM readings.

The mean glucose levels (mg/dL and mmol/L) will be calculated as the mean of the FGM glucose levels and analysed by models and test equivalent to the primary endpoint. A sensitivity analysis

using the inverse of the square root of the total number of FGM readings as inverse variance weights will be performed to account for heteroscedasticity due to a varying number of readings pr subject pr. period.

Mean HbA1c values will be analysed using a similar model as compared to the primary endpoint, but only a single two-sided test for statistically significant differences between IDeg and IGlar 100U/mL will be performed.

### 10.3.3 Exploratory endpoints

Glycaemic variability will be calculated as the standard deviation (mg/dL and mmol/L) and coefficient of variation (%) of the FGM glucose levels during the 2-week maintenance treatment periods. Both will be analysed and tested with models and tests equivalent to the primary endpoint.

Mean insulin dose in international units is calculated as the mean dose over the maintenance treatment periods for each subject. It will be analysed and tested using models and tests equivalent to the primary endpoint.

Percentage of time spent in the hypoglycaemic alert range (54-69 mg/dL (3.0-3.8 mmol/l), both inclusive) and percentage of time spent in the clinically significant hypoglycaemic range (<54 mg/dL (<3.0 mmol/L)) are calculated in the same way as the primary endpoint using the relevant ranges. A sensitivity analysis using the inverse of the square root of the number of FGM readings as inverse variance weights to account for heteroscedasticity due to a varying number of FGM readings will be performed.

All the exploratory endpoints regarding time in range are analysed and tested in the same model as the primary endpoint, i. e. one sided tests of the mean difference favouring IDeg must be statistically significantly different from zero at the 0.025 level to support superiority.

Number of hypoglycaemic episodes <54 mg/dL (<3.0 mmol/L) for at least 15 minutes and number of hypoglycaemic episodes <54mg/dL (<3.0 mmol/L) for at least 15 minutes in the nocturnal period (00:01-05:59 AM, both inclusive) will be counted as follows: At least two consecutive FGM glucose readings (i.e., readings that follow each other continuously in time) in the specified range are counted as a hypoglycaemic episode. Two hypoglycaemic episodes must be separated by at least 15 minutes above the hypoglycaemic range, equivalent to 2 consecutive FGM readings above the relevant hypoglycaemic range to be counted as two or more episodes instead of one. For the nocturnal episodes, only FGM readings in the relevant period will be used. Person years of exposure (PYE) will be calculated as

PYE=(N_FGM*15 minutes)/(365.25 days/year*(24 hours)/day*(60 minutes)/hour)

where N_FGM is the total number FGM readings in the relevant period. The number of hypoglycaemic episodes will be analysed using a negative binomial regression with treatment and

period as fixed effects, subject as a normally distributed random effect and the log(PYE) as an offset. A p-value smaller than 0.025 for the one sided test of the rate ratio in favour of IDeg will be considered as support for superiority of IDeg over IGlar 100U/mL. If this model does not converge, a Poisson regression model will be fitted.

### 10.4 Pharmacokinetic and/or pharmacodynamic modelling

Not applicable

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# 12 Appendices

## Appendix 1 Abbreviations and Trademarks

| | |
|---|---|
| ADA | American Diabetes Association |
| AE | adverse event |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| BG | blood glucose |
| CGM | continuous glucose monitoring |
| (e)CRF | (electronic) case report form |
| CTR | clinical trial report |
| DUN | dispensing unit number |
| eGFR | estimated glomerular filtration rate |
| FDA | U.S. Food and Drug Administration |
| FDAAA | FDA Amendments Act |
| FGM | flash glucose monitoring |
| FSH | follicle-stimulating hormone |
| GCP | Good Clinical Practice |
| GLP-1 | glucagon-like peptide-1 |
| HbA1c | glycated haemoglobin |
| hCG | human chorionic gonadotropin |
| HRT | hormone replacement therapy |
| IB | investigator's brochure |
| ICH | International Council for Harmonisation |
| ICMJE | International Committee of Medical Journal Editors |
| IEC | independent ethics committee |
| IMP | investigational medicinal product |
| IRB | institutional review board |
| IUD | intrauterine device |
| IUS | intrauterine hormone-releasing system |
| IWRS | interactive web response system |

| | |
|---|---|
| LSFT | last subject first treatment |
| NIMP | non-investigational medical product |
| OAD(s) | oral anti-diabetic drug(s) |
| OD | once daily |
| PCD | primary completion date |
| PP | per protocol |
| PRO | patient reported outcome |
| PYE | person years of exposure |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SMPC | summary of product characteristics |
| SMPG | self-measured plasma glucose |
| SUSAR | suspected unexpected serious adverse reaction |
| T2DM | type 2 diabetes mettilus |
| TMM | trial materials manual |
| WOCBP | woman of child bearing potential |

