Protocol

Trial ID: NN9068-3952

Including:

Protocol, dated 27 March 2013
Amendment no. 2 (Global), dated 21 August 2013

DUAL™ V – basal insulin switch

A trial comparing the efficacy and safety of insulin degludec/liraglutide versus insulin glargine in subjects with type 2 diabetes mellitus.

Trial phase: 3b

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<th>Full Form</th>
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<td>ADA</td>
<td>American Diabetes Association</td>
</tr>
<tr>
<td>AE</td>
<td>adverse event</td>
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<td>ALAT</td>
<td>alanine aminotransferase</td>
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<td>ANCOVA</td>
<td>analysis of covariance</td>
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<tr>
<td>BMI</td>
<td>body mass index</td>
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<tr>
<td>CMC</td>
<td>Calcitonin Monitoring Committee</td>
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<td>CAS</td>
<td>completer analysis set</td>
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<tr>
<td>CRF</td>
<td>case report form</td>
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<td>CRO</td>
<td>contract research organisation</td>
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<tr>
<td>CTR</td>
<td>clinical trial report</td>
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<tr>
<td>CV</td>
<td>coefficient of variation</td>
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<td>DUN</td>
<td>dispensing unit number</td>
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<td>ECG</td>
<td>electrocardiogram</td>
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<td>eCRF</td>
<td>electronic case report form</td>
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<td>EU</td>
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<td>FAS</td>
<td>full analysis set</td>
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<tr>
<td>FPFV</td>
<td>first patient first visit</td>
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<td>FPG</td>
<td>fasting plasma glucose</td>
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<tr>
<td>FU</td>
<td>follow up</td>
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<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
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<td>GLP-1</td>
<td>glucagon-like peptide-1</td>
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<tr>
<td>hCG</td>
<td>human chorionic gonadotrophin</td>
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<td>HDL</td>
<td>high density lipoprotein</td>
</tr>
<tr>
<td>IB</td>
<td>investigator’s brochure</td>
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<tr>
<td>IEC</td>
<td>independent ethics committee</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>IV/WRS</td>
<td>interactive voice/web response system</td>
</tr>
<tr>
<td>ANOCOVA</td>
<td>analysis of covariance</td>
</tr>
<tr>
<td>HbA1C</td>
<td>glycosylated haemoglobin</td>
</tr>
<tr>
<td>LDL</td>
<td>low density lipoprotein cholesterol</td>
</tr>
<tr>
<td>LLOQ</td>
<td>lower limit of quantification</td>
</tr>
<tr>
<td>LOCF</td>
<td>last observation carried forward</td>
</tr>
<tr>
<td>LPFV</td>
<td>last patient first visit</td>
</tr>
<tr>
<td>LPLV</td>
<td>last patient last visit</td>
</tr>
<tr>
<td>MEN2</td>
<td>multiple endocrine neoplasia type 2</td>
</tr>
<tr>
<td>MESI</td>
<td>medical event of special interest</td>
</tr>
<tr>
<td>MTC</td>
<td>medullary thyroid carcinoma</td>
</tr>
<tr>
<td>NIMP</td>
<td>non-investigational medicinal product</td>
</tr>
<tr>
<td>OAD</td>
<td>oral antidiabetic drug</td>
</tr>
<tr>
<td>OD</td>
<td>once daily</td>
</tr>
<tr>
<td>PD</td>
<td>pharmacodynamic</td>
</tr>
<tr>
<td>PG</td>
<td>plasma glucose</td>
</tr>
<tr>
<td>PK</td>
<td>pharmacokinetic</td>
</tr>
<tr>
<td>PP</td>
<td>per protocol</td>
</tr>
<tr>
<td>PRO</td>
<td>patient reported outcome</td>
</tr>
<tr>
<td>RMA</td>
<td>repeated measurements analysis</td>
</tr>
<tr>
<td>SAE</td>
<td>serious adverse event</td>
</tr>
<tr>
<td>SAS</td>
<td>safety analysis set</td>
</tr>
<tr>
<td>SD</td>
<td>standard deviation</td>
</tr>
</tbody>
</table>
SF-36  medical outcomes study 36-item short form

SmPC  summary of product characteristics

SMPG  self-measured plasma glucose

TEAE  treatment emergent adverse event

TMM  trial materials manual

T2DM  type 2 diabetes mellitus

TRIM-D  Treatment Related Impact Measure – Diabetes

UNR  upper normal range

UTN  Universal Trial Number

VLDL  very low density lipoprotein cholesterol
1 Summary

Objectives and endpoints:

Primary Objective

To confirm the efficacy of insulin degludec/liraglutide in controlling glycaemia in subjects with type 2 diabetes mellitus (T2DM) on previous treatment with insulin glargine.

This is done by comparing the difference in change in glycosylated haemoglobin (HbA1c) from baseline after 26 weeks of treatment to a non-inferiority limit of 0.30% for insulin degludec/liraglutide vs insulin glargine.

Secondary Objectives

- To confirm superiority of insulin degludec/liraglutide versus insulin glargine after 26 weeks of treatment on one or more of the following:
  - Change from baseline in HbA1c
  - Confirmed hypoglycaemia
  - Change from baseline in body weight

- To compare safety of insulin degludec/liraglutide to insulin glargine after 26 weeks of treatment

Primary endpoint

Change from baseline in HbA1c after 26 weeks of treatment

Key secondary endpoints

- Change from baseline in body weight after 26 weeks of treatment
- Number of treatment emergent confirmed hypoglycaemic episodes during 26 weeks of treatment

Trial design:

This is a 26-week, multi-centre, multinational, open-label, two-arm parallel, randomised, treat-to-target trial in subjects with T2DM. Patients inadequately controlled on insulin glargine at a daily dose between 20 units and 50 units (both inclusive) in combination with metformin will be eligible for the trial.

A total of 554 subjects will be randomised in a 1:1 manner. Subjects will receive either once daily (OD) insulin degludec/liraglutide or OD insulin glargine, both in combination with metformin.
The total trial duration is approximately 29 weeks, consisting of 2 weeks of screening period and 26 weeks of treatment and a follow up visit 1 week after the end of treatment.

**Trial population:**
Planned number of subjects to be randomised is 554 (277 per arm).

**Key inclusion criteria**
- Type 2 diabetes mellitus
- ≥ 18 years of age
- HbA1c 7.0-10.0% [53-86 mmol/mol] (both inclusive) by central laboratory analysis
- Current treatment with insulin glargine for at least 90 days prior to screening
- Stable daily dose of insulin glargine between 20 units and 50 units (both inclusive) for at least 56 days prior to screening. Total daily dose should be within the range of 20-50 units, both inclusive, on the day of screening, but individual fluctuations of ± 10% within the 56 days prior to screening are acceptable.
- Stable daily dose of metformin (≥ 1500 mg or max tolerated dose) for at least 90 days prior to screening
- Body mass index (BMI) ≤ 40 kg/m²

**Key exclusion criteria**
- Any use of oral antidiabetic agents (OADs) (except for metformin) within 90 days prior to Visit 1 (screening)
- Current use of any drug (except metformin and insulin glargine) or anticipated change in concomitant medication, which in the investigator’s opinion could interfere with the glucose metabolism (e.g. systemic corticosteroids)
- Previous and/or current treatment with any insulin regimen other than basal insulin, e.g. prandial or pre-mixed insulin (short term treatment due to intercurrent illness including gestational diabetes is allowed at the discretion of the investigator)
- Previous and/or current treatment with glucagon-like peptide-1 (GLP-1) receptor agonists (e.g. exenatide, liraglutide)
- Impaired liver function, defined as ALAT ≥ 2.5 times upper normal range (UNR)
- Impaired renal function defined as serum-creatinine ≥133μmol/L (≥1.5 mg/dL) for males and ≥ 125 μmol/L (1.4 mg/dL) for females, or as allowed according to local contraindications for metformin
- Screening calcitonin ≥ 50 ng/L
- Personal or family history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia type 2 (MEN2)
- History of chronic pancreatitis or idiopathic acute pancreatitis
Key efficacy assessments:

- HbA$_{1c}$
- Body weight

Key safety assessments:

- Hypoglycaemic episodes
- Adverse events (AEs)

Trial products:

- Insulin degludec/liraglutide, a fixed ratio of insulin degludec and liraglutide solution provided in a pre-filled pen-injector for subcutaneous (s.c.) injection
- Insulin glargine solution provided in a pre-filled pen-injector for s.c. injection

Metformin is considered non investigational medicinal product (NIMP) and hence will not be provided by Novo Nordisk, unless required by local law.
## 2 Flow chart

### Table 2–1 Trial assessments and schedule

For details on the different assessments specified in the flow chart below refer to section 8

<table>
<thead>
<tr>
<th>Trial Periods</th>
<th>Screen</th>
<th>Rand</th>
<th>Treatment Period</th>
<th>EOT</th>
<th>FU</th>
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<tbody>
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<td>Visit number (V)</td>
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</tr>
<tr>
<td>Time of visit</td>
<td>Weeks</td>
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<td>0</td>
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<td>Visit window</td>
<td>Days</td>
<td>≤14</td>
<td>±3</td>
<td>±3</td>
<td>±3</td>
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</table>

**SUBJECT RELATED INFO/ASSESSMENTS**

| Informed consent | x |
| Exclusion criteria | x |
| Randomisation | x |
| Withdrawal criteria | | |
| Concomitant illness | x |
| Concomitant medication | | |
| Demography | x |
| Date of diagnosis of diabetes | x |
| Diabetes complications | x |
| Diabetes treatment history | x |
| Family history of diabetes | x |
| Medical history | x |
| Smoking habits | x |

1 A phone contact may be converted to a clinical visit e.g. if further titration is needed
2 Subjects on insulin degludec/liraglutide with HbA1c ≥6.5% measured at Visit 22 who have signed the NN9068-4119 informed consent should come for a clinic visit at Visit 27 (Visit 1 for the NN9068-4119 trial), all other subjects should perform a phone contact.
3 Subjects randomised to the NN9068-4119 trial will not attend the follow-up visit (Visit 29)
4 Collection of date of birth, race and ethnicity only if applicable by local law
<table>
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<th>Trial Periods</th>
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<th>Treatment Period</th>
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**Efficacy**

- **Body measurements**
  - Body weight
  - BMI
  - Height
  - Waist circumference
  - Glucose metabolism
    - HbA1c
    - Fasting plasma glucose
    - Fasting C-peptide
    - Fasting glucagon
    - Fasting human insulin
    - Lipids
    - Self measured plasma glucose
      - Once daily
      - 9-point profile
  - SAFETY
    - Adverse events
    - Hypoglycaemic episodes

---

5 Body weight should be measured fasting in accordance with the protocol, without shoes and only wearing light clothing
6 Once daily SMPO should be measured fasting before breakfast. Diabetes medication should be withheld until after the SMPO measurement
7 9-point profile should be measured within one week prior to the site visit (on a day where unusual strenuous exercises is not anticipated). At Visit 2, 14 and 28 the pre-breakfast measurement from the once daily fasting SMPO will be a part of the 9-point profile.
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² ECG obtained within 2 weeks prior to Visit 2 as part of routine practice may replace the screening assessment, if results are available for evaluation at Visit 2

¹⁰ Eye examination, obtained within 12 weeks prior to Visit 2 as part of routine practice, may replace the screening assessment if results are available for evaluation at Visit 2

¹¹ For females of childbearing potential a urine pregnancy test should be performed at site, if pregnancy is suspected or if a menstrual period is missed. If the subject reports missing menstrual period at a phone contact, the subject will have to attend the site for an unscheduled visit as soon as possible to have urine pregnancy test performed. If positive a confirmatory serum hCG test should be sent to the central laboratory.
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13) Fasting is defined as at least eight hours without food and drink, except for water and other prescribed medication than trial product and metformin. No diabetes medication is allowed up to eight hours prior to the measurements.

14) Only subjects on insulin degludec/liraglutide with HbA1c ≥6.5% measured at Visit 22 should be informed about the NN9068-4119 trial and offered the informed consent form.
3 Background information and rationale for the trial

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

Insulin degludec/liraglutide is a fixed ratio combination drug under clinical development for treatment of type 2 diabetes mellitus (T2DM), consisting of insulin degludec and liraglutide.

Insulin degludec is a novel, long-acting insulin, being developed as a new-generation basal insulin. It forms soluble multi-hexamers upon subcutaneous injection, resulting in a depot from which insulin degludec is continuously and slowly absorbed into the circulation leading to a flat and stable glucose-lowering-effect. The duration of action of insulin degludec is beyond 42 hours within the therapeutic dose range. Insulin degludec is efficacious in terms of lowering glycosylated haemoglobin (HbA1c) and may result in a lower risk of nocturnal hypoglycaemia compared to current basal insulin products due to its distinct pharmacological profile. Insulin degludec is the active ingredient used in Tresiba®, which has been approved in EU, Iceland, Japan, Mexico, Norway and Switzerland. Detailed information on insulin degludec is available in the current edition of the IB and any updates hereof and detailed information on insulin glargine is available in the local approved labelling.

Liraglutide is an analogue of native (human) glucagon-like peptide-1 (GLP-1), which is suitable for once daily administration. GLP-1 is an incretin hormone secreted from the L-cells in the lower gut in response to meal ingestion. GLP-1 exerts its main effect by stimulating glucose-dependent insulin release (i.e. when plasma glucose levels are above normal) from the pancreatic islets. GLP-1 also decreases glucagon secretion and appetite. Liraglutide is the active ingredient used in the authorised product Victoza®, approved amongst others in the European Union (EU), the United States (US), Australia, Canada, China and Japan for the treatment of adults with T2DM to achieve glycaemic control. For more details on liraglutide, please refer to the local approved labelling for Victoza®.

Insulin degludec/liraglutide is a solution for subcutaneous injection of a fixed ratio combination of insulin degludec and liraglutide, intended for once daily (OD) treatment of T2DM. It is to be initiated and titrated to achieve adequate glycaemic control in a similar way as basal insulin therapy. The basal insulin and GLP-1 analogue combination provides effects of the two compounds on fasting and postprandial glycaemic control in one administration. One dose step of insulin degludec/liraglutide consists of 1 unit insulin degludec and 0.036 mg liraglutide. The maximum insulin degludec/liraglutide dose to be administered is 50 dose steps (50 units insulin degludec and 1.8 mg liraglutide) in an injection volume of 0.5 mL. The insulin degludec/liraglutide formulation will be provided in a multi-dose disposable pen PDS290, consisting of a pen injector with a pre-filled 3 mL cartridge (please refer to insulin degludec/liraglutide NN9068 IB and any updates hereof, for more details on the device).
Efficacy and safety of insulin degludec/liraglutide has been demonstrated in previous randomised clinical trials (NN9068-3697 and NN9068-3912) and is being evaluated in on-going randomised clinical trials (NN9068-3851 and NN9068-3951). For more information, please refer to insulin degludec/liraglutide NN9068 IB current version or any updates hereof.

Insulin glargine is a long-acting insulin analogue, indicated to improve glycaemic control in adults and children with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus. For more details on insulin glargine, please refer to the local approved labelling.

3.1  Rationale for the trial

Current anti-diabetic therapies include oral agents, injectable GLP-1 receptor agonists and insulin. The American Diabetes Association’s (ADA) Standards of Medical care in diabetes recommends lowering HbA1c to below 7% in most patients to reduce the incidence of diabetes-associated complications. However, not all current anti-diabetic therapies provide sustained glycaemic control, and those which do may be associated with an unacceptable risk of hypoglycaemia as well as with weight gain. In addition, therapies are often complicated and difficult for subjects to adhere to.

Insulin degludec/liraglutide is a fixed ratio combination of insulin degludec and liraglutide for subjects with T2DM, intended for once daily use. The basal insulin and GLP-1 analogue combination bring complimentary effects of the two compounds on fasting (insulin degludec and liraglutide) and postprandial (liraglutide) glycaemic control. The addition of liraglutide to insulin degludec may reduce the requirement of exogenous insulin (i.e. insulin sparing effect), hence minimising the risk of hypoglycaemia and weight gain, often associated with basal insulin treatment. The inherent weight reducing effect of liraglutide further contributes to the favourable weight profile of the combination drug compared to basal insulin treatment. Moreover, given the glucose dependent effect of liraglutide, the liraglutide component reduces postprandial glucose excursions, while reducing the risk of unwanted lowering of inter-prandial or fasting glucose.

The proposed trial aims to demonstrate a safe and efficacious switch of therapy from insulin glargine treatment to the fixed ratio combination of insulin degludec/liraglutide in subjects with T2DM, inadequately controlled on insulin glargine and metformin treatment. The trial will investigate if insulin degludec/liraglutide as an efficacious and safe alternative to further optimising of insulin glargine considered currently the most widely used basal insulin and therefore considered as a relevant comparator in this trial.
4 Objectives and endpoints

4.1 Objectives

Primary Objective

To confirm the efficacy of insulin degludec/liraglutide in controlling glycaemia in subjects with T2DM on previous treatment with insulin glargine.

This is done by comparing the difference in change in HbA1c from baseline after 26 weeks of treatment to a non-inferiority limit of 0.30% for insulin degludec/liraglutide vs insulin glargine.

Secondary Objective

- To confirm superiority of insulin degludec/liraglutide versus insulin glargine after 26 weeks of treatment on one or more of the following:
  - change from baseline in HbA1c
  - confirmed hypoglycaemia
  - change from baseline in body weight

- To compare safety of insulin degludec/liraglutide to insulin glargine after 26 weeks of treatment

4.2 Endpoints

Primary endpoint

Change from baseline in HbA1c after 26 weeks of treatment.

