Statistical Analysis Plan

BEGIN™: Switch 2

Trial ID: NN1250-3998

A randomised, double blind, cross-over trial comparing the safety and efficacy of insulin degludec and insulin glargine, with or without OADs subjects with type 2 diabetes

Redacted statistical analysis plan
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Table of contents

Page

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List of abbreviations

ADA	*American diabetes association*
AE	*adverse event*
ANOVA	*analysis of variance*
BG	*Blood glucose*
BID	*"Bis in die" Twice a day*
BMI	*body mass index*
CAS	*Completer analysis set*
CI	*confidence interval*
CRF	*case report form*
CTR	*clinical trial report*
EAC	*Event adjudication committee*
EoT	*end-of-text*
FAS	*full analysis set*
ITT	*intention to treat*
LOCF	*last observation carried forward*
MAR	*Missing at random*
MedDRA	*Medical Dictionary for Regulatory Activities*
MMRM	*mixed models for repeated measurement*
OD	*Once daily*
PD	*pharmacodynamics*
PK	*pharmacokinetics*
PP	*per protocol*
SAE	*serious adverse event*
SAP	*statistical analysis plan*
SAS	*safety analysis set*
SD	*standard deviation*
SE	*standard error*
SMPG	*self measured plasma glucose*

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1 Introduction

1.1 Trial information

The primary objective is to demonstrate that treatment with IDeg once daily (OD) is associated with a lower rate of severe or BG (blood glucose) confirmed symptomatic hypoglycaemia compared to IGlar OD. This is done by demonstrating that the upper limit of the 95% confidence interval of the rate ratio (IDeg OD/IGlar OD) is entirely below one.

Secondary objectives
To confirm superiority of IDeg OD compared to IGlar OD in terms of severe or BG confirmed symptomatic nocturnal hypoglycaemia.

To confirm superiority of IDeg OD compared to IGlar OD in terms of proportion of subjects with severe hypoglycaemic episodes.

To compare efficacy of IDeg OD vs. IGlar OD in controlling glycaemia with respect to change from baseline in HbA_{1c} after 32 weeks of treatment. This is done by comparing the difference in change from baseline in HbA_{1c} after 32 weeks of treatment between IDeg OD and IGlar OD to a non-inferiority limit of 0.4%.

To compare IDeg OD and IGlar OD in terms of safety, other parameters of glycaemic control and patient reported outcome (PRO).

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Trial design:

This trial is a 64-week, randomised, controlled, double blind, two-period, cross-over, multi-centre, treat-to-target trial comparing safety of IDeg and IGlar both administered once daily ± OADs in subjects with type 2 diabetes mellitus (T2DM) previously treated with basal insulin once or twice daily ± OADs excluding sulfonylureas (SUs)/glinides.

Subjects will be switched from pre-trial basal insulin ± OADs excluding (SUs)/glinides and randomly allocated into one of two treatment sequences in a blinded manner:

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- IDeg OD ± OADs followed by IGlar OD ± OADs
- IGlar OD ± OADs followed by IDeg OD ± OADs

Within each treatment arm subjects will be randomised 1:1 to morning or evening dosing. The dosing time will be kept throughout both treatment periods.

The trial includes two 32-week treatment periods in a cross-over design. Total trial duration for the individual subjects will be up to 67 weeks.

1.2 Scope of the statistical analysis plan

This statistical analysis plan (SAP) is based on the protocol "A randomised, double blind, cross-over trial comparing the safety and efficacy of insulin degludec and insulin glargine, with or without OADs in subjects with type 2 diabetes", version 3.0, and amendments no 1 and 2.

2 Statistical considerations

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

Analyses of all endpoints will be based on the Full Analysis Set (FAS). Efficacy endpoints and patient reported outcome endpoints will be summarised using the FAS. 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.

All endpoints will be summarised descriptively at each visit by treatment and in total using observed data. The endpoints are summarised by the arithmetic mean, standard deviation (SD), median, and minimum and maximum value. For endpoints assessed for each treatment period and where change from baseline is reported, the baseline value will for treatment period A be the measurement taken at Visit 2 and for treatment period B, the measurement taken at Visit 34.