# Appendix 2 Clinical laboratory tests.

- The tests detailed in Table 4 and Table 5 will be performed by the central laboratory.
- Additional tests may be performed at any time during the trial as determined necessary by the investigator or required by local regulations. Only laboratory samples specified in the protocol should be sent to the central laboratory for analysis; if additional laboratory sampling is needed, e.g. to follow up on AEs, this must be done at a local laboratory.
- The laboratory equipment may provide analyses not requested in the protocol but produced automatically in connection with the requested analyses according to specifications in the laboratory standard operating procedures. Such data will not be transferred to the trial database, but abnormal values will be reported to the investigator.
- The investigator must review all laboratory results for concomitant illnesses and AEs.
- Laboratory samples will be destroyed after analysis on an ongoing basis.

**Table 4 Protocol-required effect laboratory assessments**

| Laboratory assessments | Parameters |
|---|---|
| Glucose metabolism | • $HbA1_c$ |

**Table 5 Protocol-required safety laboratory assessments**

| Laboratory assessments | Parameters |
|---|---|
| Biochemistry[1] | • Alanine Aminotransferase (ALT)<br>• Albumin<br>• Alkaline phosphatase<br>• Aspartate Aminotransferase (AST)<br>• Creatinine<br>• Potassium<br>• Sodium<br>• Bilirubin |
| Pregnancy Testing | • Serum or urine human chorionic gonadotropin (hCG) pregnancy test (for WOCBP) |
| Other tests | • eGFR calculated by the central laboratory based on the creatinine value using the CKD-EPI equation |
| Notes :<br>[1]Details of required actions for increased liver parameters are given in Appendix 4 (Hy's Law) | |

# Appendix 3 Trial governance considerations

**1) Regulatory and ethical considerations**

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

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki[19] and applicable ICH Good Clinical Practice (GCP) Guideline[20]
- Applicable laws and regulations
- The protocol, informed consent form, investigator's brochure (as applicable) and other relevant documents (e.g. advertisements), must be submitted to an IRB/IEC and reviewed and approved by the IRB/IEC before the trial is initiated.
- Regulatory authorities will receive the clinical trial application, protocol amendments, reports on SAEs, and the clinical trial report according to national requirements.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the trial design, except for changes necessary to eliminate an immediate safety hazard to trial subjects.
- Before a trial site is allowed to start screening subjects, written notification from Novo Nordisk must be received.
- The investigator will be responsible for:
    - providing written summaries of the status of the trial annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC and/or regulatory authorities
    - notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
    - providing oversight of the conduct of the trial at the site and adherence to requirements of ICH guidelines, the IRB/IEC, and all other applicable local regulations
    - ensuring submission of the clinical trial report (CTR) synopsis to the IRB/IEC.

**2) Financial disclosure**

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

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

**3) Informed consent process**

- The investigator or his/her representative will explain the nature of the trial to the subject and answer all questions regarding the trial.
- The investigator must ensure the subject ample time to come to a decision whether or not to participate in the trial.
- Subjects must be informed that their participation is voluntary.
- Subjects will be required to sign and date a statement of informed consent that meets the requirements of local regulations, ICH guidelines[20], Declaration of Helsinki[19] and the IRB/IEC or trial site.
- The medical record must include a statement that written informed consent was obtained before any trial related activity and the date when the written consent was obtained. The authorised person obtaining the informed consent must also sign and date the informed consent form before any trial related activity.
- The responsibility of seeking informed consent must remain with the investigator, but the investigator may delegate the task of informing to a medically qualified person, in accordance with local requirements.
- Subjects must be re-consented to the most current version of the informed consent form(s) during their participation in the trial.
- A copy of the informed consent form(s) must be provided to the subject