Confirmatory secondary endpoints

If the primary objective is confirmed then the primary endpoint (change in HbA1c) will also be tested for superiority. In addition, the following two confirmatory secondary endpoints will be tested for superiority:

- Change from baseline in body weight after 26 weeks of treatment
- Number of treatment emergent confirmed hypoglycaemic episodes during 26 weeks of treatment

To protect the type 1 error rate when testing the confirmatory endpoints, a closed test procedure will be used.

Supportive secondary efficacy endpoints:

- Insulin dose after 26 weeks of treatment
- Responder after 26 weeks of treatment (yes/no):
  - HbA1c < 7.0%
  - HbA1c < 7.0% without weight gain
- HbA1c < 7.0% without treatment emergent confirmed hypoglycaemic episodes during the last 12 weeks of treatment
- HbA1c < 7.0% without treatment emergent confirmed hypoglycaemic episodes during the last 12 weeks of treatment and without weight gain
- HbA1c ≤ 6.5% without weight gain
- HbA1c ≤ 6.5% without treatment emergent confirmed hypoglycaemic episodes during the last 12 weeks of treatment
- HbA1c ≤ 6.5% without treatment emergent confirmed hypoglycaemic episodes during the last 12 weeks of treatment and without weight gain

- Change from baseline after 26 weeks of treatment in:
  - Fasting plasma glucose (FPG)
  - Waist circumference
  - Blood pressure (systolic and diastolic)
  - Mean of the 9-point profile, defined as the area under the profile (calculated using the trapezoidal method) divided by the measurement time.
  - Post-prandial plasma glucose (PG) increments (from before meal to 90 min after for breakfast, lunch and dinner). The mean increment over all meals will be derived as the mean of all available meal increments.

- Fasting C-peptide, fasting human insulin, and fasting glucagon after 26 weeks of treatment
- Fasting lipid profile [cholesterol, low density lipoprotein cholesterol (LDL cholesterol), high density lipoprotein cholesterol (HDL cholesterol), very low density lipoprotein cholesterol (VLDL cholesterol), triglycerides, and free fatty acids] after 26 weeks of treatment.

Supportive secondary safety endpoints:

- Number of treatment emergent adverse events (AEs) during 26 weeks of treatment
- Number of treatment emergent nocturnal confirmed hypoglycaemic episodes during 26 weeks of treatment
- Change from baseline in clinical evaluation after 26 weeks of treatment:
  - Pulse
  - Eye examination
  - Electrocardiogram (ECG)

- Change from baseline in laboratory assessments after 26 weeks of treatment:
  - Biochemistry
  - Haematology
  - Calcitonin
  - Amylase and lipase.

Patient reported outcome:
• Change from baseline in patient reported outcomes after 26 weeks of treatment
  o Treatment related impact measure (TRIM-D)
  o Medical outcomes study 36-item short form (SF-36)

• Qualitative results from a questionnaire to assess the reasons for patients not being optimally titrated on insulin glargine, when entering the trial (titration barrier questionnaire).
5 Trial design

5.1 Type of trial

This is a 26-week, multi-centre, multinational, open-label, two-arm parallel, randomised, treat-to-target trial in subjects with T2DM. Patients, inadequately controlled on insulin glargine at a daily dose between 20 units and 50 units (both inclusive) in combination with metformin, will be eligible for the trial.

Inadequately controlled T2DM will be defined as HbA\textsubscript{1c} level of 7.0–10.0 % [53–86mmol/mol], both inclusive. A total of 554 subjects will be randomised in a 1:1 manner, using a centralised allocation via an interactive voice/web response system (IV/WRS). Based on an anticipated screening failure rate of 40\%, 923 subjects will be screened.

Subjects will receive either once daily (OD) insulin degludec/liraglutide or OD insulin glargine, both in combination with metformin, as indicated in Figure 5–1.

![Figure 5–1 Trial design](image)

The total trial duration will be approximately 29 weeks, consisting of 2 weeks screening period, a 26-week treatment period and a follow-up visit 1 week after end of treatment.
5.2 Rationale for trial design

Based on prior experience from insulin titration trials, the duration of 26 weeks is sufficient to reach a stable HbA1c level, i.e. minimum of 12 weeks in maintenance period and to obtain sufficient data for efficacy and safety evaluation. A parallel design has been chosen rather than a cross-over design in order to keep the treatment period as short as possible for the subjects.

Subjects will be randomised in a 1:1 manner to either insulin degludec/liraglutide or insulin glargine, both in combination with metformin. The trial is open-labelled, as blinding the trial and including placebo would require a double dummy design with two subcutaneous injections, which is deemed to pose an unacceptable burden to the subjects and increase the trial design complexity, thereby increasing the risk of subjects withdrawing from the trial or being non-compliant.

The visit schedule is chosen to secure an optimal titration according to a predefined treatment algorithm and close observation of the glycaemic control of subjects in both arms. The primary endpoint HbA1c is a laboratory parameter, and consequently, the probability of assessment bias is limited. Both arms will be exposed to the same degree of self-monitoring and medical monitoring.

5.3 Treatment of subjects

Subjects with T2DM on insulin glargine and metformin treatment, in accordance with the inclusion criteria (section 6.2), are eligible for the trial. When randomised, the subjects will receive one of the treatments described below:

- Fixed ratio of insulin degludec/liraglutide, added to current metformin therapy. Subjects will discontinue the pre-trial insulin glargine treatment and start insulin degludec/liraglutide. Insulin degludec/liraglutide will be given subcutaneously once daily in the thigh, upper arm (deltoid region) or abdomen. The chosen injection area should remain unchanged throughout the trial, although rotation within the area is recommended. The starting dose of insulin degludec/liraglutide is 16 dose steps (16 units insulin degludec/0.6 mg liraglutide), and will be titrated according to a predefined titration algorithm (please refer to Appendix A) with a maximum dose of 50 dose steps (50 units insulin degludec/1.8 mg liraglutide), aiming to reach fasting plasma glucose (FPG) target between 4.0 mmol/L (71 mg/dL) and 5.0 mmol/L (90 mg/dL). The dosing can be done at any time of the day but should be approximately at the same time of the day throughout the trial for individual subjects. A pre-filled device PDS290 will be used to administer trial medication, all subjects will receive training in the device. All subjects will continue with metformin in pre-trial doses.

- Insulin glargine added to current metformin therapy. Subjects will discontinue the pre-trial insulin glargine treatment and start Novo Nordisk-provided insulin glargine. Insulin glargine will be given subcutaneously once daily at a start dose equal to the pre-trial daily dose of insulin glargine (dose to dose switch) and will be titrated according to a predefined titration...
algorithm (please refer to Appendix A), with no maximum dose, aiming to reach fasting plasma glucose (FPG) target between 4.0 mmol/L (71 mg/dL) and 5.0 mmol/L (90 mg/dL). Insulin glargine should be administered according to the approved label. A pre-filled device Lantus® SoloStar® will be used to administer trial medication, all subjects will receive training in the device. If glargine dose in the course of the trial will be too large for one injection (i.e. over 80 U), the injection should be split, and the two injections should be taken at the same time point and in the same chosen area. All subjects will continue with metformin in pre-trial doses.

Detailed information on insulin degludec/liraglutide is available in the current edition of the NN9068 IB\textsuperscript{2} and detailed information on insulin glargine is available in the local approved labelling.

The investigational medicinal products (IMP) used in this trial are, (for more details refer to section 9):

- Insulin degludec/liraglutide 100 units/3.6 mg per mL, a fixed ratio of insulin degludec (100 units/mL) and liraglutide (3.6 mg/mL) solution, provided in a 3 mL pre-filled PDS290 pen-injector for subcutaneous (s.c.) injection
- Insulin glargine 100 units/mL solution provided in a 3 mL pre-filled Lantus® SoloStar® pen-injector for s.c. injection.

The dose will be titrated twice weekly on fixed days (Mondays and Thursdays), by the subject, according to the predefined titration algorithm and based on daily fasting self-measured plasma glucose (SMPG) levels (please refer to Appendix A). Throughout the trial the investigator or delegated staff will check the titration once weekly. The surveillance of titration will be performed centrally by Novo Nordisk, as described in Appendix A.

The maximum treatment duration with trial products for individual subjects will be 26 weeks. After the end of the treatment period, or if the treatment period is discontinued earlier than expected, the subjects will be transferred to an appropriate anti-diabetic therapy at the discretion of the investigator.

5.4 Rationale for treatment

Insulin degludec/liraglutide will be investigated in this trial to demonstrate efficacy and safety, when switched from insulin glargine in T2DM subjects, inadequately controlled on insulin glargine and metformin. Insulin glargine has been chosen both as pre-trial treatment and comparator as it is currently the most widely used basal insulin.

The trial design should allow for evaluation of the potential clinical benefits, including HbA\textsubscript{1c} reduction and less risk of weight gain and hypoglycaemia, that subjects not adequately controlled on
insulin glargine will may gain from the switch as opposed to further optimisation of insulin glargine therapy. The Treat-To-Target (T-T-T) approach will be applied after randomisation in order to optimise glycaemic control throughout the trial.

The start dose of insulin degludec/liraglutide fixed combination is 16 dose steps, determined by the highest tolerable initiation dose of liraglutide in GLP-1 naïve subjects (0.6 mg, corresponding to maximum initial dose of Victoza®).

All subjects in both arms will continue with metformin at pre-trial doses (≥ 1500 mg or max tolerated dose). In case of safety concern the dose may be reduced at the discretion of the investigator. Metformin treatment will follow the locally approved label.

The duration of 26 weeks has been chosen to obtain a stabilised HbA1c ensuring an adequate length of time of trial product at steady state.
6 Trial population

6.1 Number of subjects

Countries planned to participate: Argentina, Australia, Greece, Hungary, Mexico, Russia, Slovakia, South Africa, Spain and United States.

Number of subjects planned to be screened: 923

Number of subjects planned to be randomised/started on trial products: 554

Mexico: 60 subjects are planned to be randomised/started on trial products in Mexico.

Number of subjects expected to complete the trial: 471

Expected screen failure rate 40% and withdrawal rate 15%

6.2 Inclusion criteria

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

1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial
2. Type 2 diabetes mellitus
3. ≥ 18 years of age
4. HbA1c 7.0-10.0% [53-86 mmol/mol] (both inclusive) by central laboratory analysis
5. Current treatment with insulin glargine for at least 90 days prior to screening
6. Stable daily dose of insulin glargine between 20 units and 50 units (both inclusive) for at least 56 days prior to screening. Total daily dose should be within the range of 20-50 units, both inclusive, on the day of screening, but individual fluctuations of ± 10% within the 56 days prior to screening are acceptable.
7. Stable daily dose of metformin (≥ 1500 mg or max tolerated dose) for at least 90 days prior to screening
8. Body mass index (BMI) ≤ 40 kg/m²
9. Able and willing to adhere to the protocol including performing self-measured plasma glucose profiles, to keep a trial diary and to use pre-filled pen device.

6.3 Exclusion criteria

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

1. Known or suspected hypersensitivity to trial products or excipients
2. Previous participation in this trial. Participation is defined as screening. Re-screening is not allowed.
3. Females of child-bearing potential who are pregnant, breast-feeding or intend to become pregnant or are not using adequate contraceptive methods (adequate contraceptive measures as required by local law or practice)
   **Argentina:** Barrier methods (condom or diaphragm) with spermicide; contraceptive pills or intrauterine devices (IUD). Birth control methods will be reimbursed by sponsor.
   **Spain:** Acceptable forms of birth control (barrier methods, contraceptive pills, IUD, sterilisation, approved hormonal implant, contraceptive patch).
4. Receipt of any investigational medicinal product within 30 days prior to Visit 1 (screening)
5. Any use of oral antidiabetic agents (OADs) (except for metformin) within 90 days prior to Visit 1 (screening)
6. Current use of any drug (except metformin and insulin glargine) or anticipated change in concomitant medication, which in the investigator’s opinion could interfere with the glucose metabolism (e.g. systemic corticosteroids)
7. Previous and/or current treatment with any insulin regimen other than basal insulin, e.g. prandial or pre-mixed insulin (short term treatment due to intercurrent illness including gestational diabetes is allowed at the discretion of the investigator)
8. Previous and/or current treatment with GLP-1 receptor agonists (e.g. exenatide, liraglutide)
9. Impaired liver function, defined as ALAT ≥ 2.5 times upper normal range (UNR)
10. Impaired renal function defined as serum-creatinine ≥ 133 μmol/L (≥ 1.5 mg/dL) for males and ≥ 125 μmol/L (≥ 1.4 mg/dL) for females, or as allowed according to local contraindications for metformin
11. Screening calcitonin ≥ 50ng/L
12. Personal or family history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia type 2 (MEN2)
13. Cardiovascular disorders defined as; congestive heart failure [New York Heart Association (NYHA) class III-IV], diagnosis of unstable angina pectoris, cerebral stroke and/or myocardial infarction within the past 26 weeks prior to Visit 1 and/or planned coronary, carotid or peripheral artery revascularisation procedures
14. Severe uncontrolled treated or untreated hypertension (systolic blood pressure ≥ 180 mmHg or diastolic blood pressure ≥ 100 mmHg)
   **Argentina:** Severe uncontrolled treated or untreated hypertension (defined as systolic blood pressure ≥ 150 mmHg and/or diastolic blood pressure ≥ 90 mmHg)
15. Proliferative retinopathy requiring acute treatment or maculopathy (macular oedema), according to the investigator’s opinion
16. Subjects with clinically significant, active (during the past 12 months) disease of the gastrointestinal, pulmonary, endocrinological (excluding T2DM), neurological, genitourinary or haematological system, that in the opinion of the investigator may confound the results of the trial or pose additional risk in administering trial drug
17. Mental incapacity, unwillingness or language barrier precluding adequate understanding of the trial procedures or cooperation with the trial personnel
18. Known or suspected abuse of prescription drugs, alcohol or illicit substances
19. History of chronic pancreatitis or idiopathic acute pancreatitis
20. Suffer from a life threatening disease including malignant neoplasms and medical history of malignant neoplasms within the last 5 years (except basal and squamous cell skin cancer)
21. Argentina: Active diabetic ulcer or subjects with a history of diabetic foot (ulcers and/or amputation) in a period of 1 year prior to screening.

6.4 Withdrawal criteria

1. The subject may withdraw at any time without explanation.
2. The subject may be withdrawn from the trial at the discretion of the investigator due to a safety concern or if judged non-compliant with trial procedures.
3. A subject must be withdrawn immediately if he/she is randomised into the trial in contravention of the inclusion and/or exclusion criteria.
   A subject must be withdrawn if the following applies:
4. Initiation of any systemic treatment with products which in the investigator’s opinion could interfere with glucose metabolism (e.g. systemic corticosteroids)
5. Pregnancy or intention of becoming pregnant
6. If the fasting SMPG values taken on 3 consecutive days or if any of the FPG samples analysed by the central laboratory exceeds the limit of:
   - 15.0 mmol/L (270 mg/dL) from baseline to week 6
   - 13.3 mmol/L (240 mg/dL) from week 7 to week 12
   - 11.1 mmol/L (200 mg/dL) from week 13 to week 26,
   action is to be taken by the investigator as soon as possible to call the subject in for an unscheduled visit and obtain a confirmatory FPG (analysed by the central laboratory) given there is no intercurrent cause for the hyperglycaemia. If there is no intercurrent cause for the hyperglycaemia, and FPG exceeds the limits described above, the subject must be withdrawn.
7. If the investigator suspects acute pancreatitis, all drugs suspected to relate to this condition should be discontinued until confirmatory tests have been conducted and appropriate treatment should be initiated. Subjects who are diagnosed with acute pancreatitis (as a minimum 2 of 3: characteristic abdominal pain, amylase and/or lipase >3x UNR or characteristic findings on ultrasound, computed tomography (CT)/magnetic resonance imaging (MRI)), must be withdrawn from the trial
8. Argentina: Repeated asymptomatic and/or symptomatic hypoglycaemia defined as asymptomatic and/or symptomatic hypoglycaemic events during 3 consecutive days despite appropriate dose reduction of insulin treatment (i.e. reduction according to the titration algorithm detailed in Appendix A).
9. Argentina: A single episode of severe hypoglycaemia without clear and correctable triggers defined as a hypoglycaemic event requiring assistance of another person to actively administer
carbohydrate, glucagon or other resuscitative measures, due to the subject being unable to take any form of action.

6.5 **Subject replacement**

Subjects who are withdrawn after randomisation will not be replaced.

6.6 **Rationale for trial population**

Subjects with T2DM, inadequately controlled with insulin glargine and metformin and in need of treatment intensification to achieve glycaemic control, are the target population for inclusion in this trial.

Eligible subjects are presenting with a HbA\textsubscript{1c} of 7.0–10.0% [53-86 mmol/mol], both inclusive. These subjects have been treated with insulin glargine for at least 90 days prior to screening and have been on a stable daily dose between 20 units and 50 units (both inclusive) within the 56 days prior to screening (individual fluctuations of \pm 10% within these 56 days are acceptable). In addition, the subjects must be treated with metformin in an unchanged dose for at least 90 days prior to screening.