Presentation of results from a statistical analysis will include the estimated mean treatment effects (LSMeans) for absolute values. Estimated mean treatment ratios will be presented together with two-sided 95% confidence intervals for all endpoints analysed statistically. p-values will only be presented for the primary endpoint and confirmatory secondary endpoints for which formal statistical testing will be performed. The family-wise type I error rate will be controlled in the strong sense using a hierarchical (fixed sequence) testing procedure. This is based on an a priori ordering of the null-hypotheses and testing them in this order using the two-sided 95% confidence interval approach until an insignificant result appears. The effect is that superiority only will be confirmed for endpoints where all previous null-hypotheses have been rejected. The other endpoints are considered supportive.

For endpoints measured over time, mean values will be plotted to explore the trajectory over time. Adverse events and hypoglycaemic episodes collected before randomisation and during follow-up are not considered treatment emergent and will only be summarised descriptively and appear in subject listings.

AEs and hypoglycaemic episodes are summaries by actual treatment. Actual treatment is the first treatment in the randomised sequence from time of first drug date till last drug date on treatment 1.

Actual treatment is the second treatment in the randomised treatment sequence from last drug date on treatment 1 plus one day till last drug date on treatment 2.

For summaries and statistical analysis of all endpoints the first non-missing value is used. The value should be taken according to protocol, e.g. a non-fasting FPG value is not used. Re-tests of non-missing values are included in subject specific listings.

2.1 Definition of analysis sets

The following analysis sets are defined in accordance with the ICH-E9 guidance.[30]

- Full Analysis Set (FAS): includes all randomised subjects. In exceptional cases subjects from the FAS may be eliminated. 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".

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

- Completer analysis set (CAS): includes all subjects that complete both treatment periods, if a subject withdraw during follow-up following the second treatment period the subject is considered a completer.

Before data are released for statistical analysis, a review of all data will take place to ensure a sufficient data quality and to ensure the planned statistical analyses are applicable. Any data decisions not foreseen in the protocol will be documented before database lock.

2.2 Missing data

Subjects that withdraw or drop-out of the trial will be explored with the purpose of investigating whether in particular the population that drop out prior to first maintenance period is different from the population that is exposed in the first maintenance period and whether there are any differences in drop-out between the two treatments.

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2.3 Primary endpoint

The primary endpoint is number of treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes during the maintenance period, i.e. after 16 weeks of treatment, in each treatment period (Week 16−32 and Week 48−64).

Statistical analysis

Before the primary endpoint is tested, the secondary supportive efficacy endpoint "Change from baseline in HbA_{1c} after 32 weeks of treatment" will be tested for non-inferiority as a prerequisite for testing the primary endpoint. The analysis will be made for each treatment period separately.

All observed HbA_{1c} measurements available post randomisation, at scheduled measurement times for subjects with trial exposure in the maintenance period A will be analysed with a mixed model for repeated measurement (MMRM) with an unstructured covariance matrix. The model includes treatment, visit, sex, antidiabetic treatment at screening and dosing time as fixed effects, and age and baseline HbA1c as covariates. Interactions between visit and all factors and covariates are also included in the model. For treatment period B the analysis above will be repeated including subjects with any HbA1c measurement after visit 34.

Dosing time is a factor with the following two levels: morning dosing and evening dosing.

Antidiabetic therapy at screening is a factor with two levels: <OADs vs ≥2 OADs.

If this model does not converge, another model will be fitted with a simplified covariance matrix.

Non-inferiority will be considered confirmed if the upper bound of the two-sided 95% confidence interval is below or equal to 0.4% or equivalent if the p-value for the one-sided test of

$$H_0: D > 0.4\% \text{ against } H_A: D \leq 0.4\%,$$

is less than 2.5%, where D is the treatment difference (IDeg OD minus IGlar OD).

If non-inferiority is confirmed for both treatment periods, the primary endpoint will be tested.