**4) Information to subjects during trial**

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

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

**5) Data protection**

- Subjects will be assigned a 6-digit unique identifier, a subject number which will remain the same throughout the trial. Each site is assigned a 3-digit number and all subject numbers will start with the site number. Any subject records or datasets that are transferred to Novo Nordisk will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.
- The subject and any biological material obtained from the subject will be identified by subject number, visit number and trial ID. Appropriate measures such as encryption or

leaving out certain identifiers will be enforced to protect the identity of subjects as required by local, regional and national requirements, for Canada please see Appendix 7.
- The subject must be informed that his/her personal trial related data will be used by Novo Nordisk in accordance with local data protection law. The disclosure of the data must also be explained to the subject.
- The subject must be informed that his/her medical records may be examined by auditors or other authorised personnel appointed by Novo Nordisk, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

**6) Committee structure**

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

**7) Publication policy**
The information obtained during the conduct of this trial is considered confidential, and may be used by or on behalf of Novo Nordisk for regulatory purposes as well as for the general development of the trial product. All information supplied by Novo Nordisk in connection with this trial shall remain the sole property of Novo Nordisk and is to be considered confidential information.

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

Novo Nordisk may publish on its clinical trials website a redacted clinical trial report for this trial. One investigator will be appointed by Novo Nordisk to review and sign the clinical trial report (signatory investigator) on behalf of all participating investigators.

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

The results of this trial will be subject to public disclosure on external web sites according to international and national regulations. Novo Nordisk reserves the right to defer the release of data until specified milestones are reached, for example when the clinical trial report is available. This

includes the right not to release the results of interim analyses, because the release of such information may influence the results of the entire trial.

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

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

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

Authorship of publications should be in accordance with the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals by the International Committee of Medical Journal Editors[21].

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

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

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

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

**8) Dissemination of clinical trial data**

Information of the trial will be disclosed at clinicaltrials.gov and novonordisk-trials.com. It will also be disclosed according to other applicable requirements such as those of the International Committee of Medical Journal Editors (ICMJE)[22], the Food and Drug Administration Amendment Act (FDAAA)[23], European Commission Requirements[24] [25] and other relevant recommendations or regulations. If a subject requests to be included in the trial via the Novo Nordisk e-mail contact at these web sites, Novo Nordisk may disclose the investigator's contact details to the subject. As a result of increasing requirements for transparency, some countries require public disclosure of investigator names and their affiliations.

The Primary Completion Date (PCD) is the last assessment of the primary endpoint, and is for this trial Last Subject First Treatment (LSFT) + 36 weeks corresponding to visit 39. If the last subject is withdrawn early, the PCD is considered the date when the last subject would have completed visit 39. The PCD determines the deadline for results disclosure at clinicaltrials.gov according to FDAAA.

**9) Data quality assurance**

**Case Report Forms (CRFs)**

- Novo Nordisk or designee is responsible for the data management of this trial including quality checking of the data.
- All subject data relating to the trial will be recorded on electronic CRFs unless transmitted electronically to Novo Nordisk or designee (e.g. laboratory and FGM data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- eCRF will be used in this trial, as well as diaries to capture subject reported data
- The following will be provided as paper CRFs:
    - Pregnancy forms
- The following will be provided as paper CRFs to be used when access to the CRF is revoked or the CRF is temporarily unavailable:
    - AE forms
    - Safety information forms
    - Technical complaint forms (also to be used to report complaints that are not subject related, e.g. discovered at trial site before allocation)
- Corrections to the CRF data may be made by the investigator or the investigator's delegated staff. An audit trail will be maintained in the CRF application containing as a minimum: the old and the new data, identification of the person entering the data, date and time of the entry and reason for the correction. If corrections are made by the investigator's delegated staff after the date when the investigator signed the CRF, the CRF must be signed and dated again by the investigator.

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

**Monitoring**

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

- Trial monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorised site personnel are accurate, complete and verifiable from source documents; that the safety and rights of subjects are being protected, to monitor drug accountability and collect completed paper CRF pages, if applicable, and that the trial is being conducted in accordance with the currently approved protocol and any other trial agreements, ICH GCP, and all applicable regulatory requirements.