The HbA\textsubscript{1c} range is chosen to include T2DM subjects on insulin glargine and metformin, who are not optimally controlled on their current treatment and may benefit from a treatment regimen with less risk of hypoglycaemia and weight gain, when switching to insulin degludec/liraglutide.

Stable treatment prior to trial enrolment prevents carry over effect on trial endpoints.

A BMI limit of \leq 40 kg/m\textsuperscript{2} is chosen to include as broad a population as possible, while excluding morbidly obese individuals, who are extremely insulin resistant.
7 Trial schedule

Planned duration of recruitment period (FPFV–LPFV): 28 weeks

Planned date for first patient first visit (FPFV): 23 September 2013

Planned date for last patient last visit (LPLV)/end of trial (Visit 29): 27 October 2014

Planned completion of clinical trial report (CTR): 30 March 2015

The end of the clinical trial is defined as LPLV.

All countries will have a grace period of 20 weeks, starting from 23 September 2013. Within this grace period, the recruitment target in each country will remain unchanged. The recruitment and retention strategies will be evaluated by the Local Trial Manager and the International Trial Manager. If a country is behind their target up to the 20 week cut off, the recruitment target may be decreased for that country, and subjects may be re-allocated within the region, otherwise to another region. The reallocation of subjects will be managed throughout the final 8 weeks until the global recruitment target is met.

Recruitment will be closed as soon as the total number of subjects is achievable, taking the number of screened subjects and the screening failure rate into account. All subjects, who are in screening when recruitment closes, will be randomised, if found eligible.

Information of the trial will be disclosed at clinicaltrials.gov and novonordisk-trials.com. According to the Novo Nordisk Code of Conduct for Clinical Trial Disclosure, it will also be disclosed according to other requirements such as those of the International Committee of Medical Journal Editors (ICMJE)⁶, the Food and Drug Administration Amendment Act (FDAAA)⁷, European Commission Regulation for EudraCT⁸ and other relevant recommendations or regulations. In this connection be informed that the investigators name and site information may be made publicly available. If a patient 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 patient.
8 Methods and assessments

8.1 Visit procedures

Procedures and assessments for the scheduled visits and phone contacts are described in this section. The timing of assessments are outlined in the flow chart (please refer to section 2).

8.1.1 Investigator’s assessment

Review of diaries, PROs, laboratory reports, ECGs, eye examination (funduscropy/fundusphotography), physical examination etc. must be documented with the investigator’s dated signature either on the front page of the documents and/or in the subject’s medical record. The signed documents must be retained at the investigator site as source documentation.

At screening (Visit 1) any abnormal clinically significant finding (laboratory reports, ECGs, eye examination, physical examination, etc) must be recorded by the investigator in the subject’s medical record and the medical history/concomitant illness form in the eCRF. At subsequent visits any clinically significant changes or new clinically significant findings must be reported as an AE according to section 12.

8.1.2 Visit schedule

If a site visit/phone contact for some reason is not performed at the scheduled time point, the investigator must arrange for the site visit/phone contact to be performed as soon as possible and within the scheduled visit windows. Date of visit and visit windows are calculated in relation to the randomisation visit (Visit 2). The follow-up visit (Visit 29) is relative to Visit 28 and must take place at least 1 week after Visit 28.

It is the responsibility of the investigator to ensure that all site visits and phone contacts occur according to the flow chart (section 2). A phone contact may be converted to a site visit, if needed.

8.1.3 Fasting visits

The subject must attend Visit 2, 6, 10, 14, 18, 22 and 28 in a fasting state. Fasting is defined as at least eight hours without food and drink, except for water and any other prescribed medication. No diabetes medication is allowed up to eight hours prior to blood sampling and fasting SMPGs. Trial products and other glucose lowering agents cannot be taken until after blood sampling has been performed.

If the subject attends a fasting visit in a non-fasting state, laboratory sampling and weight must be re-scheduled within the visit window. The date of collection must be updated with the new sampling date on the specific visit in the eCRF.
8.1.4 Screening visit (Visit 1)

Before screening takes place, subjects must be provided with written and oral information about the trial and the procedures involved, in accordance with International Conference Harmonisation Good Clinical Practice Guideline (ICH GCP) and local requirements. Subjects must be fully informed, orally and in writing, of their responsibilities and rights while participating in the trial, as well as of possible advantages/disadvantages when being treated with the trial product. Subjects will have the opportunity to ask questions and have ample time to consider participation. The informed consent process must take place before any screening visit procedures (Visit 1).

Subjects, who wish to participate in the trial must sign and date the Subject Information/Informed Consent (SI/IC) before any trial-related procedures. All subjects must be provided with a copy of their own signed and dated informed consent form.

Screening of subjects will be carried out by using IV/WRS (see sections 10 and 11). At screening, the subjects will be assigned unique subject identification (ID) numbers which will remain the same throughout the trial. The subject ID number will consist of six digits (the first three digits indicating site number and the last three digits indicating subject number).

Subjects enrolled in the trial should be provided with a Subject Participation Card stating the participation in the trial and whom to contact in case of emergency. The subjects must be informed to keep the card with them at all times. At the end of the trial the card must be destroyed.

If the investigator is not the subject’s primary physician, the investigator should preferably notify the primary physician about the subject’s trial participation. If required, permission should be obtained from the subject.

The investigator must keep a Subject Screening Log, a Subject Identification Code List and a Subject Enrolment Log. The Subject Screening Log and Subject Enrolment Log may be combined in one log and may be generated from IV/WRS.

For assessments to be performed at the screening visit please refer to the flow chart (section 2).

8.1.4.1 Screening failures

If the subject for some reason is not eligible to be enrolled in the trial the subject will be considered a screening failure. In this case the investigator must:

- Perform a screening failure session using the IV/WRS
- Complete the screening failure form in the eCRF with the reason for not continuing in the trial
- Transcribe all serious and non-serious AEs into the eCRF.
When trial related procedures have been finalised for screening failures, no more AEs should be entered in the eCRF. Screening failures, experiencing a Medical Event of Special Interest (MESI) that would otherwise qualify for adjudication, will not be adjudicated as screening failures have not received trial product. Follow-up of serious adverse events (SAEs) should be made according to section 12. When data has been source data verified and all queries have been resolved, the case book must be signed by the investigator in the eCRF.

Re-screening of screen failure subjects is not allowed.

8.1.5 Randomisation visit (Visit 2) to follow-up visit (Visit 29)

After careful review of all inclusion and exclusion criteria (including central laboratory results), eligible subjects will be randomised to the treatment arms. The randomisation visit (Visit 2) should take place no more than two weeks after the screening visit (Visit 1).

Randomisation of subjects will be carried out using IV/WRS (see sections 10 and 11). The subject will keep the same subject ID number as allocated at the screening visit.

At the randomisation visit (Visit 2) subject will be supplied with the trial product. For subjects randomised to receive insulin degludec/liraglutide, the investigator should:

- Inform the subject that the trial product should be injected s.c. into the thighs, upper arm (deltoid region) or abdomen. The injection area chosen should remain unchanged throughout the trial, but rotation within the area is recommended
- Advise the subject that the dosing time can be any time of the day but should be approximately at the same time throughout the trial
- Advise the subject to take the first dose of trial product either on the day of randomisation (Visit 2) or the day after
- Instruct the subject in the titration algorithm
- Provide the subject with directions for use of PDS290 pen-injector. The investigator must document that direction for use is given to each subject orally and/or in writing at each dispensing visit
- Instruct the subject not to exceed the max dose of 50 dose steps. If this happens, the subject should be instructed at the next contact to reduce the dose to 50 dose steps (for further information please refer to Appendix A).

For subjects randomised to receive insulin glargine, the investigator should:

- Instruct the subject to keep their current injection site and dosing time unchanged throughout the trial period
- Instruct the subject in the titration algorithm
• Provide the subject with directions for use of the Lantus® SoloStar® pen-injector. The investigator must document that direction for use is given to each subject orally and/or in writing at each dispensing visit.

For further information on trial products please refer to section 9.

At Visit 3, information on first dose of trial product, including date and time of administration, must be recorded in the eCRF. At the last treatment visit (Visit 28) information on last date and dose on trial product must be recorded.

All subjects will continue on their current metformin treatment at stable pre-trial dose and frequency throughout the trial. At each contact to site the subject should confirm that their metformin treatment is unchanged. In case of safety concern the dose may be reduced at the discretion of the investigator. The reason and duration of the change should be recorded in the eCRF. The concomitant medication form should also be updated if changes are permanent or prolonged.

For assessments to be performed at randomisation visit (Visit 2) to follow-up visit (Visit 29), please refer to the flow chart (section 2).

Before Visit 27, subjects on insulin degludec/liraglutide with HbA1c ≥ 6.5% measured at Visit 22 will be informed about the NN9068-4119 trial and offered the informed consent form. Subjects who have signed the NN9068-4119 informed consent should come into a clinic visit at Visit 27 (Visit 1 for the NN9068-4119 trial), all other subjects will be contacted by phone.

At the last treatment visit (Visit 28) subjects not randomised to treatment in the NN9068-4119 will transfer from trial product to an alternative anti-diabetic therapy at the discretion of the investigator.

Subjects randomised to treatment in the NN9068-4119 trial will not attend the follow-up visit (Visit 29).

Due to the long half-life of insulin degludec the follow-up, visit (Visit 29) procedures should be undertaken at least one week after last treatment visit (Visit 28). If the end-of-trial safety assessments (Visit 29) are not performed, the investigator must include the reason in the subject’s medical record.

8.1.6 Diaries

At each site visit subjects will be provided with a new diary. The diary must be collected at the next site visit, and retained at the site as source data in accordance with section 14.

Site staff is only allowed to record the following data in the diary:
• Subject ID number
• Site contact details
• Time and date of next visit or phone contact
• Prescribed dose of trial product
• Doses and SMPGs from previous diary, if required to complete next dose adjustment

The subject must record the following information in the diary:

• Date, time and value of the once daily fasting SMPG measurements
• Date, time and value of 9-point profile SMPG measurements prior to Visit 2, 14 and 28
• Date, time and dose of trial product
• Hypoglycaemic episodes (see section 8.5.7)
• Any changes in medical condition
• Any changes to concomitant medication

Based on the SMPG measurements, the investigator/subject will assess whether the trial product dose needs adjustment according to the Titration Guideline (Appendix A).

The diary must be reviewed by the investigator to ensure that AEs, including any overall change in health and concomitant medication, are reported (see section 8.3.1, 8.3.2 and 12.2).

In addition, the investigator should consider whether the reported SMPG values should be reported as a hypoglycaemic episode (see section 8.5.7). The investigator or delegated staff must transcribe data from the diary into the eCRF within 24 hours after each site visit/phone contact. The review of the diary must be documented either on the front page of the documents and/or in the subjects medical records.

If clarification of entries or discrepancies in the diaries is needed, the subject should be questioned and a conclusion made in the subjects medical record. Care should be taken not to influence the subject’s clarification.

8.1.7 Unscheduled visits

Unscheduled visits can be performed at any time at the discretion of the investigator. An unscheduled visit should be performed, if:

• An AE occurs that needs further attention
• Additional laboratory sample is needed due to a MESI, for examples lack of efficacy suspected due to neutralising antibody formation or if measurement of immunoglobulin E (IgE) isotype of antibody in case of acute hypersensitivity (allergic reaction)
• A confirmatory pregnancy test is needed
• A confirmatory FPG test for withdrawal criteria number 6 is required
An unscheduled visit form must be completed in the eCRF, indicating reason for the visit.

An unscheduled visit form should not be completed, if the subject attends the clinic for additional trial products, auxiliary supplies or for a blood re-sample related to a specific visit (blood samples which have been lost or could not be analysed). If a subject needs additional trial product, an additional dispensing session should be made in the IV/WRS, and the subject’s medical record should be updated accordingly.

8.1.8 Premature withdrawal

Subjects randomised in error (i.e. violating any inclusion or exclusion criteria) must be withdrawn from the trial immediately.

If a subject is prematurely withdrawn from the trial, the investigator should aim to perform all Visit 28 procedures and, if possible, perform the follow-up visit (Visit 29).

Although a subject is not obliged to give his/her reason(s) for withdrawing from the trial, the investigator should make a reasonable effort to ascertain the primary reason, while fully respecting the subject’s rights. Where the reason(s) are obtained, the primary reason (withdrawal criterion, AE, non-compliance with protocol or other) for discontinuation must be specified in the end-of-trial form in the eCRF.

A withdrawal session must be completed in the IV/WRS and final drug accountability must be performed. When all data has been monitored and all queries have been resolved, the case book in the eCRF must be signed by the investigator.

Even if the subject is not able to attend the visit, trial products should be returned to the site.

8.2 Laboratory assessments

The laboratory analyses will be performed by a central laboratory, unless otherwise specified. Descriptions of assay methods, laboratory supplies and procedures for obtaining samples, handling and storage of samples and information regarding who will perform the assessments, will be described in a trial-specific laboratory manual, provided by a central laboratory (for central laboratory details, see Attachment I).

Mexico: The handling, transportation and storage of biological samples are described in the laboratory manual (for central laboratory details, see Attachment I).

Laboratory equipment in laboratories may provide standard analyses not requested in the protocol but produced automatically in connection with the requested analyses. Such data will not be transferred to the CRF or the trial database, but abnormal values will be reported to the investigator.
The investigator must review all laboratory results for concomitant illnesses and AEs and report these according to this protocol.

Laboratory samples not drawn on the day of the actual visit, should preferably be drawn on another day within the visit window stated in the flow chart (see section 2). For some of the samples drawn during the trial it is required that the subject is fasting. Hence subjects will be asked to attend the relevant site visits fasting (fasting is defined in section 8.1.3). Samples will be coded in order to keep subject identity anonymous.

Laboratory results will be sent by the central laboratory to the investigator on an on-going basis. For laboratory values outside the reference range, the investigator must specify on the laboratory report whether the value is non-clinically or clinically significant. All laboratory reports must be signed and dated by the investigator on the day of evaluation. The signed laboratory report is retained at the investigator’s site as source documentation.

All samples will be destroyed on an ongoing basis after analysis or at the latest at the completion of the clinical trial report (CTR).

The investigator should ensure that lab samples taken at the subjects last site visit (Visit 28) are shipped to the central laboratory immediately and no later than 24 hours after the samples are drawn.

8.3 Subject related information and assessments

8.3.1 Concomitant illness and medical history

A medical history is any relevant condition/illness that the subject has experienced in the past.

A concomitant illness is any relevant condition/illness that is present at the start of the trial (i.e. at the screening visit). Concomitant illness includes any pre-planned procedures/surgeries and any intermittent illness (e.g. allergy to food, medication, pollen or others) that may not be apparent at the time of screening.

Details of all medical history and concomitant illnesses must be recorded at the screening visit. The information collected for a medical history/concomitant illness should include diagnosis, date of onset, date of resolution or continuation. Any change to a concomitant illness should be recorded during the trial. A clinically significant worsening of a concomitant illness must be recorded and reported as an AE according to section 12.

Diabetes treatment history/diabetes complication is an account in the eCRF of medical events and complications related to diabetes, for examples diabetic retinopathy/neuropathy/nephropathy and macro angiopathy (including peripheral vascular disease). Details of all relevant diabetes
Complications must be recorded at trial entry (i.e. at screening visit). The information collected for a diabetes complication should include diagnosis and date of onset.

**Date of diagnosis of diabetes** is an account in the eCRF of the date of diagnosis of diabetes.

**Family history of diabetes** is an account in the eCRF where information about the family history of diabetes is collected.

### 8.3.2 Concomitant medication

**Concomitant medication** is any medication (except for trial products) taken in the screening period and during the trial including pre-trial metformin therapy. Details of any concomitant medication must be recorded at trial entry (i.e. at the screening visit). Any changes in concomitant medication must be recorded at each visit as they occur. The information collected for each concomitant medication includes (as a minimum) trade name or generic name, indication, start date and stop date or continuation. For the pre-trial metformin therapy the total daily dose should also be recorded.

If a change in medication is due to an AE this must be recorded and reported according to section 12. If the change influences the subject’s eligibility to continue in the trial the monitor must be informed.

**Argentina:** Subjects are not allowed to receive any treatment with glucose-lowering agent(s) other than trial product and metformin. Subjects are allowed to start any concomitant medication as far as it does not interfere with the glucose level. Optimisation of lipid lowering treatment is allowed during the trial according to local clinical practice.

### 8.3.3 Demography

Demography consists of:

- Date of birth or age (according to local regulations)
- Sex
- Race (according to local regulations)
- Ethnicity (according to local regulations)

### 8.3.4 Smoking habits

At Visit 1 it should be recorded if the subject:

- Never smoked
- Is a previous smoker
  - Cessation date
  - Average number of cigarettes per day
  - Approximate years of smoking
- Is a current smoker
  - Average number of cigarettes per day
  - Approximate years of smoking

### 8.4 Assessments for efficacy

#### 8.4.1 Blood samples

Blood samples will be drawn in accordance with the flow chart (section 2) and analysed at the central laboratory to determine levels of the following laboratory parameters:

- Glucose metabolism:
  - HbA\(_{1c}\)
  - FPG
  - Beta cell function (fasting C-peptide and fasting human insulin)
  - Glucagon (fasting)

- Fasting lipid profile:
  - Triglycerides
  - Cholesterol
  - LDL cholesterol
  - HDL cholesterol
  - VLDL cholesterol
  - Free fatty acids

HbA\(_{1c}\) will be measured and reported in both the Système International (SI) units (mmol/mol – no decimals) and derived National Glycohemoglobin Standardization Program (NGSP) units (%) - one decimal). SI units are mainly used in EU and the NGSP units are used in the rest of the world.