The number of treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes during the maintenance period will be analysed using a Poisson model with subject as a random effect, treatment, period, sequence and dosing time as fixed effects and time exposure to trial drug in each hypoglycaemia counting period as an offset.

Superiority is considered confirmed if the 95% confidence interval for the rate ratio (IDeg OD/IGlar OD) is entirely below one or equivalently if the p-value for the one-sided test of

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$$H_0: RR \geq 1 \text{ against } H_A: RR < 1$$

is less than 2.5%, where RR is the estimated rate ratio IDeg OD / IGlar OD.

Sensitivity analysis

In the primary analysis subjects that are not exposed in the second maintenance period contribute to the estimation of the treatment difference. This implies that these subjects are assumed to behave

like subjects that are exposed in both maintenance periods, i.e. a missing completely at random (MCAR) assumption. To investigate how this assumption influences the primary results a sensitivity analysis has been added that only include patients that are exposed in both maintenance periods. This analysis follows the randomisation principle [1], in that the same subjects are analysed on both treatments. The treatment estimate from this analysis is an unbiased estimate in the subset of subjects that were exposed to the maintenance period for both treatments, under the assumption that missing data for subjects that drop-out in the second maintenance period are missing at random (MAR). Since data from subjects that were only exposed in the first maintenance period are excluded, the pragmatic effectiveness principle [1] is violated.

A secondary sensitivity analysis has been added that only includes subjects from the CAS. The estimated treatment difference from this sensitivity analysis is unbiased in the subset of subjects that complete both maintenance periods, and does not rely on any assumptions regarding missing data. This analysis follows the randomisation principle, but violates the pragmatic effectiveness principle since data from all subjects not completing both maintenance periods are excluded. This analysis estimates the principal stratum direct effect [1].

The negative binomial model will be explored on the primary endpoint and the results will be compared with the Poisson model. The specification of the model will be identical to the primary analysis except that the distribution will be a negative binomial instead of a Poisson distribution. Due to the random patient effect in the model it is likely that the negative binomial model will be over-parameterized, and hence will not converge.

Hypoglycaemic episodes will be defined in section 2.4.2.1.

2.4 Secondary endpoints

2.4.1 Confirmatory secondary endpoints

If IDeg OD has a significant reduction in severe or BG confirmed symptomatic hypoglycaemia compared to IGlar OD, a number of confirmatory secondary endpoints will be tested to show that IDeg is significantly better than IGlar. The confirmatory secondary endpoints are given below together with the direction of the test. The order of the endpoints defines the testing sequence.

The following safety endpoints will be assessed: in the maintenance period, i.e. after 16 weeks of treatment, in each treatment period (Week 16−32 and Week 48−64):

1. Number of treatment emergent severe or BG confirmed symptomatic nocturnal hypoglycaemic episodes
2. Proportion of subjects with one or more severe hypoglycaemic episodes

Hypoglycaemic episodes will be defined in section 2.4.2.1.

Number of treatment emergent severe or BG confirmed symptomatic nocturnal hypoglycaemic episodes during the maintenance period will be tested using the same model and sensitivity analysis as for the primary endpoint.

Proportion of subjects with one or more severe hypoglycaemic episodes in the maintenance period will be tested for superiority using McNemar's test.

2.4.2 Supportive secondary endpoints

2.4.2.1 Safety endpoints

The following safety endpoints will be assessed during 32 weeks of treatment:

- Number of treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes
- Number of treatment emergent severe or BG confirmed symptomatic nocturnal hypoglycaemic episodes
- Number of treatment emergent severe hypoglycaemic episodes
- Number of treatment emergent hypoglycaemic episodes according to ADA definition

The following safety endpoints will be assessed for the maintenance period, i.e. after 16 weeks of treatment, in each treatment period (Week 16−32 and Week 48−64):

- Number of treatment emergent total hypoglycaemic (severe or BG confirmed) episodes
- Number of treatment emergent nocturnal total hypoglycaemic (severe or BG confirmed) episodes
- Number of treatment emergent severe hypoglycaemic episodes
- Number of treatment emergent hypoglycaemic episodes according to ADA definition
- Number of treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes occurring during sleep in the time span between 10:01 pm and 07:59 am