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

- Monitors will review the subject's medical records and other source data e.g. the diaries and PROs, to ensure consistency and/or identify omissions compared to the CRF.

**Protocol compliance**

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

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

**10) Source documents**

- All data entered in the CRF must be verifiable in source documentation other than the CRF.
- The original of the completed diaries and PROs must not be removed from the trial site, unless they form part of the CRF and a copy is kept at the site.
- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the trial site.

- Data reported on the paper CRF or entered in the electronic CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records. Also, current medical records must be available.
- It must be possible to verify subject's medical history in source documents such as subject's medical record.
- The investigator must document any attempt to obtain external medical information by noting the date(s) when information was requested and who was contacted.
- Definition of what constitutes source data can be found in a source document agreement at each trial site. There will only be one source document defined at any time for any data element.
- The database hosted by the supplier is considered source data for the laboratory and FGM data during the trial.

**11) Retention of clinical trial documentation**

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

**12) Trial and site closure**

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

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

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

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

**13) Responsibilities**

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

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

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

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

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

## 14) Indemnity statement

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

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

Novo Nordisk accepts liability in accordance with:

- The Civil Code and the Pharmaceutical Law dated 6 September 2001 (uniform version Journal of Laws of 2008 No.45 item 271 with amendments) for Poland, please see Appendix 7.

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

| **AE definition** |
|---|
| • An AE is any untoward medical occurrence in a clinical trial subject that is temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.<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 meeting the AE definition** |
| • Any abnormal laboratory test results or safety assessments, including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.<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 NOT meeting the AE definition** |
| • Pre-existing conditions, anticipated day-to-day fluctuations of pre-existing conditions, including those identified during screening or other trial procedures performed before exposure to trial product.<br>Note: pre-existing conditions should be recorded as medical history/concomitant illness.<br><br>• Pre-planned procedures, unless the condition for which the procedure was planned has worsened from the first trial related activity after the subject has signed the informed consent. |

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

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

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

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

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

**Medication error:**

A medication error concerning trial products is defined as:

- Administration of wrong drug.
  Note: Use of wrong DUN is not considered a medication error unless it results in a confirmed administration of wrong drug.
- Wrong route of administration, such as intramuscular instead of subcutaneous.
- Administration of an overdose with the intention to cause harm, misuse or abuse of trial product.
- Accidental administration of a lower or higher dose than intended: That is a dose lower or higher than 20%' of the prescribed/intended dose; however, the administered dose must deviate from the intended dose to an extent where clinical consequences for the trial subject were likely to happen as judged by the investigator, although they did not necessarily occur.

**AE and SAE recording**

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

| **Assessment of severity** |
|---|
| The investigator will assess intensity for each event reported during the trial and assign it to one of the following categories:<br>• **Mild**: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.<br>• **Moderate**: An event that causes sufficient discomfort and interferes with normal everyday activities.<br>• **Severe**: An event that prevents normal everyday activities.<br>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.<br><br>Relationship between an AE/SAE and the relevant trial product*(s)* should be assessed as:<br><br>• Probable - Good reason and sufficient documentation to assume a causal relationship.<br>• Possible - A causal relationship is conceivable and cannot be dismissed.<br>• Unlikely - The event is most likely related to aetiology other than the trial product.<br><br>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.<br><br>The investigator should use the current version of investigator's brochure for IDeg and (or) SmPC for comparator 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 with alternative aetiology whenever applicable.<br><br>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**.<br><br>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.<br><br>The causality assessment is one of the criteria used **when determining regulatory reporting requirements**. |

| **Final outcome** |
|---|
| The investigator will select the most appropriate outcome:<br>• **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.<br>• **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.<br>• **Recovered/resolved with sequelae:** The subject has recovered from the condition, but with lasting effect due to a disease, injury, treatment or procedure. If a sequelae meets an SAE criterion, the AE must be reported as an SAE.<br>• **Not recovered/not resolved:** The condition of the subject has not improved and the symptoms are unchanged or the outcome is not known. |

- **Fatal:** This term is only applicable if the subject died from a condition related to the reported AE. Outcomes of other reported AEs in a subject before he/she died should be assessed as "recovered/resolved", "recovering/resolving", "recovered/resolved with sequelae" or "not recovered/not resolved". An AE with a fatal outcome must be reported as an SAE.
- **Unknown:** This term is only applicable if the subject is lost to follow-up.