HbA\(_{1c}\) and FPG results out of range do not need to be reported as an AE, unless the result is unexpected by the investigator.

If FPG results from central laboratory are equal to or below 3.9 mmol/L (70 mg/dL), the investigator must report it as a hypoglycaemic episode according to section 8.5.7.

#### 8.4.2 Body measurements

**Body weight**

Body weight should be measured in kilograms (kg) or pounds (lb) without shoes and only wearing light clothing. Body weight should be assessed on the same equipment throughout the trial, if possible, and be recorded with one decimal. The subjects must attend these visits in a fasting state, except for the screening visit (Visit 1).
Height

Height is measured without shoes in centimetres or inches and rounded to the nearest cm or inch.

Waist circumference

The waist circumference is defined as the minimal abdominal circumferences located midway between the lower rib margin and the iliac crest.

Three consecutive measurements of waist circumference should be performed and recorded in the eCRF. The waist circumferences will be measured to the nearest 0.5 centimetre (cm) or 0.2 inch (in), using a non-stretchable measuring tape (measuring tapes will be provided to the sites by Novo Nordisk).

The subject should be measured in a standing position with an empty bladder and wearing light clothing with accessible waist. The subject should be standing with arms down their side and feet together. The tape should touch the skin but not compress soft tissue and twists in the tape should be avoided. The subject should be asked to breathe normally, and the measurement should be taken when the subject is breathing out gently.

BMI

BMI will be calculated using the eCRF.

BMI calculation: $\text{BMI kg/m}^2 = \frac{\text{Body weight (kg)}}{\text{Height (m)} \times \text{Height (m)}} \times \frac{\text{703}}{\text{lb/in}^2}$.

8.4.3 Self-measured plasma glucose

At the screening visit, subjects should be supplied with a BG meter which must be used for all SMPG measurements during the trial. The subject should be supplied with oral and written directions for use of the device, including the performance of regular calibrations according to the manufacturer’s instructions. Sites should, as necessary, repeat the directions for use to the subject at subsequent visits.

The BG meters use test strips calibrated to plasma values. Therefore, all glucose measurements performed with drawn capillary blood are automatically calibrated to plasma equivalent glucose values. These values will be shown on the display and should be recorded in the subject diary.

Subjects should be instructed how to record the results of the SMPG values in the provided diaries and should only record the SMPG values based on measurements obtained with the provided BG meter. The record of each SMPG measurement should include date, time and value.

The investigator or delegated site staff must transcribe the data during/after a phone contact into the eCRF. When the subject comes to the next site visit, if there is a discrepancy between the diary and
the SMPG data in the eCRF for a phone contact, the values should be corrected to reflect the actual values used for titration (the values in the diary) and a comment explaining that the values have been changed due to a discrepancy should be entered into the eCRF.

8.4.4 Once daily fasting self-measured plasma glucose profile

Subjects will be instructed to perform a fasting SMPG measurement once daily before breakfast, using the BG meter provided. Subject will record the date, time and value of the once daily SMPG measurement along with the date, time and dose of trial product in the diary. Diabetes medication should be withheld until after the SMPG measurement. For definition of fasting state refer to section 8.1.3.

These measurements are required for optimal dose adjustment and maintenance as described in the Titration Guideline (Appendix A).

8.4.5 9-point self-measured plasma glucose profile

The subject will be instructed to perform a 9-point SMPG profile 3 times during the trial, preferably within one week prior to site visit according to section 2, on a day where the subject does not anticipate unusual strenuous exercise.

The plasma glucose levels should be measured and recorded in the diary (including date, time and value) at the following time points, always starting with the first measurement before breakfast:

- Before breakfast (Day 1)
- 90 min after the start of breakfast
- Before lunch
- 90 min after the start of lunch
- Before dinner
- 90 min after the start of dinner
- Before bedtime
- At 4 am
- Before breakfast the following day (Day 2)

At Visit 2, 14 and 28 the pre-breakfast measurement from the once daily fasting SMPG will be a part of the 9-point profile.
8.5 Assessment for safety

8.5.1 Blood samples

Blood samples will be drawn in accordance with the flow chart (section 2) and analysed at the central laboratory to determine levels of the following laboratory parameters:

Haematology:
- Erythrocytes
- Haematocrit
- Haemoglobin
- Leucocytes
- Thrombocytes
- Differential count (eosinophils, neutrophils, basophils, monocytes and lymphocytes)

Biochemistry:
- Amylase
- Lipase
- Alanine aminotransferase (ALAT /SPGT)
- Aspartate aminotransferase (ASAT /SGOT)
- Alkaline phosphatase (AP)
- Albumin
- Bilirubin (total)
- Calcium
- Calcium (albumin corrected)
- Creatinine
- Potassium
- Sodium

Hormones:
- Calcitonin

Pregnancy test:
- Serum/plasma hCG

8.5.2 Vital signs (diastolic, systolic blood pressure and pulse)

Diastolic blood pressure, systolic blood pressure and pulse should be assessed while the subject is in a sitting position. Measurements should be performed after 5 minutes of rest.

At the screening visit (Visit 1) blood pressure needs to be measured three times and all three values should be recorded. The mean value will be calculated by the eCRF and must be in accordance with the relevant exclusion criterion, see section 6.3.
If the investigator suspects white coat hypertension at the screening and/or randomisation visits, one re-assessment of the systolic and diastolic blood pressure (as described above) is allowed.

Pulse (beats per minute) should be recorded after resting for 5 minutes in a sitting position.

8.5.3 Electrocardiogram – 12 lead

A 12-lead ECG must be performed by the investigator or delegated staff. The ECG must be interpreted, signed and dated by the investigator to verify that the data has been reviewed. The results must be transcribed to the eCRF as:

- Normal
- Abnormal, not clinically significant
- Abnormal, clinically significant

Any “abnormal, clinically significant” findings at screening must be recorded in the subject’s medical record and on the medical history/concomitant illness form in the eCRF.

Any clinically significant deterioration of a pre-existing condition, as well as any new clinically significant signs or symptoms, should be reported as an AE in accordance with section 12.2.

An ECG performed for any reason unrelated to this trial, but within 2 weeks prior to the Visit 2, is acceptable and should not be repeated, if the results are available for evaluation at Visit 2, and if no clinical signs or symptoms suggestive of cardiac disease have occurred in the meantime. The investigator must interpret, sign and date the ECG.

If the ECG is performed before the subject consented to participate in the trial, it must also be stated in the subject medical records that this procedure was not performed in relation to the trial.

An ECG performed within 2 weeks prior to Visit 28 is acceptable, if the results are available for evaluation at Visit 28.

8.5.4 Eye examination

Funduscop/fundusphotography will be performed at the screening visit by the investigator, a local ophthalmologist or an optometrist according to local practice. Results of the funduscop/fundusphotography will be interpreted by the investigator. Dilation is not a requirement.

The eye examination must be signed and dated by the investigator to verify that the data has been reviewed. The results must be transcribed to the eCRF as:

- Normal
Any “abnormal, clinically significant” findings at screening must be recorded in the subject’s medical record and on the medical history/concomitant illness in the eCRF.

Any clinically significant deterioration of a pre-existing condition, as well as any new clinically significant signs or symptoms, should be reported as an AE in accordance with section 12.2.

If a funduscopy/fundusphotography has been performed within 12 weeks prior to Visit 2, the procedure does not need to be repeated, if the results are available for evaluation at Visit 2 and no worsening of visual function since the last examination has occurred. The investigator must interpret, sign and date the funduscopy/fundusphotography. If the funduscopy/fundusphotography is performed before the subject consented to participate in the trial, it must also be stated in the subject medical records that this procedure was not performed in relation to the trial.

If a funduscopy/fundusphotography has been performed within 2 weeks prior to Visit 28, the procedure does not need to be repeated, if the results are available for evaluation at Visit 28 and no worsening of visual function since the last examination has occurred. The investigator must interpret, sign and date the funduscopy/fundusphotography.

8.5.5 Physical examination

A physical examination must include:

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

8.5.6 Pregnancy test

Females of childbearing potential will have a blood pregnancy test (beta-human chorionic gonadotropin (beta-hCG)) performed according to the trial flow chart (section 2).
Urine pregnancy tests using urine dipsticks will be performed at site during the trial for females of childbearing potential if a menstrual period is missed or if pregnancy is suspected. If the urine test is positive, a confirmatory hCG serum test should be taken and sent to the central laboratory for analysis. It should be documented in an unscheduled visit, describing pregnancy test under “other” in the eCRF.

8.5.7 Recording of hypoglycaemic episodes

Plasma glucose should always be measured and recorded when a hypoglycaemic episode is suspected.

All plasma glucose values:

- equal to or below 3.9 mmol/L (70 mg/dL)
- or higher than 3.9 mmol/L (70 mg/dL) when they occur in conjunction with hypoglycaemic symptoms, should be recorded by the subject in the subject diary.

These must be transcribed from the subject diary into the eCRF (hypoglycaemic episode form) throughout the trial from Visit 2 to Visit 29.

The record should include the following information:

- The plasma glucose level before treating the episode (if available)
- Date and time of hypoglycaemic episode
- Whether the episode was symptomatic
- Whether the subject was able to treat him/herself (if not answered, the investigator must provide an explanation in the eCRF)
- If the subject was not able to treat him/herself, whether he/she recovered with oral administration of carbohydrates
- Time of last trial product administration prior to episode
- Type of last trial product prior to episode
- Time of last main meal prior to episode
- Whether the episode occurred in relation to exercise

The answer to the question: “Was subject able to treat him/herself?” should be answered “No” if oral carbohydrates, glucagon or IV glucose had to be administered to the subject by another person. Oral carbohydrates should not be given, if the subject is unconscious.

A hypoglycaemic episode form must be filled in for each hypoglycaemic episode. If the hypoglycaemic episode fulfils the criteria for an SAE and/or a medical event of special interest...
(MESI) then an adverse event (AE) form and a safety information form must also be filled in according to section 12.1 and 12.2. Severe hypoglycaemic episodes must be recorded as MESIs.

8.6 Other assessments

8.6.1 Patient reported outcome questionnaires (PRO questionnaires)

The following PRO questionnaires should be completed in accordance with the flow chart (section 2):

- TRIM-D
- SF-36
- Barriers to titration

The questionnaires will be administered to all participating subjects, irrespective of their treatment arm. The questionnaires will be supplied in a linguistically validated version in all languages relevant for this trial.

The questionnaires must be completed by the subject him/herself and should be completed before any other visit related activities. The investigator is only allowed to fill in the headings of the questionnaires.

It is the responsibility of the investigator to review the PRO questionnaires to ensure that AEs and any reported change in concomitant medication are reported. The investigator should only review the PRO questionnaires for possible AEs, changes in concomitant medication and blank fields. The content of the subject’s replies should not be considered further. The review of the PRO questionnaires must be documented either on the front page of the documents and/or in the subjects medical records, when returned by the subject.

If clarification of entries in the PRO questionnaires is needed, the subject should be questioned and a conclusion made in the medical record. Care should be taken not to influence the subject’s clarifications.

All PRO questionnaires must be transcribed into the eCRF.

8.7 Subject compliance

At each visit the investigator should emphasise the necessity for the subject to adhere to trial procedures in order to encourage subject compliance. In addition, subject compliance will be assessed by monitoring of drug accountability. The unused amount of trial product will be assessed against the dispensed amount and, in case of discrepancies, the subject must be asked to clarify.

Substantial failure to comply with the prescribed trial product dosage regimen can lead to withdrawal. In addition, the investigator should assess the compliance of the subject at each visit.
based on a review of glycaemic control, adherence of the visit schedule, completion of the subject’s diary including the SMPG profiles. If a subject is discovered to be non-compliant, the investigator must inform the subject of the importance of taking trial products and comply with trial procedures as directed.

For specification of subjects’ evaluation in regard to the statistical analysis, please refer to section 17.
9 Trial supplies

Trial supplies comprise trial products and auxiliary supplies for example needles and containers for used needles. Details concerning labelling, handling, storage and distribution of trial products are included in the trial materials manual (TMM), which will be distributed to investigational sites prior to trial start.

9.1 Trial products

Refer to the NN9068 IB\(^5\) and/or local approved labelling for more detailed information regarding the trial products listed below:

- Insulin degludec/liraglutide 100 units/3.6 mg per mL, a fixed ratio of insulin degludec (100 units/mL) and liraglutide (3.6 mg/mL) solution provided in a 3 mL pre-filled PDS290 pen-injector for s.c. injection
- Insulin glargine 100 units/mL solution provided in a 3 mL pre-filled Lantus® SoloStar® pen for s.c. injection.

Insulin degludec/liraglutide is manufactured and supplied by Novo Nordisk, Denmark. Insulin glargine is packed for use in clinical trials and supplied by Novo Nordisk.

9.2 Non-investigational medicinal product

Metformin is considered NIMP and hence will not be provided by Novo Nordisk, unless required by local law.

NIMP should be purchased or otherwise delivered to subjects in accordance with local health plans.

**Argentina:** Metformin will be reimbursed by Novo Nordisk Pharma Argentina S.A.

9.3 Labelling

Trial products will be packed and labelled by Novo Nordisk and provided in non-subject specific boxes.

Labelling of the trial products will be in accordance with Annex 13\(^{10}\), local law and trial requirements.

Each investigational site will be supplied with sufficient trial product for the trial. This is controlled by the IV/WRS system.
9.4 Storage, accountability and destruction

9.4.1 Storage and handling

The investigator must ensure the availability of proper storage conditions, and record and evaluate the temperature. The investigator must inform Novo Nordisk (via the assigned monitor) immediately, if any trial product has been stored outside defined conditions (e.g. outside temperature range). Please refer to the TMM for details on requirements for temperature monitoring device or system.

Trial products stored outside the temperature range are not to be used and must be stored separately within allowed temperature range until after evaluation of condition. Evaluation will be performed by Novo Nordisk. Trial products that have been stored improperly must not be dispensed to any subject before it has been re-evaluated and approved for further use by Novo Nordisk.

Storage conditions for insulin degludec/liraglutide:

Not in use:
- Store in a refrigerator (+2°C to +8°C/+36°F to +46°F)
- Do not freeze
- Protect from light

In use:
- Do not refrigerate
- Do not store above +30°C (+86°F)
- Use within 2 weeks

Insulin degludec/liraglutide both in use and not in use must not be exposed to excessive heat or direct sunlight. Insulin degludec/liraglutide must not be used, if it does not appear clear and colourless.

Storage condition insulin glargine:

Not in use:
- Store in a refrigerator (+2°C to +8°C/+36°F to +46°F)
- Do not freeze
- Protect from light
- Keep away from the freezer compartment

In use:
- Do not refrigerate
- Do not store above +25°C (AR and US: Store below +30°C/86°F)
- Use within 4 weeks (AR and US: 28 days)
- Protect from light
Insulin glargine both in use and not in use must not be exposed to excessive heat or direct sunlight. Insulin glargine must not be used, if the solution does not appear clear and colourless, with no solid particles visible.

For non-investigational medicinal product (metformin) storage and handling should be in accordance with locally approved label.

### 9.4.2 Drug accountability and destruction of trial products and non-investigational products

The trial products will be dispensed to each subject as required according to treatment group. The IV/WRS will allocate trial product to the subject at each dispensing visit. The correct dispensing unit number (DUN) must be dispensed to the subject.

The investigator or delegated person is responsible for ensuring:

- Trial products must not be dispensed to any person not included in the trial
- Drug accountability is performed using the IV/WRS drug accountability module
- Subjects are instructed to return all used, partly used and unused trial product including empty packaging material at each dispensing visit
- All returned trial product(s) (used/partially used or unused including empty packaging material) must be stored separately from non-allocated trial product(s).

The monitor will:

- Reconcile the drug accountability using the IV/WRS drug accountability module
- Arrange the destruction of used, partially used and unused trial product. The destruction of trial products will be done according to local procedures and must be recorded on a destruction form, which will be signed by the person responsible for the destruction.

The accountability for the non-investigational medicinal product (metformin) consists of a confirmation in the eCRF that the dose is unchanged.

### 9.5 Auxiliary supply

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

- Needles for pre-filled pen systems
- Blood glucose meters, including lancets, plasma-calibrated test strips and control solutions
- Direction for use for devices.

After trial completion any surplus of auxiliary supplies can be disposed of locally.
10 Interactive voice/web response system

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

IV/WRS is used for:

- Screening
- Screening failure
- Randomisation
- Medication arrival
- Dispensing
- Withdrawal
- Treatment completion
- Drug accountability
- Data change

An IV/WRS user manual will be provided to each trial site.

11 Randomisation procedure

At the randomisation visit (Visit 2) subjects will be randomised either to receive OD insulin degludec/liraglutide in combination with metformin or OD insulin glargine in combination with metformin. The treatment is open-labelled, and the randomisation will be carried out in a 1:1 manner (i.e. 277 subjects in the insulin degludec/liraglutide arm and 277 subjects in the insulin glargine arm).

It is important that the trial sites dispense the trial products allocated by IV/WRS in order to:

- Provide the correct trial product (correct DUN) according to randomisation and dispensing visits
- Secure available stock at site to cover the drug supply need for all enrolled subjects
- Ensure that no subjects receive trial product that will expire in between dispensing visits
- Secure that drug accountability is possible.
12 Adverse events, technical complaints and pregnancies

12.1 Definitions

12.1.1 Adverse event

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

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

Note: This includes events from the first trial related activity after the subject has signed the informed consent and until post treatment follow-up period as defined in the protocol.