The following safety endpoints will be assessed for each 32 week treatment period:

- Incidence of treatment emergent adverse events during 32 weeks of treatment
- Change from baseline in clinical evaluations after 32 weeks of treatment
  - Vital signs (including blood pressure and pulse)
  - Fundoscopy or fundus photography
  - Electrocardiogram (ECG)
- Change from baseline in laboratory assessments after 32 weeks of treatment
  - Haematology (haemoglobin, haematocrit, erythrocytes, thrombocytes, leucocytes)
  - Biochemistry (creatinine, alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), alkaline phosphatase, sodium, potassium, albumin, total bilirubin)
- Change from baseline in body weight after 32 weeks of treatment
- Total daily insulin dose after 32 weeks of treatment

Due to the cross-over design, hypoglycaemic episodes will be attributed to the treatment given in the period in which the event occurred. That is, events occurring in the time period from start of treatment in the first treatment period up to start of treatment in the second treatment period will be attributed to the treatment given in the first period. Events occurring between start of treatment in the second treatment period up to the last day of randomised treatment will be attributed to the treatment given in the second treatment period.

Data on 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 severe or BG confirmed symptomatic hypoglycaemic episodes, severe or BG confirmed symptomatic nocturnal hypoglycaemic episodes, severe hypoglycaemia, total hypoglycaemia (severe or BG confirmed) episodes and total nocturnal hypoglycaemia (severe or BG confirmed) episodes. All events of severe hypoglycaemia will be prospectively adjudicated by an independent, external expert in a blinded manner. All tables are made for the maintenance period as well as for the whole treatment period.

The number of treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes during the entire treatment period, severe or BG confirmed symptomatic nocturnal hypoglycaemic episodes during the entire treatment period, severe hypoglycaemic episodes during the entire treatment period, total hypoglycaemia (severe or BG confirmed) episodes during the maintenance period, total nocturnal hypoglycaemia (severe or BG confirmed) episodes during the maintenance period, severe hypoglycaemic episodes during the maintenance period, severe or BG confirmed symptomatic hypoglycaemic episodes during sleep during the maintenance period will be analysed separately using the same model as for the primary analysis, i.e. a Poisson model with subject as a random effect, treatment, period, sequence and dosing time as fixed effects, and time exposure to trial drug in each hypoglycaemia counting period as an offset.

The proportions of subjects with one or more treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes during the maintenance periods and the proportions of subjects with one or more severe or BG confirmed symptomatic nocturnal hypoglycaemic episodes during the maintenance periods will be analysed with the McNemar's test.

The number of treatment emergent hypoglycaemic episodes according to ADA definition (maintenance and entire treatment period) will be summarized descriptively.

Hypoglycaemic episodes

Definition of Hypoglycaemia

Treatment emergent: hypoglycaemic episodes will be defined as treatment emergent if the onset of the episode occurs on or after the first day of IMP administration, and no later than the last day on IMP.

Nocturnal hypoglycaemic episodes: are episodes with time of onset between 00:01 and 05.59 both inclusive.

In normal physiology, symptoms of hypoglycaemia occur below a plasma glucose level of 3.1 mmol/L (56 mg/dL).[32] Therefore, Novo Nordisk has included hypoglycaemia with plasma glucose levels below this cut-off point in the definition of BG confirmed hypoglycaemia (see Figure 2–1).