**Follow-up of AE and SAE**

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

New or updated information will be recorded in the CRF.

**SAE reporting via electronic CRF**

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

**SAE reporting via paper CRF**

- Relevant CRF forms (AE and safety information form) must be forwarded to Novo Nordisk either by fax, e-mail or courier.
- Initial notification via telephone is acceptable, although it does not replace the need for the investigator to complete the AE and safety information form within the designated reporting time frames (as illustrated in Figure 2):
  - AE form within 24 hours.
  - Safety information form within 5 calendar days.
  - Both forms must be signed within 7 calendar days.

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

**Reporting of AEs for Non-Novo Nordisk medical devices provided by Novo Nordisk for use in the trial**

Reporting of AEs on:

- FreeStyle Libre Pro device and supplies
- BG meter device and supplies.

All complaints (including AEs) should be reported directly to the manufacturer.

# Appendix 5 Contraceptive guidance and collection of pregnancy information

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

**Definitions**

**Woman of Childbearing Potential (WOCBP)**

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

**Women in the following categories are not considered WOCBP**

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

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

**Contraception guidance**

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

**Table 6 Highly effective contraceptive methods**

| **Highly effective contraceptive methods that are user dependent** [a]<br>Failure rate of <1% per year when used consistently and correctly. |
|---|
| • Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation b<br>• oral |

| |
|---|
| • intravaginal<br>• transdermal |
| Progestogen only hormonal contraception associated with inhibition of ovulation<br>• oral<br>• injectable |
| **Highly effective methods that are user independent** [a] |
| Implantable progestogen only hormonal contraception associated with inhibition of ovulation [b]<br>• Intrauterine Device (IUD)<br>• Intrauterine hormone-releasing System (IUS)<br>• Bilateral tubal occlusion |
| **Vasectomised partner**<br>A vasectomised partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. |
| **Sexual abstinence**<br>Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial product. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject. |
| Notes:<br>[a]Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical trials.<br>[b]Hormonal contraception may be susceptible to interaction with the trial product, which may reduce the efficacy of the contraceptive method. In this case, two highly effective methods of contraception should be utilised during the treatment period and for at least 7 days after the last dose of trial product. |

### Table 7 Acceptable effective contraceptive methods

| **Acceptable effective contraceptive methods**[a] |
|---|
| Failure rate of >1% per year when used consistently and correctly<br>• Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action.<br>• Male or female condom with or without spermicide<br>• Cap, diaphragm or sponge with spermicide |
| Note:<br>[a]Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical trials. |

## Pregnancy testing

- WOCBP should only be included after a negative highly sensitive serum pregnancy test.
- Additional urine pregnancy testing should be performed at monthly intervals during the treatment period, if required locally.
- Pregnancy testing should be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

**Collection of pregnancy information**

**Female subjects who become pregnant**

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

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

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

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

Examples of technical complaints:

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

| **Time period for detecting technical complaints** |
|---|
| • All technical complaints, which occur from the time of receipt of the product at trial site until the time of the last usage of the product, must be collected for products predefined on the technical complaint form. |
| **Reporting of technical complaints to Novo Nordisk** |
| Contact details (fax, e-mail and address) for Customer Complaint Center – refer to Attachment I<br>Technical complaints must be reported on a separate technical complaint form:<br>1. One technical complaint form must be completed for each affected DUN<br>2. If DUN is not available, a technical complaint form for each batch, code or lot number must be completed |
| **Timelines for reporting of technical complaints to Novo Nordisk** |
| The investigator must complete the technical complaint form in the CRF within 24 hours if related to an SAE. All other technical complaints with or without associated AEs within 5 calendar days. If the CRF is unavailable or when reporting a technical complaint that is not subject related, the information must be provided on a paper form by fax, e-mail or courier to Customer Complaint Center, Novo Nordisk, within the same timelines as stated above. When the CRF becomes available again, the investigator must enter the information on the technical complaint form in the CRF. |
| **Follow-up of technical complaints** |
| The investigator is responsible for ensuring that new or updated information will be recorded on the originally completed form. |
| **Collection, storage and shipment of technical complaint samples** |
| The investigator must collect the technical complaint sample and all associated parts that were packed in the same DUN and notify the monitor within 5 calendar days of obtaining the sample at trial site. The sample and all associated parts must be sent as soon as possible to Customer Complaint Center, Novo Nordisk, together with a copy of the completed technical complaint form. The technical complaint sample should contain the batch, code or lot number and, if available, the DUN. If the technical complaint sample is unobtainable, the reason must be stated on the technical complaint form. If several samples are shipped in one shipment, the sample and the corresponding technical complaint form should be kept together.<br>Storage of the technical complaint sample must be done in accordance with the conditions prescribed for the product. |
| **Reporting of technical complaints for Novo Nordisk products not included in technical complaint form** |
| Technical complaints on Novo Nordisk products not included in the technical complaint form should be reported to local Novo Nordisk affiliate with a reference to trial ID. |