AEs include:

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

The following should not be reported as AEs:

- Pre-existing conditions, including those found as a result of screening procedures (pre-existing conditions should be reported as medical history or concomitant illness).
- Pre-planned procedures unless the condition for which the procedure was planned has worsened from the first trial related activity after the subject has signed the informed consent.

Note: Non-serious hypoglycaemia are AEs, but are reported on hypoglycaemic forms instead of on AE forms.

An AE is either a serious AE (SAE) or a non-serious AE.

AE severity assessment definitions:

- **Mild** – no or transient symptoms; no interference with the subject’s daily activities.
- **Moderate** – marked symptoms; moderate interference with the subject’s daily activities.
- **Severe** – considerable interference with the subject’s daily activities; unacceptable.
AE causality definitions

The following terms and definitions are used when assessing the relationship between each AE and the relevant trial products:

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

AE outcome definitions

The following terms and definitions are used in assessing the final outcome of an AE:

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

12.1.2 Serious adverse event (SAE):

An SAE is an experience that at any dose results in any of the following:

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

a The term “life threatening” in the definition of SAE refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it was more severe.

b The term “hospitalisation” is used when a subject:

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

Medical judgement must always be exercised, and when in doubt, the hospital contact should be regarded as a hospitalisation. Hospitalisations for administrative, trial related and social purposes do not constitute AEs and should therefore not be reported as AEs or SAEs. Hospital admissions for surgical procedures, planned before trial inclusion, are not considered AEs.

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

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

12.1.3 Non-serious adverse event:

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

In addition to being either an SAE or a non-serious AE some AEs fulfil the below medical event of special interest criteria which must be evaluated by the investigator for each AE.

12.1.4 Medical events of special interest (MESI)

A medical event of special interest (MESI) is an event which, in the evaluation of safety, has a special focus. For reporting timeline requirements please refer to section 12.2.

Note: MESIs can be both serious and non-serious AEs and should not be confused with the seriousness criteria “Important medical event”.
The following are defined as MESIs in this trial and the definitions and rationales for the MESIs in this trial are outlined in Appendix B.

1. Acute coronary syndrome
2. Cerebrovascular event
3. Heart failure requiring hospital admission
4. Revascularisation procedure
5. Cardiac Arrhythmia
6. Pancreatitis or clinical suspicion of pancreatitis, see section 12.1.4.1
7. Neoplasm
8. Thyroid disease, see section 12.1.4.2
9. Altered renal function
10. Severe hypoglycaemic event
11. Allergic reactions, see section 12.1.4.3
12. Immune-complex disease, see section 12.1.4.4
13. Lack of efficacy suspected to be due to neutralising antibody formation
14. Medication errors concerning trial products:
   (a) Administration of wrong drug
   (b) Wrong route of administration, such as intramuscular instead of subcutaneous
   (c) Administration of a high dose with the intention to cause harm (e.g. suicide attempt)
   (d) Administration of an accidental overdose, i.e. dose which may lead to health consequences, as judged by the investigator, irrespective of whether the SAE criteria are fulfilled or not

Any events confirmed or suspected to be a MESI must be reported as such. Additionally, in case the Sponsor identifies potentially missed MESIs through predefined review of available data, the investigator will be asked to reconsider if this is a MESI.

Along with fatal events (fatal non-MESI), certain events will be adjudicated by an external independent Event Adjudication Committee as described in section 12.7.2. For further information regarding definitions, rationales, and events that will be adjudicated, please refer to Appendix B. The following sections specify the requirement and further analysis for some of the MESIs.

When reporting a MESI, the following forms must be completed: the AE form, safety information form (SIF), specific MESI follow-up form and, if applicable, the event adjudication document collection form in the eCRF, as described in section 12.2 and also illustrated in Figure 12–1.

12.1.4.1 Pancreatitis
Pancreatitis or suspicion of pancreatitis should always be reported to Novo Nordisk as a MESI irrespective of seriousness. Confirmed cases of pancreatitis should be followed-up with
investigations of other potential causes (tests such as gallbladder ultrasound, triglycerides, liver enzymes, detailed history of concomitant medications or alcohol will be suggested for follow up as part of the investigators consideration relative to local standards of practice). Please refer to Appendix B for further definition.

12.1.4.2 Thyroid disease

All disorders of thyroid gland must be reported to Novo Nordisk as a MESI irrespective of seriousness. Subjects scheduled for thyroidectomy (partial or total) for any reason during the trial, must be instructed to inform the investigator prior to their operation.

Thyroidectomy pathology slides

A set of pathology (histology) slides of the excised thyroid tissue routinely made after thyroidectomies will be reviewed by the pathology laboratory of the hospital, where the operation was performed, and a pathology report with the diagnosis will be prepared. In addition, Novo Nordisk requests a set of pathology slides to be sent for a second reading by a central pathologist with expertise in thyroid and C-cell pathology. The central pathologist will be blinded to both trial treatment and the diagnosis from the hospital. Once the samples are re-examined, they will be sent back to the pathology laboratory. Both the initial hospital pathology report and the central pathology report will be reviewed by the Calcitonin Monitoring Committee (CMC) and undergo event adjudication (see section 12.7.2).

The investigator will be provided with the recommendation from the CMC, in order to take appropriate action. The action taken will be at the discretion of the investigator.

Blood samples for genetic testing only in case of confirmed C-cell pathology changes (i.e. hyperplastic or neoplastic thyroid C-cell disease) after thyroidectomy

Subjects will be asked to have a blood sample drawn for extraction of genetic material (DNA, deoxyribonucleic acid) to identify germline RET gene mutations associated with MEN2 syndrome. In case the subject is willing to have a blood sample drawn for this genetic testing, the subject will be asked to sign a separate informed consent form. The blood sample must not be drawn before the separate informed consent has been obtained with signature and date.

The testing procedure for genetic material (DNA) is considered standard in specialised clinics treating patients with neoplastic C-cell pathology. No other genetic testing than this will be performed. The blood sample should be collected at the first coming visit to the clinic after the confirmation of C-cell pathology or after a recommendation from the CMC is known. The blood sample will be tested and destroyed on an ongoing basis or at the latest at the completion of the CTR. The extraction of DNA will be performed by central laboratory, whereas the identification of
gene mutations will be performed by a defined specialised laboratory (for details please see Attachment I).

12.1.4.3  **Suspicion of acute hypersensitivity (allergic reaction) to trial product**

If acute hypersensitivity (allergic reaction) to trial product is suspected, local testing for blood (within a few hours) tryptase concentration (total and/or mature tryptase) is recommended\[11\].

If trial product is discontinued as a consequence of suspicion of acute hypersensitivity (allergic reaction), blood sampling for central assessment of the following (as applicable depending on received trial product) should be conducted at least seven days after trial product discontinuation: anti-liraglutide antibodies including IgE-isotype antibodies and anti-insulin degludec antibodies including IgE-isotype.

Tryptase concentrations (if measured) as well as results of anti-liraglutide antibody including IgE-isotype and anti-insulin degludec antibodies including IgE-isotype, will be sent to Novo Nordisk. Results should be included in the final report of the MESI.

12.1.4.4  **Suspicion of immune-complex disease**

If immune-complex disease is suspected, blood sampling for central assessment of complement levels (C3 and C4) should be conducted. Results should be included, when reporting a MESI.

12.1.5  **Injection site reactions**

If injection site reactions are reported spontaneously, these must be recorded on the adverse event form in the eCRF.

Furthermore, the following should also be recorded in the eCRF on the injection site reaction form:

1. Previous allergy. If yes, specify
2. History of current reaction(s):
   - Was the skin normal before the reaction? If no, specify
   - Time of appearance after injection
   - Associated local symptoms (burning, pain, numbness, itching)
   - Associated systemic symptoms (malaise, fatigue, fever, etc)
   - Duration of reaction
   - Have the symptoms been relieved? (e.g. did reaction disappear spontaneously during continued administration of trial product or was trial product discontinued)?
   - Type of trial product taken prior to onset of reaction
   - Date and time of last injection
   - Trial product dose (units/dose steps)
   - Type of needle (new or previously used)
• Injection angle (vertical, oblique)
• Injection into skin fold or flat skin
• Unusual discomfort during injection

3. Clinical examination and detailed description including:
• The time between injection and inspection of the reaction
• The anatomical site of reaction
• Measurement of the size of the reaction
• Dermatological description of the reaction (redness, swelling, macula, haemorrhage/bleeding)

12.1.6 Technical complaint

A technical complaint is any communication that alleges defects on trial supplies. The technical complaint may be associated with an AE, but does not concern the AE itself. Technical complaints should be reported according to section 12.4.1.

Examples of technical complaints:
• The physical or chemical appearance of trial products (e.g., discoloration, particles or contamination)
• The packaging material (e.g., leakage, cracks, rubber membrane issues or errors in labelling text)
• Problems related to devices (e.g., to the injection mechanism, dose setting mechanism, glucose measurement, push button or interface between the pen and the needle)

12.2 Reporting of adverse events

All events meeting the definition of an AE must be collected and reported. This includes events from the first trial-related activity after the subject has signed the informed consent until the end of the post-treatment follow-up period (Visit 29). The follow-up visit is relative to Visit 28 and must take place at least 1 week after Visit 28. The events must be recorded in the applicable eCRF forms in a timely manner.

During each contact with the trial site staff (site visits and telephone contacts), the subject must be asked about AEs and technical complaints. This can be done for example by asking “have you experienced any problems since the last contact?”

All AEs, either observed by the investigator or reported by the subject, must be reported by the investigator and evaluated. Novo Nordisk assessment of expectedness is performed according to the following reference documents:

• Insulin degludec/liraglutide: NN9068 IB² current version or any updates hereof
• Comparator product (insulin glargine): local approved labelling, current version
The investigator should report the diagnosis, if available. If no diagnosis is available, the investigator should record each sign and symptom as an individual AE. If or when a final diagnosis is obtained, the investigator should update the AE description.

All AEs, SAEs and MESIs must be recorded by the investigator on the AE form in the eCRF. A separate AE form should be used for each diagnosis or sign and symptom. For each SAE and MESI a safety information form should be completed in addition to the standard AE form, see Figure 12–1. If several symptoms or diagnoses occur as part of the same clinical picture, one safety information form may be used to describe all the SAEs. All concerned AE numbers must be included in the AE number field.

MESIs, regardless of seriousness, must be reported using both the AE form and the safety information form and a specific MESI follow-up form. The MESI form is a form tailored to collect specific information related to the individual MESIs.

For MESIs qualifying for adjudication, the Event Adjudication Document Collection forms also has to be completed in the eCRF within 14 calendar days, if applicable.

The investigator must ensure that the worst case severity and seriousness of an event is kept throughout the trial.

- If the AE fulfils the seriousness criteria the investigator must:
  
  o Enter the AE in the eCRF and tick the seriousness box within 24 hours of obtaining knowledge of the SAE
  o Complete and forward the safety information form to Novo Nordisk within 5 calendar days of obtaining knowledge of the SAE

- If a SAE fulfils the MESI criteria the investigator must complete and forward the MESI form to Novo Nordisk in the eCRF within 14 calendar days of obtaining knowledge of the AE

- If a non-serious AE fulfils the MESI criteria the investigator must complete and forward the AE form, SIF and MESI form to Novo Nordisk in the eCRF within 14 calendar days of obtaining knowledge of the AE.
Figure 12–1  Reporting of adverse events

If for some reason the eCRF is unavailable, the AE form and SIF for MESIs should be completed on paper case report form (CRF) and reported to Novo Nordisk by fax, telephone, e-mail or courier within the same timelines.

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

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

Novo Nordisk must inform the Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) in accordance with local requirement and GCP, unless locally this is an obligation of the investigator, as for example in the US.

Novo Nordisk must always inform the regulatory authorities in accordance with local requirements and GCP.
12.3 Follow-up of adverse events

During and following a subject’s participation in a clinical trial, the investigator should ensure that adequate medical care is provided to the subject for any AE, including significant laboratory values related to the trial. The investigator should inform the subject when medical care is needed for AE(s) of which the investigator becomes aware.

All SAEs and MESIs must be followed up until the outcome of the event is “recovered”, “recovered with sequelae” or “fatal”, and until all queries have been resolved. Cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE) may be closed with the outcome “recovering” or “not recovered”, when the subject has completed the follow up period. The follow-up information on SAEs should only include new (corrections or new or additional) information and should be reported within 24 hours of obtaining knowledge of the information. This is also the case for previously non-serious AEs which subsequently become SAEs.

Follow-up information on MESIs (not also fulfilling the SAE criteria) should only include new (corrections or new or additional) information and should be reported within 14 calendar days of obtaining knowledge of the information. This is also the case for previously non-serious AEs which subsequently fulfil the MESI criteria.

Non-serious AEs (not also fulfilling the MESI criteria) must be followed until the outcome of the event is “recovering”, “recovered” or “recovered with sequelae” or until the end of the follow-up period (Visit 29), whichever comes first, and until all queries related to these AEs have been resolved. Cases of chronic conditions or cancer or AEs ongoing at time of death (where death is due to another AE) may be closed with the outcome “recovering” or “not recovered”.

The investigator must record follow-up information on non-serious AEs by updating the AE form in the eCRF.

Queries or follow-up requests from Novo Nordisk should be responded to within 14 calendar days, unless otherwise specified. This must be done by updating the AE form, SIF, MESI follow-up questions and/or event adjudication document collection form in the eCRF, if applicable.

The investigator must forward follow-up information on SAEs within 24 hours of obtaining the follow-up information by updating the AE form in the eCRF and/or completing a new safety information form marked follow-up, and forward this to Novo Nordisk. If for some reason the eCRF is unavailable or, after access to edit the eCRF is revoked, the investigator must record any SAE follow-up information on the provided paper CRFs and send the information by fax, telephone, e-mail or courier to Novo Nordisk.

The investigator must forward follow-up information on MESIs (not fulfilling the SAE criteria) within 14 calendar days of obtaining the follow-up information by updating the AE form in the
eCRF and/or completing a new safety information form and/or MESI form marked follow-up, and forward this to Novo Nordisk. If for some reason the eCRF is unavailable or, after access to edit the eCRF is revoked, the investigator must record any SAE follow-up information on the provided paper CRFs and send the information by fax, telephone, e-mail or courier to Novo Nordisk.

The investigator must record follow-up information on non-serious AEs (not fulfilling the MESI criteria) by updating the AE form in the eCRF. If the access to edit the eCRF is revoked, the investigator must record any follow-up information on the provided paper CRFs.

12.4 Technical complaints and technical complaint samples

12.4.1 Reporting of technical complaints

All technical complaints on any of the follow trial products:

- Insulin degludec/liraglutide 100 units/3.6 mg per mL, a 3 mL pre-filled PDS290 pen-injector for s.c. injection
- Insulin glargine 100 units/mL, a 3 mL pre-filled Lantus® SoloStar® pen for s.c. injection
- Provided needles

which occur from the time of first usage of trial supplies until the time of the last usage of trial supplies, must be collected and reported to Novo Nordisk.

The investigator must assess whether the technical complaint is related to any AE(s), SAE(s) and/or MESI(s).

Technical complaints must be reported on a separate technical complaint form and must be completed for each trial product and for auxiliary supplies listed on the technical complaint form. If the technical complaint involves more than one batch number or DUN, a technical complaint form for each batch number or DUN must be completed.

The investigator must complete the technical complaint form in the eCRF **within 24 hours** of the trial site obtaining knowledge of a technical complaint related to an SAE. All other technical complaints should be reported **within 5 calendar days**.

If the eCRF is unavailable, the information should be completed on paper CRF and reported to Novo Nordisk by fax, e-mail or courier, within the same timelines.
12.4.2 Collection, storage and shipment of technical complaint samples

The investigator must collect the technical complaint sample and notify the monitor within 5 calendar days. The monitor must coordinate the initiation of the shipment to Novo Nordisk and ensure the sample is sent in accordance with local regulations and as soon as possible to Novo Nordisk Customer Complaint Centre. A copy or a print of the technical complaint form should be sent with the sample.

The investigator must ensure that the technical complaint sample contains the batch number and, if available, the DUN.

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

Storage of the technical complaint sample must be done in accordance with the conditions prescribed for the product (see section 9 and the TMM). The shipment of the technical complaint sample should be done in accordance with the same conditions as for storage.

12.5 Pregnancies

12.5.1 Pregnancies in females subjects

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

US: the male subject must also notify the investigator, if his partner becomes pregnant during the trial (see section 12.5.2)

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

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

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

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

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

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

Forms and timelines for reporting AEs:

Non-serious AEs:
  - Paper AE form* within 14 calendar days of the investigator's first knowledge of the initial or follow-up information to the non-serious AE.

SAEs:
  - Paper AE form* within 24 hours of the investigator's first knowledge of the SAE.
  - Paper safety information form within 5 calendar days of the investigator's first knowledge of the SAE.
  - SAE follow-up information to the AE form and/or safety information form within 24 hours of the investigator's first knowledge of the follow-up information.
  * It must be clearly stated in the AE diagnosis field on the AE form if the event occurred in the subject, foetus or newborn infant.