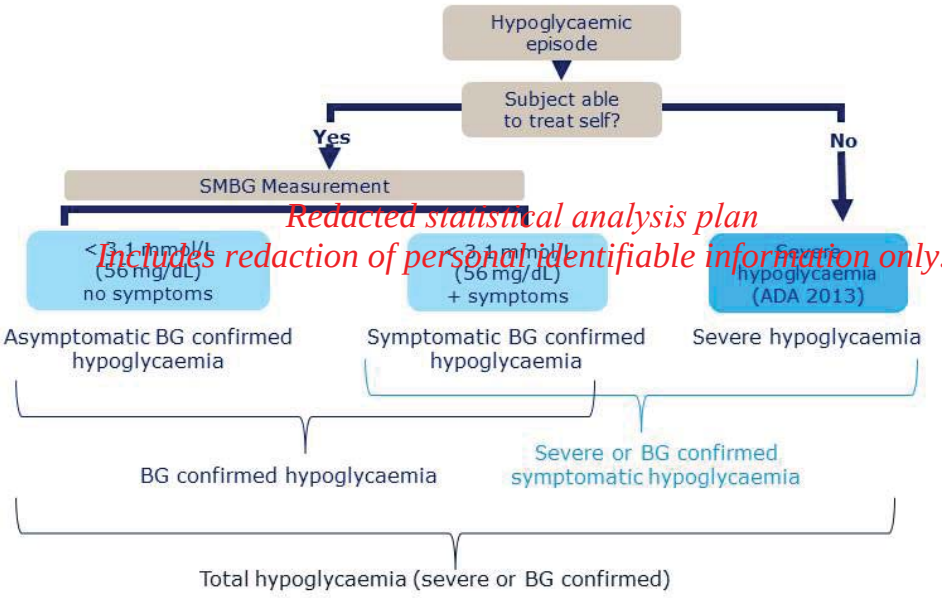

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Figure 2–1 Novo Nordisk definition of hypoglycaemia to improve specificity of clinical trial episodes (in addition to ADA classification)

Total hypoglycaemia (severe or BG confirmed)

Are defined as episodes that are:

- severe (positively adjudicated according to ADA definition) and/or
- BG confirmed by a plasma glucose value of <3.1 mmol/L (56 mg/dL), with or without symptoms consistent with hypoglycaemia

Severe or BG confirmed symptomatic hypoglycaemia

Are defined as episodes that are severe and/or BG confirmed by a plasma glucose value of <3.1 mmol/L (56 mg/dL), with symptoms consistent with hypoglycaemia.

Severe hypoglycaemia

Severe hypoglycaemic episodes are defined according to the ADA classification as stated below.

ADA classification of hypoglycaemia

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

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Hypoglycaemic episodes are classified as severe only if confirmed by the EAC.

Severe hypoglycaemic episodes reported by investigator but not confirmed by EAC are re-classified according to information on eCRF. If the BG measurement is missing or non-confirmed and presence of symptoms is unknown the episodes is re-classified as unable to selftreat – unclassifiable.

For adjudicated events the onset date is determined by the EAC. Hence, in case there is a discrepancy between the investigator-provided onset date and the EAC-provided time of onset date then the EAC date is used. For hypoglycaemic episodes that are not confirmed by the EAC the onset date is the investigator reported onset date.

Adjudicated events occurring before the date of randomisation and after the last day of treatment, as determined by the EAC, are not included in the statistical analysis or treatment emergent summary tables.

Data collected before the randomisation date and in the follow-up period will only be included in subject specific listings.

Adverse Events

Adverse Events will be coded using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA) coding. All adverse events will be presented based on system organ class and preferred terms.

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 the last day of randomised treatment. This is due to the cross-over design. Adverse events will be attributed to treatment similarly as previously described for hypoglycaemic episodes.

TEAEs are summarised descriptively by treatment. 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 (R). Furthermore, TEAE data are summarised by seriousness, severity, relation to insulin treatment, relation to device, withdrawal due to AEs and outcome.

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Furthermore, summary tables based on system organ class and preferred term are made for

- All TEAEs
- Serious TEAEs
- Possibly or probably related TEAEs
- Severe TEAEs
- TEAEs with preferred term that are experienced by at least 5% of the subjects in any treatment sequence or by at least 5% of all subjects

Vital Signs

The measurements and their change from baseline will be summarised descriptively by treatment .

Laboratory Assessments

Individual laboratory values will be flagged as being below or above existing relevant reference ranges. Change from baseline will be summarised descriptively by treatment.

Funduscopy / fundus photography

Funduscopy and fundus photography findings will be summarised descriptively by treatment including summaries of the change from baseline.

ECG

ECG findings will be summarised descriptively by treatment including summaries of the change from baseline.