# Appendix 7 Country-specific requirements

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

- For Slovakia: It is necessary that the Trial Sponsor covers all costs for treatment of the disease studied. It is necessary to cover the whole diabetes medication, payment for insulin, OADs listed in Inclusion criteria no. 5 and rescue medication, if used.

# Appendix 8 Titration guideline

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

**Initiation of trial products**

IGlar 100U/mL and IDeg should be injected subcutaneously into the thigh, upper arm (deltoid area) or the abdomen. The chosen region should be the same throughout the trial for each trial products. Rotation of injection sites within a given region is recommended.

Both IMPs should be taken once daily any time of the day, but at the same time every day.

At randomisation (Visit 3) subjects will initiate treatment according to local label for the relevant IMP. At cross-over (Visit 21) the subjects should switch according to local label for the relevant IMP.

**Dose adjustment of trial products during the trial**

After randomisation the insulin dose will be evaluated and possibly adjusted once weekly by the investigator in connection with the scheduled visits/phone contacts during the titration periods.

The dose adjustment will be based on the mean of three fasting SMPG values measured on two days prior to titration and on the day of the visit/contacts according to Table 8. If one of the SMPG values is below target (<3.9 mmol/L or 70 mg/dL) then dose adjustment will be based on the lowest SMPG values according to Table 9.

If one or more SMPGs values are missing, the adjustment should be performed on the remaining SMPG value(s).

**Table 8 Increase of insulin dose**

| Mean pre-breakfast SMPG values | | Increase of basal insulin dose |
|---|---|---|
| mmol/L | mg/dL | U |
| **3.9 – 5.0** | **70 – 90** | **No adjustment** |
| 5.1 – 7.0 | 91 – 126 | + 2 |
| 7.1 – 8.0 | 127 – 144 | + 4 |
| 8.1 – 9.0 | 145 – 162 | + 6 |
| > 9.0 | > 162 | + 8 |

**Table 9 Reduction of insulin dose**

| Lowest pre-breakfast SMPG value | | Reduction of basal insulin dose |
|---|---|---|
| mmol/L | mg/dL | U |
| 3.1 – 3.8 | 56 – 69 | - 2 |
| <3.1 | < 56 | - 4 |

**Deviations from the algorithm**
It is recommended that the algorithm is followed. However, it is also important that the decision to adjust insulin doses is based on all relevant information. A reason for deviating from the algorithm should be entered into the eCRF by the investigator as applicable.

**Data surveillance**
Surveillance of titration data will be performed centrally by Novo Nordisk in an unbiased or, if possible, a blinded manner. The data will be reviewed and significant changes from the titration algorithm will be followed up.

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

The titration data should be reviewed by Novo Nordisk within 24 hours (on workdays). The reviewer may contact the investigator by e-mail or phone to clarify reasons for deviation or to request entry of missing data. When the investigator receives an inquiry, a response should be received at Novo Nordisk within 24 hours (on workdays).

In addition, Novo Nordisk will monitor changes in HbA1c. Novo Nordisk may visit or phone sites to discuss progress in glycaemic control and titration of individual subjects.

## Global and country key Novo Nordisk staff

Attachments I and II (if applicable) to the protocol are located in the Trial Master File.

Content: Global key staff and Country key staff