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

12.5.2 Pregnancies in female partners of male subjects in the insulin degludec/liraglutide treatment arm (only applicable to US)

Male subjects in the insulin degludec/liraglutide treatment arm must be instructed to notify the investigator if their female partner becomes pregnant during the trial, except in the screening period. At the last scheduled visit, male subjects must be asked if their female partner has become pregnant.

If a female partner has become pregnant during the trial, the investigator must follow-up on the pregnancy outcome and until the newborn infant is one month of age, irrespective of whether the
trial is completed or not. The investigator must ask the male subject and assess, if the pregnancy outcome is normal or abnormal.

When the pregnancy outcome is normal this information is recorded in the subject's medical record only, no further information is collected and reported to Novo Nordisk. When the pregnancy outcome is abnormal (i.e. congenital anomalies, foetal death including spontaneous abortion and/or any anomalies of the foetus observed at gross examination or during autopsy), the following must be reported by the investigator to Novo Nordisk electronically (e.g. in PDF format) or by fax:

- **Reporting of pregnancy information**
  Information from the male subject has to be reported on the Paternal Form. Furthermore, information from the female partner (including information about the pregnancy outcome and health status of the infant until the age of one month) has to be reported on the Maternal Forms 1A, 1B and 2, after an informed consent has been obtained from the female partner.

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

- **Reporting of AE information**
  The following AEs in the foetus and newborn infant have to be reported:

    - Non-serious AEs evaluated as possible/probably related to the father's treatment with the trial product(s).
    - SAEs in the foetus and newborn infant - whether or not related to the father's treatment with the trial product(s). This includes an abnormal outcome - such as foetal death (including spontaneous abortion) and congenital anomalies (including those observed at gross examination or during autopsy of the foetus).

Forms and timelines for reporting AEs:

Please see section 12.5.1, point 2, "Forms and timelines for reporting AEs;"

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

During treatment with insulin there is a risk of hypoglycaemia.

Symptoms of hypoglycaemia usually occur suddenly and may include cold sweat, nervousness or tremor, anxious feelings, unusual tiredness, confusion, difficulty in concentrating, excessive hunger, temporary vision changes, headache, nausea and palpitation. Severe hypoglycaemia may lead to unconsciousness.

Hypoglycaemic episodes should be treated according to best practise at the discretion of the investigator. Attention should be given to the fact that the action profile of the insulin component in insulin degludec/liraglutide is flat and of somewhat longer duration than currently marketed long-acting insulin preparations. It may therefore take several hours more before stable normal blood glucose is achieved after a hypoglycaemic episode when comparing to existing long acting insulin analogues.

Symptoms of minor hypoglycaemia should be treated with ingestion of carbohydrate. Severe hypoglycaemia resulting in loss of consciousness must be treated according to best medical practice (for examples 25 mL of 50% dextrose solution given intravenously, or 0.5-1 mg of glucagon given s.c. or intramuscularly).

Please be aware that the insulin degludec/liraglutide will be in a PDS290 pen-injector where it is possible to dial up to 80 dose steps, even though the maximum intended dose with insulin degludec/liraglutide is 50 dose steps. The investigator should therefore remember to inform the subjects not to inject more than the maximum dose of 50 dose steps.

From clinical trials and marketed use of Victoza®, overdoses up to 40 times the recommended maintenance dose (72 mg) have been reported. Events reported included severe nausea and severe vomiting. None of the reports included severe hypoglycaemia. All patients recovered without complications.

When initiating treatment with insulin degludec/liraglutide, the subject may in some cases experience loss of fluids/dehydration, due to vomiting, nausea or diarrhoea. It is important to avoid dehydration by drinking plenty of fluids.

For further information please refer to the NN9068 IB² or any update hereof and approved labelling for insulin glargine.
12.7 Committees related to safety

12.7.1 Novo Nordisk safety committee

Novo Nordisk will constitute an internal safety committee to perform ongoing safety surveillance. The Safety Committee will conduct ongoing monitoring of blinded safety data. In addition, the Safety Committee will be informed about the results of ongoing safety surveillance activities for the individual monocomponents, insulin degludec and liraglutide, respectively.

12.7.2 Event adjudication committee

An external independent Event Adjudication Committee (EAC) is established for this trial to perform adjudication, standardisation and assessment of the following events (please also see Appendix B):

- Fatal events, if not already covered by a MESI
- Acute coronary syndrome (All types of myocardial infarction or hospitalisation for unstable angina)
- Cerebrovascular event (transient ischemic attack and stroke)
- All heart failures requiring hospitalisation
- Coronary revascularisation
- Pancreatitis or clinical suspicion of pancreatitis
- Neoplasms
- Thyroid disorders requiring thyroidectomy

The events are reviewed by the EAC in an independent and blinded manner. Adjudication will be completed based on a review of data collected from sites. The provided data will be anonymised by identifiers.

The EAC is composed of permanent members who cover required medical specialities. The EAC members must disclose any potential conflicts of interest and must be independent of Novo Nordisk. The role of the EAC is solely to adjudicate events in a blinded manner. The EACs will have no authorisations to impact on trial conduct, trial protocol or amendments.

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

The events will be adjudicated according to FDA requirements. The EAC will review translated copies in English of medical documentation received in the adjudication packages (for example X-ray, ECGs, ultrasound images, discharge summaries,
pathology reports, and death certificates). The investigator must provide medical documentation as soon as possible, when they receive the request from Novo Nordisk.

The assessments made by the EAC will be included in the CTR, as well as assessments made by the investigator. However, the adjudication made by an EAC, given its independence and in-depth analysis of each event, will be attributed with greater importance of the two. The outcomes of adjudication will be kept in the clinical trial database.

12.7.3 **Calcitonin monitoring committee (CMC)**

Please refer to Appendix D for further details.
13 Case report forms

Novo Nordisk will provide a system for the eCRF. This system and support services to the system will be supplied by a vendor. The activities of this vendor will be under the direction and supervision of Novo Nordisk.

Rules for completing the eCRFs

- Ensure that all relevant questions are answered, and that no empty data fields exist
- If a test/assessment has not been done and/or will not be available, indicate this by writing “ND” (not done) in the appropriate answer field in the eCRF. If the question is irrelevant (e.g. is not applicable) indicate this by writing “NA” (not applicable) in the appropriate answer field. Further guidance can be obtained from the instructions in the eCRF

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

13.1 Corrections to electronic case report forms (eCRF)

Corrections to the eCRF data will be made by the investigator or the investigator’s authorised staff. An audit trail will be maintained in the eCRF application containing as a minimum: the old and the new data, identification of the person entering the data, date and time of the entry and reason for the correction.

If corrections are made by the investigator’s authorised staff after the date the investigator has signed the case book, the case book must be signed and dated again by the investigator.

13.2 Case report form flow

The investigator must ensure that data are recorded in the eCRF as soon as possible after the visit/phone contact, preferably within 5 calendar days.

Once data have been entered, they will be available to Novo Nordisk for data verification and validation purposes. Queries will be generated in the eCRF on an ongoing basis, and the investigator should solve these queries preferably within 3 business days.

The SMPG measurements and corresponding insulin doses for titration purpose must be entered within 24 hours after the site visit/phone contact throughout the trial.
At the end of trial the investigator must ensure that all remaining data have been entered into the eCRF **no later than 24 hours** after the subjects’ last visit at the site. In addition, queries must be solved immediately in order to ensure the planned lock of the database.

Site specific eCRF data (in an electronic readable format) will be provided to the investigator after the trial database is locked, and access to update the trial data in eCRF has been revoked. This data will be retained by the site.

When the final CTR is available, the data will be archived by Novo Nordisk.

**13.3 Paper CRFs**

The pregnancy forms are provided as paper CRFs and must be handled according to section 12.5.

The PRO questionnaires will be completed by the subjects on paper, and then the data must be transcribed into the eCRF. The completed documents must be retained at the investigator site as source documentation.

In addition, the AE, SIF and technical complaint forms will be provided as paper CRFs, if for some reason the eCRF is unavailable.

When completing paper CRFs print legibly, using a ballpoint pen. Ensure that all questions are answered, and that no empty data blocks exist. Ensure that no information is recorded outside the data blocks on the paper CRF, as these data will not be captured in the Novo Nordisk trial database.
14 Monitoring procedures

During the course of the trial, the monitor will visit the trial site to ensure that the protocol is adhered to, that all issues have been recorded, to perform source data verification and to monitor drug accountability. The visit intervals will depend on the outcome of the remote monitoring of the eCRFs, the trial site's recruitment rate and the compliance of the trial site to the protocol and GCP, but will not exceed 12 weeks. However, more frequent monitoring visits may be required during peak period such as recruitment and finalisation of the trial.

14.1 Source data verification

There must be a source document agreement at each site, clearly identifying the location of each of the source documents. There should only be one source defined at any time for any data element, for example, source documentation for a laboratory value will be located in the faxed and signed laboratory report. All data collected in the eCRF must be verifiable in source documentation other than the eCRF.

The monitor must be given direct access to source documents (original documents, data and records). Direct access includes permission to examine, analyse, verify and reproduce any record(s) and report(s) that are important to the evaluation of the trial. If electronic medical record are used at site and do 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 phone).

Monitors must review the medical records and other source data (e.g. the diaries and PROs) to ensure consistency and/or identify omissions compared to the eCRF. If discrepancies are found, the investigator must be questioned about these. The original subject diaries and PROs must not be removed from the site. The monitor will ensure that the CRFs are completed and that any paper CRFs are collected.

For SMPG measurements it is accepted that the earliest practically retainable record should be considered as the source data. Therefore, the data recorded by the BG meter and transcribed into the diary by the subject will be considered as the source data. The diary will be considered as source document with respect to:

- Date, time and value of once daily fasting SMPG measurements
- Date, time and value of all 9-point profile SMPG measurements
- Date, time and dose of trial product
- Date and time for hypoglycaemic episodes

For screening failed subjects only informed consent form and screening failure reason must be source data verified.
15  Data management

Data management is always the responsibility of Novo Nordisk Headquarters. Data management may be delegated under an agreement of transfer of responsibilities to another data management unit within Novo Nordisk.

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

Laboratory data from the central laboratory will be transferred electronically from the laboratory performing the analyses. The electronic laboratory data will be considered source data. In cases where laboratory data are transferred via non-secure electronic networks, data will be encrypted during transfer.

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

16  Computerised systems

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

Investigators working on the trial may use their own electronic systems to capture source data. Novo Nordisk will collect information on the practical use of these systems within the conduct of this clinical trial.
17 Statistical considerations

Novo Nordisk will analyse and report data from all sites together.

All analyses of efficacy and safety endpoints will be based on the full analysis set (FAS). The analysis of the primary endpoint will be repeated on the per-protocol (PP) analysis set and the completer analysis set (CAS) for sensitivity purposes. All efficacy endpoints and patient reported outcome endpoints will be summarised using the FAS and safety endpoints will be summarised using the safety analysis set (SAS).

The impact of protocol deviations and outliers may be investigated further in sensitivity analyses if deemed relevant.

Unless otherwise specified, all continuous measurements will be summarised descriptively at each visit by treatment using observed data. After 26 weeks of treatment, descriptive statistics will be presented based both on observed and last observation carried forward (LOCF) imputed data. Endpoints that are analysed untransformed and endpoints that are not formally analysed are summarised by the arithmetic mean, standard deviation (SD), median, and minimum and maximum value. Endpoints that are analysed log-transformed are supplemented with the geometric mean and coefficient of variation (CV).

For measurements over time, mean values will be plotted to explore the trajectory over time. LOCF imputed data will be used as the basis for plotting data, if not otherwise specified. For endpoints that are analysed log-transformed, the geometric mean values will be plotted.

A standard analysis of covariance (ANCOVA) model will be applied for primary and secondary endpoints. The model includes treatment and region as fixed factors and the corresponding baseline value as a covariate. In the following, this model will be referred to as the standard ANCOVA model. Region is a factor with the following 5 levels: Africa, Australia, Europe, North America and South America.

Presentation of results from a statistical analysis will include the estimated mean treatment effects (Least Square Means [LSMeans]) for absolute values and change from baseline. In addition, estimated mean treatment difference (or ratio) will be presented together with the two-sided 95% confidence interval and corresponding two-sided 5% p-value.

Handling of missing data

The expected percentage of missing data is around 15%. In accordance with industry guidance\textsuperscript{13}, endpoints will be assessed at frequent visits and also on subjects who withdraw prematurely. This will facilitate an analysis in accordance with ITT principles. Also, the combined information on
frequent outcomes and information on reason for drop-out is assumed to account for the missing data anticipated.

If an assessment has been made both at screening (Visit 1) and randomisation (Visit 2), and if not otherwise specified, the value from the randomisation visit will be used as the baseline value. If the value measured at the randomisation visit is missing and the assessment also has been made at screening, then the screening value will be used as the baseline value.

Missing values (including intermittent missing values) will be imputed using the LOCF method. LOCF has been a standard approach in diabetes trials for many years, and was used as the primary analysis in both insulin degludec/liraglutide and degludec phase 3a trials. LOCF is considered to be an appropriate method in the context of treat-to-target trials, where subjects after withdrawal typically continue their therapy using commercially available insulin. In previous treat-to-target trials with insulin degludec/liraglutide and degludec, LOCF has generally provided similar results to alternative methods applied to handle missing data, such as repeated measures models and completer analyses. In this trial, similar sensitivity analyses will be made to examine the robustness of the LOCF method. The LOCF approach will also be used to impute missing values in CAS.

Laboratory values below the lower limit of quantification (LLOQ) will be put to LLOQ/2.

17.1 Sample size calculation

The primary objective of this trial is to confirm efficacy of insulin degludec/liraglutide in controlling glycaemia in subjects with T2DM. This is established by showing that the upper boundary of the 95% confidence interval for the mean HbA\textsubscript{1c} treatment difference (insulin degludec/liraglutide minus insulin glargine) is below a non-inferiority margin of 0.30%. This is equivalent to using a one-sided test of size 2.5%, which means that the type 1 error rate is controlled at 2.5%. The primary endpoint will be change from baseline in HbA\textsubscript{1c} after 26 weeks of treatment.

Formally, let D be the mean treatment difference for change in HbA\textsubscript{1c}. The null-hypothesis will be tested against the alternative hypothesis of non-inferiority as given by

$$H_0: \quad D \geq 0.30\% \quad \text{against} \quad H_A: \quad D < 0.30\%$$

Sample size is calculated using a t-statistic under the assumptions of a one-sided test of size 2.5%, a mean treatment difference of 0.0%, a standard deviation of SD=1.0%, and a non-inferiority margin of 0.30%. It is also assumed that 15% of the randomised subjects will be excluded from the PP analysis set. Non-inferiority will be investigated for both the FAS and the PP analysis set in line with the Committee for Proprietary Medicinal Products (CPMP) Points to Consider\textsuperscript{14}. The above assumptions are based on experience from the phase 3a development programmes for insulin degludec/liraglutide and insulin degludec. From these assumptions and based on a 1:1 randomisation the sample size is set to 277 subjects per treatment arm; in total 554 subjects will be
randomised. This will ensure a power of at least 90% for confirming the primary objective in the PP analysis set.

17.2 Definition of analysis sets

The following analysis sets are defined in accordance with the ICH-E9 guidance\textsuperscript{15}.

- **Full Analysis Set (FAS):** includes all randomised subjects. In exceptional cases, subjects may be eliminated from the full analysis set. In such cases the elimination will be justified and documented. The statistical evaluation of the FAS will follow the intention-to-treat (ITT) principle and subjects will contribute to the evaluation “as randomised”.

- **Per-Protocol (PP) analysis set:** includes all subjects in the Full Analysis Set who fulfils the following criteria:
  - Have not violated any inclusion criteria
  - Have not fulfilled any exclusion criteria
  - Have a non-missing HbA\textsubscript{1c} at screening or randomisation
  - Have at least one non-missing HbA\textsubscript{1c} after 12 weeks of exposure
  - Have at least 12 weeks of exposure

Subjects will contribute to the evaluation “as treated”.

- **Safety Analysis Set (SAS):** includes all subjects receiving at least one dose of the investigational product or comparator. Subjects in the safety set will contribute to the evaluation “as treated”.

- **Completer Analysis Set (CAS):** includes all randomised subjects who have completed the trial. Subjects in the completer analysis set will contribute to the evaluation “as randomised”.

Randomised subjects who are lost to follow up and where no exposure information of the investigational product or comparators is available after randomisation will be handled as unexposed.

Before data are released for statistical analysis, a review of all data will take place to identify protocol deviations that could potentially affect the results. Any decision to exclude any subject or observation from the statistical analysis is the joint responsibility of the members of the study group. The subjects or observations to be excluded and the reason(s) for their exclusion will be documented and signed by all parties. The documentation will be stored together with the remaining trial documentation.
17.3 Primary endpoint

The primary endpoint, change from baseline in HbA\textsubscript{1c} after 26 weeks of treatment, will be analysed using an ANCOVA model with treatment and region as fixed effects and baseline HbA\textsubscript{1c} value as covariate.

Non-inferiority of insulin degludec/liraglutide vs. insulin glargine will be considered as confirmed if the 95% confidence interval for the mean treatment difference lies entirely below 0.30%.