Insulin dose

Prescribed and actual basal insulin dose will be recorded three days before the site visit or phone contact. Actual time point of basal insulin dose will be recorded once weekly.

The insulin dose will be summarised descriptively by visit and treatment as dose in units and units/kg. The summaries will also include information on time of basal insulin administration in order to document the time of the day patients inject their basal insulin and the degree to which patient shift injection times during the trial.

To describe compliance to the randomised dosing times morning dosing is defined as the time from 03:00 to 14:59 and evening dosing is from 15:00 to 02:59.

Body weight

Body weight will be summarised descriptively by treatment including summaries of the change from baseline.

2.4.2.2 Efficacy endpoints

The following efficacy endpoints will be assessed for each 32 week treatment period:

3. HbA_{1c} (% and mmol/mol) after 32 weeks of treatment
4. FPG after 32 weeks of treatment
5. Self-measured plasma glucose measurements (SMPG):
    6. 9-point profiles:
        - Mean of the 9-point profiles after 32 weeks of treatment
    7. SMPGs obtained for insulin dose adjustment

8. Mean plasma glucose before breakfast after 32 weeks of treatment

HbA_{1c}

See Section 2.3.

FPG

FPG will be summarised descriptively by treatment including summaries of the change from baseline.

SMPG

9-point profile (SMPG)

The endpoint from the 9-point profiles (SMPG) is:
Mean of the 9-point profile (SMPG) after 32 weeks of treatment

The mean of the 9-point profile (SMPG) is defined as the area under the profile divided by the measurement time and is calculated using the trapezoidal method. It will be summarised descriptively by treatment including summaries of the change from baseline.

Pre-breakfast SMPG values used for dose adjustment

The endpoints from SMPG measurements obtained throughout the trial for dose adjustment will be:
9. Mean plasma glucose before breakfast after 32 weeks of treatment

2.5 Patient reported outcomes

The following questionnaires will be used to assess patient reported outcomes:
10. Health Related Quality of Life Questionnaire (SF-36®v2) after 32 weeks of treatment in each treatment period
11. Treatment Related Impact Measure – Minor Hypoglycaemic Events (TRIM-HYPO) after 32 weeks of treatment in each treatment period

The domain scores for the health-related quality of life questionnaire will be summarised descriptively by treatment. The domain scores for the Treatment Related Impact Measure for minor Hypoglycaemic events will be summarised descriptively by treatment.

The following interview questionnaire will be used to assess costs associated with hypoglycaemia:
12. Hypoglycaemic episodes – Interview questionnaire during 32 weeks of treatment in each treatment period

The data collected from the Hypoglycaemic episode – Interview questionnaires will to provide information to be used in health economic analyses.

2.6 Switch from BID to OD

A judgement of safety will be made on the switch from twice daily dosing (BID) pre-trial to once daily (OD) IDeg. Subjects will be categorized as BID or OD at screening based on their pre-trial insulin treatment regimen.

3 Changes to the statistical analyses planned in the protocol

The sensitivity analysis to the primary analysis is changed compared to the sensitivity analysis specified in final protocol version 3.0. A fixed effect model cannot be fitted if there are subjects that do no experience any hypoglycaemic episodes on both treatments.

The sensitivity analysis on the CAS is added to further investigate the missing at random assumption for subjects that drop-out in the second maintenance periods.

The sensitivity analysis exchanging the Poisson model with the negative binomial model is due to FDA expressing concerns regarding the Poisson model and suggesting the negative binomial model as a supportive analysis.

The analysis of proportions of subjects with one or more severe or BG confirmed symptomatic hypoglycaemic episodes and proportions of subjects with one or more severe or BG confirmed symptomatic nocturnal hypoglycaemic episodes are added to follow the recommendation of FDA.

In addition output on the safe switch from pre-trial insulin treatment regimen and missing data is specified in the SAP. This is for transparency that these output were intented prior to unblinding data.

4 References

[1] Permutt, T. (2015) A taxonomy of estimands for regulatory clinical trials with discontinuations. Statist. Med., doi: 10.1002/sim.6841.

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