17.3.1 Sensitivity analysis

The primary efficacy analysis will be repeated on the PP analysis set and the CAS. A repeated measurements analysis (RMA) of HbA\textsubscript{1c} from baseline to week 26 will be performed on the FAS to evaluate the sensitivity of using LOCF. All HbA\textsubscript{1c} values available post baseline at scheduled measurement times will be analysed in a linear mixed normal model using an unstructured residual covariance matrix for HbA\textsubscript{1c} measurements within the same subject. The model will include treatment, visit, and region as fixed factors and baseline HbA\textsubscript{1c} value as covariate. Furthermore, the model will include interaction terms between treatment and visit, between region and visit, and between baseline HbA\textsubscript{1c} and visit.

The treatment difference after 26 weeks of treatment will be compared to the results of the ANCOVA method using LOCF for imputation of missing data. Any marked difference between the RMA and ANCOVA LOCF approach regarding the estimated treatment difference will be commented upon in the CTR.

17.4 Secondary endpoints

17.4.1 Confirmatory secondary endpoints

If the primary objective is confirmed then the primary endpoint (change in HbA\textsubscript{1c}) will also be tested for superiority. In addition, the following two confirmatory secondary endpoints will be tested for superiority.

- Change from baseline in body weight after 26 weeks of treatment
- Number of treatment emergent confirmed hypoglycaemic episodes during 26 weeks of treatment

The tests for superiority will be based on the FAS. The family-wise type I error rate for all three endpoints tested for superiority (the primary and the two secondary confirmatory endpoints) will be controlled in the strong sense using the Holm-Bonferroni method. Superiority for change in HbA\textsubscript{1c}, and body weight will be considered confirmed if both the two-sided p-value is strictly below the adjusted significance level and the estimated mean treatment difference (insulin degludec/liraglutide minus insulin glargine) is strictly below zero. For confirmed hypoglycaemic episodes superiority
will be considered confirmed, if both the two-sided p-value is strictly below the adjusted significance level, and the estimated mean treatment ratio (insulin degludec/liraglutide vs. insulin glargine) is strictly below one. The Holm-Bonferroni method controls the family-wise error rate for all the three comparisons at a 2.5% level in the strong sense.

Operationally, the Holm-Bonferroni method implies that a two-sided p-value should be calculated for each of the three comparisons for the confirmatory endpoints, and then ordered from the smallest to the largest. Testing will proceed until an insignificant result shows as detailed in the three steps below:

(i) If the smallest of the p-values is below the adjusted significance level of 0.05/3 and the associated estimated mean treatment difference (ratio) is strictly below zero (one) superiority will be considered confirmed and the testing can proceed. Otherwise the testing should stop with no additional claims of superiority.

(ii) If the testing is allowed to proceed and the second smallest p-value is below the adjusted significance level of 0.05/2 and the associated estimated mean treatment difference (ratio) is strictly below zero (one) superiority will be considered confirmed and the testing can proceed. Otherwise the testing should stop with no additional claims of superiority.

(iii) If the testing is allowed to proceed and the largest p-value is below the adjusted significance level of 0.05/1 and the associated estimated mean treatment difference (ratio) is strictly below zero (one) superiority will be considered confirmed.

The change from baseline in body weight after 26 weeks of treatment will be analysed using an ANCOVA model with treatment and region as fixed effects and baseline body weight value as covariate. Superiority of insulin degludec/liraglutide vs. insulin glargine will be considered as confirmed if the mean treatment difference lies below zero and the p-value lies below the Holm-Bonferroni’s adjusted significance level.

Number of treatment emergent confirmed hypoglycaemic episodes from randomisation to 26 weeks of treatment will be analysed using a negative binomial regression model with a log-link function and the logarithm of the time period in which a hypoglycaemic episode is considered treatment emergent as offset. The model will include treatment and region as fixed factors. Superiority of insulin degludec/liraglutide vs. insulin glargine will be considered as confirmed if the mean treatment ratio lies below one and the p-value lies below the Holm-Bonferroni’s adjusted significance level.

The test for superiority of change from baseline in HbA1c after 26 weeks of treatment will be done using the same model as applied for the primary analysis. Superiority of insulin degludec/liraglutide vs. insulin glargine will be considered as confirmed if the mean treatment difference lies below zero and the p-value lies below the Holm-Bonferroni’s adjusted significance level.
17.4.2 Supportive secondary endpoints

17.4.2.1 Efficacy endpoints

Insulin dose after 26 weeks of treatment

The actual daily insulin dose after 26 weeks of treatment will be analysed using an ANCOVA model including treatment and region as fixed factors and baseline HbA1c value and baseline insulin dose as covariates.

HbA1c responder endpoints after 26 weeks of treatment (yes/no)

Two dichotomous endpoints (responder/non-responder) will be defined based on whether a subject has met a specific target level after 26 weeks of treatment:

- ADA HbA1c target (HbA1c < 7.0%)
- International Diabetes Federation (IDF) HbA1c target (HbA1c ≤ 6.5%)

Analysis of each of the two responder endpoints will be based on a logistic regression model with treatment and region as fixed factors and baseline HbA1c value as a covariate.

HbA1c responder endpoints without weight gain

Responder for HbA1c without weight gain after 26 weeks of treatment will be defined as HbA1c < 7.0% or ≤ 6.5% at end of treatment and change in body weight from baseline below or equal to zero. Analysis of each of the two responder endpoints will be based on a logistic regression model with treatment and region as fixed factors and baseline HbA1c and body weight values as covariates.

HbA1c responder endpoints without hypoglycaemic episodes

Responder for HbA1c without confirmed hypoglycaemic episodes after 26 weeks of treatment will be defined as HbA1c < 7.0% or ≤ 6.5% at end of treatment and without confirmed episodes during the last 12 weeks of treatment. Analysis of each of the two responder endpoints will be based on a logistic regression model with treatment and region as fixed factors and baseline HbA1c values as a covariate.

HbA1c responder endpoints without hypoglycaemic episodes and weight gain

Responder for HbA1c without hypoglycaemic episodes and weight gain after 26 weeks of treatment will be defined as HbA1c < 7.0% or ≤ 6.5% at end of treatment, without confirmed episodes during the last 12 weeks of each treatment period, and change in body weight from baseline below or equal to zero. Analysis of each of the two responder endpoints will be based on a logistic regression model.
model with treatment and region as fixed factors and baseline HbA$_{1c}$ and body weight values as covariates.

**Fasting plasma glucose (FPG)**

Change from baseline in FPG after 26 weeks of treatment will be analysed using the standard ANCOVA model.

**Waist circumference**

Change from baseline in waist circumference after 26 weeks of treatment will be analysed using the standard ANCOVA model.

**Systolic and diastolic blood pressure**

Change from baseline in systolic and diastolic blood pressure after 26 weeks of treatment will be analysed separately using the standard ANCOVA model.

**Self measured plasma glucose (SMPG) 9-point profile**

Two endpoints from the 9 point SMPG profile will be defined:

- Mean of the 9-point profile, defined as the area under the profile (calculated using the trapezoidal method) divided by the measurement time.
- Post-prandial PG increments (from before meal to 90 min after for breakfast, lunch and dinner). The mean increment over all meals will be derived as the mean of all available meal increments.

Change from baseline after 26 weeks of treatment in mean of the 9-point profile and post-prandial increment endpoints will be analysed separately using the standard ANCOVA model. The endpoint obtained at baseline will be used as covariate.

**Fasting human insulin, fasting pro-insulin and fasting C-peptide**

These endpoints after 26 weeks of treatment will be analysed separately using the standard ANCOVA model. In these statistical analyses the endpoint will be log-transformed and so will the baseline covariate.

**Fasting lipid profile**

Cholesterol, LDL-cholesterol, HDL-cholesterol, VLDL-cholesterol, triglycerides and free fatty acids will after 26 weeks of treatment be analysed separately using the standard ANCOVA model.
In these statistical analyses, the endpoint will be log-transformed and so will the corresponding baseline covariate.

17.4.2.2 Safety endpoints

Adverse events

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

A Treatment Emergent Adverse Event (TEAE) is defined as an event that has onset date on or after the first day of exposure to randomised treatment and no later than seven days after the last day of randomised treatment. If the event has onset date before the first day of exposure on randomised treatment and increases in severity during the treatment period and until 7 days after the last drug date, then this event should also be considered as a TEAE.

TEAEs are summarised descriptively, whereas non-treatment emergent AE’s are presented in listings. TEAE data will be displayed in terms of the number of subjects with at least one event (N), the percentage of subjects with at least one event (%), the number of events (E) and the event rate per 100 years of exposure (R).

Summaries of TEAEs and of serious TEAEs will be presented as an overview including all AEs, serious AEs, number of deaths, AEs by severity, AEs by relation to treatment and AEs of special interest including AEs leading to withdrawal.

Furthermore summary tables based on system organ class and preferred terms are made for:

- All TEAEs
- Serious TEAEs
- Possibly or probably related TEAEs
- Severe, moderate and mild TEAEs
- TEAEs reported by safety areas of interest
- TEAEs with preferred term that are experienced by at least 5% (1%) of the subjects in any treatment arm or by at least 5% (1%) of all subjects

A listing for non-treatment emergent adverse events with onset date before the first day of exposure to randomised treatment will be presented. A listing will also be presented for non-treatment emergent adverse events collected after the treatment emergent period according to the definition of TEAE.
Hypoglycaemic episodes

Hypoglycaemic episodes are recorded by subjects in their trial diaries throughout the trial. The information collected includes PG before treating the episode and whether the subject was able to treat him/herself. This information is used by Novo Nordisk to classify an episode according to the confirmed hypoglycaemia definition and the ADA definition\textsuperscript{16} (severe, documented symptomatic, asymptomatic, probable symptomatic and relative).

Definition of hypoglycaemia

A hypoglycaemic episode will be defined as treatment emergent if the onset of the episode occurs on or after the first day of trial product administration, and no later than 7 days after the last day on trial product.

Hypoglycaemic episodes will be defined as nocturnal if the time of onset is between 00:01 and 05.59 inclusive.

Confirmed hypoglycaemia

Confirmed hypoglycaemic episodes are defined as episodes that are either:

- severe (i.e. an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions) or
- an episode biochemically confirmed by a plasma glucose value of $< 3.1$ mmol/L (56 mg/dL), with or without symptoms consistent with hypoglycaemia.

In normal physiology, symptoms of hypoglycaemia occur below a plasma glucose level $3.1$ mmol/L (56 mg/dL)\textsuperscript{17}. Therefore, Novo Nordisk has included hypoglycaemia with plasma glucose levels below this cut-off point in the definition of confirmed hypoglycaemia.

ADA classification of hypoglycaemia

**Severe hypoglycaemia:** An episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.

**Asymptomatic hypoglycaemia:** An episode not accompanied by typical symptoms of hypoglycaemia, but with a measured plasma glucose concentration $\leq 3.9$ mmol/L (70 mg/dL).

**Documented symptomatic hypoglycaemia:** An episode during which typical symptoms of hypoglycaemia are accompanied by a measured plasma glucose concentration $\leq 3.9$ mmol/L (70 mg/dL).
Relative hypoglycaemia: An episode during which the person with diabetes reports any of the typical symptoms of hypoglycaemia, and interprets those as indicative of hypoglycaemia, but with a measured plasma glucose concentration > 3.9 mmol/L (70 mg/dL).

Probable symptomatic hypoglycaemia: An episode during which symptoms of hypoglycaemia are not accompanied by a plasma glucose determination (but that was presumably caused by a plasma glucose concentration ≤ 3.9 mmol/L [70 mg/dL]).

**Figure 17–1** ADA classification of hypoglycaemia

Data on treatment emergent hypoglycaemic episodes are presented in terms of the number of subjects with at least one event (N), the percentage of subjects with at least one event (%), the number of events (E) and the event rate per 100 years (R). Separate summaries are made by severity considering all confirmed hypoglycaemic episodes, nocturnal confirmed hypoglycaemic episodes and the ADA classification of hypoglycaemia.

The number of treatment emergent nocturnal confirmed hypoglycaemic episodes will be analysed using the same model as used for the treatment emergent confirmed hypoglycaemic episodes.

**Pulse**

Change from baseline in pulse after 26 weeks of treatment will be analysed using the standard ANCOVA model.

**Clinical evaluations (physical examination, eye examination and ECG)**
Eye examination (fundoscopy/fundusphotography) and ECG findings will be summarised descriptively, including:

- summaries
- the change from baseline after 26 weeks of treatment

Any findings in the physical examination evaluation at screening will be presented as listings. Any clinically significant deterioration of a pre-existing condition after the screening visit, as well as any new clinically significant findings will be recorded as adverse events.

**Laboratory assessments**

All laboratory parameters will be summarised descriptively.

The following tables will be presented based on both observed and LOCF imputed data:

- Shift tables from baseline to after 26 weeks of treatment
- Proportion of subjects with measurements outside reference range by treatment and week.

Laboratory values will be presented graphically as box plots by treatment and week.

For each laboratory parameter, individual values outside the reference ranges (abnormal values) will be listed.

**17.5 Health economics and/or patient reported outcomes**

The following questionnaires will be used to compare patient reported outcomes between treatments:

- Change from baseline in patient reported outcomes after 26 weeks of treatment
  - TRIM-D
  - SF-36
- Titration barrier questionnaire at baseline (a questionnaire to assess the reasons for patients not being optimally titrated when entering the trial)

For each questionnaire, the score will be summarised descriptively. For the questionnaires SF-36 and TRIM-D, the change from baseline in total score will be analysed separately using the standard ANCOVA model.
18 Ethics

The trial will be conducted in compliance with ICH GCP\(^9\) and applicable regulatory requirements, and in accordance with the Declaration of Helsinki.\(^{18}\)

All subjects included in the trial will be treated with insulin degludec/liraglutide or insulin glargine, both in combination with metformin, in order to improve their glycaemic control.

Randomised subjects will be transferred to a treatment regimen (fixed ratio combination of insulin degludec/liraglutide or insulin glargine) anticipated to be better than or equal to the treatment they received prior to entering the trial. All participating subjects will need to spend some extra time as additional visits to the clinic are required, and some of the required tests performed during the trial are outside the normal practice.

Inclusion and exclusion criteria have been defined in order to ensure that subjects are eligible for trial participation at the time of enrolment. Furthermore, withdrawal criteria are defined to ensure that subjects are considered for withdrawal, if the level of glycaemic control exceeds acceptable limits during trial participation.

Insulin degludec and liraglutide have shown to be effective in lowering blood glucose levels. It can therefore be expected that the majority of subjects with insufficiently controlled blood glucose, randomised to treatment with fixed combination of insulin degludec/liraglutide, will experience an improved glucose control during the trial. In addition, these subjects may benefit from the effect of treatment on weight previously demonstrated for liraglutide.

Subjects remaining on insulin glargine may also experience an improved glucose control during the trial due to the increased focus on titration and frequent site contact. The reason for continuing unchanged pre-trial therapy in insulin glargine arm is to investigate the distinct efficacy and safety associated with a switch of therapy to insulin degludec/liraglutide in subjects inadequately controlled with basal insulin. The trial design will allow for measurements of the clinical benefit in terms of HbA1c reduction, that subjects not adequately controlled on basal insulin will gain from the switch.

There is no information available today indicating that an overall risk associated with the use of insulin degludec/liraglutide could exceed the risks associated with the use of the individual compounds.

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

There have been a few clinical reported events of acute pancreatitis (inflammation of the pancreas) presenting with persistent severe abdominal pain (usually accompanied by vomiting) with liraglutide treatment. As a consequence of the known events of acute pancreatitis, Novo Nordisk will analyse blood samples for amylase and lipase during the trial to monitor the subjects’ safety.

Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumours at clinically relevant exposures in both genders of rats and mice. It is unknown whether liraglutide causes thyroid C-cell tumours, including MTC, in humans, as human relevance could not be ruled out by clinical or non-clinical studies. Liraglutide is contraindicated in subjects with a personal or family history of MTC and in subjects with MEN2. Based on the findings in rodents, monitoring with serum calcitonin or thyroid ultrasound was performed during clinical trials, but this may have increased the number of unnecessary thyroid surgeries. It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate human risk of thyroid C-cell tumours. An independent CMC will evaluate the calcitonin levels throughout the trial (refer to Appendix D for more information).

Dorsal skin sarcomas at the injection site were significantly increased in male mice at the highest dose of 3 mg/kg/day. These fibrosarcomas were attributed to the high local concentration of drug near the injection site. The liraglutide concentration in the clinical formulation (6 mg/ml) is 10-times higher than the concentration in the formulation used in the carcinogenicity study (0.6 mg/ml). The observed increase in skin sarcomas in high-dose male mice is of unknown relevance for human safety.

In reproduction and development toxicity studies liraglutide has been shown to be teratogenic in rats and rabbits including reduced growth and major abnormalities at systemic exposures below human exposure at the maximum recommended human dose (MRHD) of 1.8 mg/day. The US Victoza® Prescribing Information includes the Pregnancy Category C (US FDA Pharmaceutical Pregnancy Categories: “Animal reproduction studies have shown an adverse effect on the foetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks”).

Areas of special interest with regards to safety of trial products are described in detail in the insulin degludec NN1250 IB¹ current version or any updates hereof, the liraglutide local approved labelling current version or any updates hereof and/or the insulin degludec/liraglutide NN9068 IB² current version or any updates hereof.

The subjects will have the right to withdraw from the trial at any time, without giving a specific reason.
When treatment with trial products ends, the subject and the investigator will decide on the best available treatment.

18.1 Informed consent

In seeking and documenting informed consent, the investigator must comply with applicable regulatory requirements and adhere to ICH GCP\textsuperscript{2} and the requirements in the Declaration of Helsinki\textsuperscript{18}.

Before any trial-related activity, the investigator must give the subject oral and written information about the trial in a form that the subject can read and understand. Subjects must be fully informed about their responsibilities and rights while participating in the trial, as well as about possible advantages/disadvantages when being treated with trial product. Subjects must have the opportunity to ask questions, and the investigator must ensure the subject has ample time to come to a decision whether or not to participate in the trial.

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

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

Prior to participation in the trial the subject should receive a copy of the signed and dated written informed consent form.

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

In this trial an additional informed consent form must be obtained if:

- A genetic blood test for detection of MEN2 syndrome is to be performed in subjects with confirmed C-cell abnormalities after thyroidectomy
- A female subject becomes pregnant during the trial, the male partner should be asked to sign a separate informed consent form (when an abnormality is found in the foetus or newborn infant)
- A male subject report that his female partner becomes pregnant during the trial, the female partner should be asked to sign a separate informed consent form (only applicable for US).
18.2 Data handling

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

- Data already collected will be retained by Novo Nordisk, entered into the trial database and used for the trial report
- Safety events will be reported to Novo Nordisk and regulatory authorities according to local/national requirements

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

18.3 Premature termination of the trial and/or trial site

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

If a trial is suspended or prematurely terminated, the investigator must inform the subjects promptly and ensure appropriate therapy and follow-up. The investigator and/or Novo Nordisk should also promptly inform the IRBs/IECs and provide a detailed written explanation. The relevant regulatory authorities should be informed.

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

Deviations from the protocol should be avoided.

Novo Nordisk does not allow exceptions to the inclusion or exclusion criteria defined in the protocol. In rare cases where a subject has been randomised into the trial in error despite ineligibility, the subject should be withdrawn immediately and the local IEC/IRB and regulatory authorities should be notified in accordance with local requirements.

If deviations do occur, the investigator must inform the monitor and the implications of the deviation must be reviewed and discussed.

Investigators must document and explain protocol deviations by stating the reason, date, and the action(s) taken. Some deviations, for which corrections are not possible, can be acknowledged and confirmed via edit checks in the eCRF or via listings from the clinical database.

Documentation on all protocol deviations must be kept in the investigator’s trial file and Novo Nordisk trial master file.

20 Audits and inspections

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

Before a site is allowed to start screening subjects, the following documents must be available to Novo Nordisk:

- Regulatory approval and/or acknowledgement of notification as required
- Curricula vitae of investigator and sub-investigator(s) (current, dated and signed and/or supported by an official regulatory document. Must include documented GCP training or a certificate)
- Signed receipt of IB
- Signed and dated agreement on the final protocol and any substantial protocol amendment, if applicable
- Approval/favourable opinion from IRBs/IECs clearly identifying the documents reviewed as follows: protocol, any substantial protocol amendments, SI/IC form, any other written information to be provided to the subject and subject recruitment materials
- List of IRB/IEC members and/or constitution
- Financial agreement(s)
- Source document agreement
- Central laboratory certification and normal ranges
- Insurance statement, if applicable
- Signed and dated investigator agreement
- Financial disclosure form for all investigators


US sites: FDA form 1572 must be completed and signed by each principal investigator. All sub-investigators and other clinical trial staff performing significant clinical investigation-related duties should be listed in the FDA form.

FDA form 1572:

For US sites:

- Intended for US sites
- Trial conducted under the investigational new drug (IND) application
- Each US principal investigator must complete and sign the FDA form 1572 as indicated above

For sites outside the US:

- Not intended for participating sites outside of the US
- Trial not conducted under the IND
- All investigators outside of the US will not sign FDA form 1572
Novo Nordisk will use ‘mynovotrial.com’, an investigator portal (secure website), to distribute and confirm receipt of trial documentation.

Novo Nordisk will analyse and report data from all sites together. As documented in writing by protocol signature, each investigator agrees to comply fully with ICH GCP\(^2\), applicable regulatory requirements and the Declaration of Helsinki\(^18\).
22 Responsibilities

All staff (Novo Nordisk, site, laboratory, Clinical Research Organisation (CRO), etc) will conduct the trial in compliance with ICH GCP\(^9\), applicable regulatory requirements and the Declaration of Helsinki\(^{18}\).

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

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

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

22.1 Source data handling

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’s trial file. The documents should be kept in a secure locked facility, so no unauthorised persons can get access to the data. The subject ID list should be kept securely and separate from the personal 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.

22.2 Delegation of responsibilities

During any period of unavailability, the investigator should 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 of investigator (e.g. if he/she retires), a new investigator will be appointed in consultation with Novo Nordisk.

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

The information obtained during the conduct of this trial is considered confidential, and may be used by Novo Nordisk for regulatory purposes and for the general development of the trial product. All information supplied by Novo Nordisk in connection with this trial shall remain the sole property of Novo Nordisk and is to be considered confidential information. No confidential information shall be disclosed to others without prior written consent from Novo Nordisk. Such information shall not be used except in the performance of this trial. The information obtained during this trial may be made available to other physicians, who are conducting other clinical trials with the trial product, if deemed necessary by Novo Nordisk.

Novo Nordisk will be responsible for preparation of the CTR. The CTR will be reviewed and signed by one or more investigator(s) (Signatory Investigator(s)) appointed by Novo Nordisk.

23.1 Communication of results

Novo Nordisk commits to communicating, and otherwise making available for public disclosure, results of trials regardless of outcome. Public disclosure includes publication of a paper in a scientific journal, abstract submission with a poster or oral presentation at a scientific meeting, or disclosure by other means.

Novo Nordisk reserves the right to defer the release of data until specified milestones are reached, for example when the CTR is available. This includes the right not to release the results of interim analyses, because the release of such information may invalidate the results of the entire trial.

At the end of the trial, one or more public disclosures 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.

The results of this trial will be subject to public disclosure on external web sites according to international regulations, as reflected in the Novo Nordisk Code of Conduct for Clinical Trial Disclosure.

In all cases the trial results will be reported in an objective, accurate, balanced and complete manner, with a discussion of the strengths and limitations. All authors will be given the relevant statistical tables, figures, and reports needed to support the planned publication. In the event of any disagreement on the content of any publication, both the investigators’ and Novo Nordisk opinions will be fairly and sufficiently represented in the publication.

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

23.1.1  Authorship

Authorship of publications should be in accordance with the Uniform Requirements of the International Committee of Medical Journal Editors (sometimes referred to as the Vancouver Criteria20).

The investigator(s) offered authorship will be asked to comment and approve the publication. No permission to publish will be granted to any CRO involved in the trial described in this protocol.

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

For a multi-centre clinical trial, analyses based on single-site data usually have significant statistical limitations and frequently do not provide meaningful information for healthcare professionals or subjects, and therefore may not be supported by Novo Nordisk. It is a Novo Nordisk policy that such individual reports do not precede the primary manuscript and should always reference the primary manuscript of the trial.

Novo Nordisk reserves the right to prior review of such publications and to ask for deferment of publication of individual site results until after the primary manuscript is accepted for publication. Novo Nordisk intends to comply with the industry policy to have a publication submitted for publication no later than 12-18 months after study completion.

23.2  Investigator access to data and review of results

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

Individual investigators will have access to their research participants’ data. The clinical data submitted in the eCRF by the investigator will be available on a compact disc (CD) containing the subjects’ eCRF data in PDF format.
24 Retention of clinical trial documentation

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

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

The investigator must be able to access his/her trial documents without involving Novo Nordisk in any way. Site-specific CRFs and other subject data (in an electronic readable format or as paper copies or prints) will be provided to the investigator before access is revoked to the systems and/or electronic devices supplied by Novo Nordisk. These data must be retained by the site. If the Novo Nordisk provided data (e.g. the CD-ROM) is not readable during the entire storage period, the investigator can request a new copy, as a copy of all data will be stored by Novo Nordisk.

Novo Nordisk will maintain Novo Nordisk documentation pertaining to the trial for as long as the product is on the market plus 20 years.

The files from the investigator site/institution must be retained for 15 years after the completion of the trial, or longer if required by national regulations. The deletion process must ensure confidentiality of data and must be done in accordance with local requirements.

25 Institutional review boards/independent ethics committees and regulatory authorities

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

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

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

**Regulatory Authorities**

Regulatory authorities will receive the clinical trial application (CTA), substantial/non-substantial protocol amendments, updates to the IB, reports on SAEs, and the CTR according to national requirements.

**26 Indemnity statement**

Novo Nordisk carries product liability for its products, and liability is 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 by the clinics or doctors conducting experiments, or by persons for whom the said clinic or doctors are responsible.

Novo Nordisk accepts liability in accordance with:

**Australia (AU):** Comply with Medicines Australia Form of Indemnity for clinical trials version 160104B dated 16 January 2004

**Russia (RU):** Federal Law of 12 April 2010 No. 61-FZ “On Medicinal Drugs’ Circulation”

**Spain (ES):** Royal decree 223/2004, of 6th February, establishing the requisites concerning clinical trials
27 References


8 European Commission Regulation for EudraCT. 2011.


12 FDA Centre for Drug Evaluation and Research (CDER), Division of Metabolism and Endocrinology Products. Standardized Definitions for Endpoint Events Cardiovascular Trials: Draft Recommendations. 20-Oct-2010.


14 EMEA-Committee for Proprietary Medicinal Products. CPMP/EWP/482/99 - Points to consider on switching between superiority and non-inferiority. 27-Feb-2000.


Common Technical Document Summaries

Insulin degludec/liraglutide (IDegLira)

2.7.3: Appendix 6.2

Statistical Methods

This confidential document is the property of Novo Nordisk. No unpublished information contained herein may be disclosed without prior written approval from Novo Nordisk. Access to this document must be restricted to relevant parties.
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List of abbreviations

ANOVA  analysis of variance
HbA\textsubscript{1c}  glycosylated haemoglobin
IDegLira  insulin degludec/liraglutide
k  number of confirmatory secondary endpoint
SD  standard deviation
1 Multiple imputation (pattern mixture model)

After withdrawal, subjects in the IDegLira arm were assumed to have the same mean response distribution as the subjects treated with the comparator. This means that the treatment effect of IDegLira was assumed to wear off after subject withdrawal.

For continuous endpoints, this method implied that in the first step intermittently missing values were imputed using a Markov Chain Monte Carlo method in order to obtain a monotone missing data pattern. One thousand (1000) copies of the dataset were generated. In the second step, for each dataset copy, an analysis of variance (ANOVA) model with the same factors and covariates as the primary model was fitted to the first post-baseline visit value for the comparator group only. The estimated parameters, and their variances, from this model were used to impute missing values at the first post-baseline visit for subjects in all treatment groups. Subsequently, missing values at the next planned visit were imputed in the same manner, but also included the parameter value from the previous visit as a covariate in the model. This was done in a stepwise manner for all available planned visits.

In Trial 3697 which had three treatment arms, the imputation followed the hypothesis being tested. When estimating the IDegLira vs. IDeg treatment contrast the imputation in the IDegLira arm was based on IDeg values, whereas for the IDegLira vs. liraglutide treatment contrast the imputation in the IDegLira arm was based on liraglutide values. For each analysis, the third arm was still to be kept in the model.

For each complete dataset, the change from baseline to week 26 was analysed using an ANOVA model with the same set of factors and covariates as the primary analysis. The estimates and standard deviations (SD) were then pooled to one estimate and associated SD using Rubin’s rule.

For the evaluation of non-inferiority in terms of change in HbA

1c

, subjects on IDegLira were assumed to be switched to a treatment inferior to comparator (trial-specific): i.e., 0.3% was added to the imputed values in the IDegLira arm prior to the final ANOVA.

For the sensitivity analysis of HbA

1c

responder endpoints, missing data at the end of the trial were imputed by applying the responder criterial to the imputed HbA

1c

values. The resulting estimates and SD were then pooled using Rubin’s formula.

For confirmed hypoglycaemic episodes, samples from the posterior distribution of model parameters using a Bayes negative binomial log-link model with the same covariates as in the original analysis and log of the treatment-emergent exposure time as an offset were extracted. For each imputed set of model parameters (1000), the expected number of episodes after withdrawal, conditional on the observed number of episodes, was imputed from a negative binomial distribution.
based on the expected episode rates before and after withdrawal. To mimic an intention-to-treat scenario where withdrawn subjects were assumed to be switched to comparator treatment after withdrawal, each withdrawn subject’s expected episode rate after withdrawal was assumed to be the same as in the comparator group. The imputed number of episodes was then analysed using a negative binomial model with log link and the same covariates as in the original analysis as well as with log of the total treatment-emergent exposure as offset. Total treatment-emergent exposure time for withdrawn subjects was assumed to be a maximum of either 27 weeks or a maximum of all treatment-emergent exposure times for withdrawn subjects within a trial. Finally, the estimates were pooled to one estimate and associated SD using Rubin’s formula.

*Copy reference*

After withdrawal, subjects in the IDegLira arm were assumed to have the same mean response as the subjects treated with the comparator. This means that subjects who withdrew from the IDegLira arm were assumed to have been treated with the comparator treatment during the trial.

For continuous variables the imputation was based on a sequential approach and post-baseline measurements from withdrawn IDegLira subjects were not used in this imputation. This method implied that in the first step intermittently missing values were imputed using a Markov Chain Monte Carlo method in order to obtain a monotone missing data pattern. One thousand (1000) copies of the dataset were generated. In the second step, for each dataset copy, an ANOVA model with the same factors and covariates as the primary model was fitted to the first post-baseline visit value for the comparator group only. The estimated parameters, and their variances, from this model were used to impute values at the first post baseline visit for all withdrawn subjects in the IDegLira group and missing values in the comparator group. Subsequently, missing values at the next planned visit were imputed in the same way, but now included the parameter value from the previous visit as a covariate in the model. This was done in a stepwise manner for the available planned visits.

In Trial 3697 which had three treatment arms, the imputation followed the hypothesis being tested. When estimating the IDegLira vs. IDeg treatment contrast, the imputation in the IDegLira arm was based on IDeg values, whereas for the IDegLira vs. liraglutide treatment contrast the imputation in the IDegLira arm was based on liraglutide values. For each analysis, the third arm was still to be kept in the model.

For each complete dataset, the change from baseline to week 26 was analysed using an ANOVA model with the same set of factors and covariates as the primary analysis. The estimates and SD were then pooled to one estimate and associated SD using Rubin’s rule.
For the evaluation of non-inferiority in terms of change in HbA\textsubscript{1c}, subjects on IDegLira were assumed to be switched to a treatment inferior to comparator (trial-specific): i.e., 0.3% was added to the imputed values in the IDegLira arm prior to the final ANOVA.

For the corresponding sensitivity analysis of HbA\textsubscript{1c} responder endpoints, missing data at end-of-trial were imputed by applying the responder criteria to the imputed HbA\textsubscript{1c} values. Resulting estimates and SD were then pooled using Rubin’s formula.

For confirmed hypoglycaemic episodes, samples from the posterior distribution of model parameters using a Bayes negative binomial log-link model with the same covariates as in the original analysis and log of the treatment-emergent exposure time as an offset were extracted.\textsuperscript{1} For each imputed set of model parameters (1000), the expected number of episodes after withdrawal conditional on the observed number of episodes was imputed from a negative binomial distribution based on the expected episode rates before and after withdrawal. To mimic an intention-to-treat scenario where withdrawn subjects were assumed to be on comparator treatment throughout the entire trial, each withdrawn subject’s expected episode rate both before and after withdrawal was assumed to be the same as in the comparator group. The imputed number of episodes was then analysed using a negative binomial model with log link and the same covariates as in the original analysis as well as with log of the total treatment-emergent exposure as offset. Total treatment-emergent exposure time for withdrawn subjects was assumed to be a maximum of either 27 weeks or a maximum of all treatment-emergent exposure times for withdrawn subjects within a trial. Finally, the estimates were pooled to one estimate and associated SD using Rubin’s formula.
2 The Holm-Bonferroni method of adjustment for multiplicity

The family-wise type-I error rate for the four confirmatory secondary hypotheses in Trial 3697 and the three confirmatory hypotheses in Trial 3952 was controlled in the strong sense using the Holm-Bonferroni method.²

The Holm-Bonferroni method implied that a two-sided p-value was calculated for each of the comparisons for the confirmatory secondary hypotheses and then ordered from the smallest to the largest. The p-values were then evaluated against an adjusted significance threshold determined by the number of confirmatory hypotheses being tested as described below. If the smallest of the p-values was below the adjusted significance threshold of 0.05/k, where k was the number of confirmatory secondary hypotheses (four in Trial 3697 and three in Trial 3952), this result was considered to be statistically significant, and superiority confirmed if the 95% confidence interval for the estimated treatment difference was entirely below 0%. The testing could then proceed to the comparison with the second smallest p-value. If the smallest p-value was above the adjusted significance threshold, further testing of confirmatory hypotheses was not to be performed. If the testing was allowed to proceed, the second smallest p-value was then to be evaluated against an adjusted significance threshold of 0.05/(k-1) in the manner described above. If the second smallest p-value was ≥0.05/(k-1), further testing was not to be performed. If the second smallest p-value was below 0.05/(k-1), the testing was allowed to proceed and the third smallest p-value was then to be compared to 0.05/(k-2) in the same manner as described above. Further testing continued along these principles. Overall, this pre-specified confirmatory statistical testing strategy controlled the type I error rate at a 2.5% level (1-sided) in the strong sense.
3 References
