Cover Page for Statistical Analysis Plan

Sponsor name:	Novo Nordisk A/S
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Official title of study:	A Trial Comparing Efficacy and Safety of Insulin Degludec/Insulin Aspart and BIAsp 30 in Subjects with Type 2 Diabetes
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16.1.9 Documentation of statistical methods

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Statistical Analysis Plan

Trial ID: NN5401-3598

A trial comparing efficacy and safety of insulin degludec/insulin aspart and BIAsp 30 in subjects with type 2 diabetes

Redacted statistical analysis plan
Includes redaction of personal identifiable information only.

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List of abbreviations

ACS	acute coronary syndrome
ADA	American Diabetes Association
AE	adverse event
ALT	alanine aminotransferase
ANOVA	Analysis of Variance
a.m.	ante meridiem (Latin for before noon)
AP	alkaline phosphatase
AST	aspartat aminotransferase
BHI 30	biphasic human insulin 30
BIAsp 30	biphasic insulin aspart 30
BID	twice daily
BMI	body mass index
CNS	central nervous system
CPMP	Committee for Proprietary Medicinal Products
CRF	case report form
CRO	contract research organisation
CTR	clinical trial report
CV	cardiovascular
CV(stat sect.)	coefficient of variance
CVD	cardiovascular disease
EAC	event adjudication committee
ECG	electrocardiogram

eCRF	electronic case report form
EDC	electronic data capture
EMA	European Medicines Agency
FAS	Full Analysis Set
FPG	fasting plasma glucose
FPFV	first patient first visit
FU	Follow up visit
GCP	Good Clinical Practice
GLP-1	glucagon like peptide 1
HbA_{1c}	glycosylated haemoglobin
HDL	high density lipoprotein
hh:mm	hour hour:minute minute
HI	human insulin
IAsp	insulin aspart
IB	investigator's brochure
ICH	International Conference on Harmonisation
ICMJE	The International Committee of Medical Journal Editors
ID	identification
IDeg	insulin degludec
IDegAsp	insulin degludec/insulin aspart (70 vol% insulin degludec + 30 vol% insulin aspart) 100 U/mL also known as IDegAsp 30
IDF	International Diabetes Federation
IMP	Investigational Medicinal Product

ITT	intention to treat
iv	intravenous
IWRS	interactive web response system
LDL	low density lipoprotein
LLOQ	Lower Limit of quantitation
LOCF	Last Observation Carried Forward
LOV	Last Observed Value
LPFV	last patient first visit
LPLV	last patient last visit
LSMeans	estimated mean treatment effects
MAO	monoamine oxidase
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
NCR	non carbon required
NIMP	non-investigational medicinal product
NYHA	New York Heart Association
OAD	oral antidiabetic drug
OC	oracle clinical
OD	once daily
PDF	portable document format
PG	plasma glucose
PP	per protocol
PRO	patient reported outcome

SAE	serious adverse event
SAS	statistical analysis system
sc	subcutaneous
SD	standard deviation
SF-36	short form with 36 questions (health related quality of life questionnaire)
SFDA	State Food and Drug Administration
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SMPG	self-measured plasma glucose
SPC	summary of product characteristics
SU	sulphonylurea
SUSAR	suspected unexpected serious adverse reaction
TEAE	Treatment Emergent Adverse Event
TMM	Trial Materials Manual
TRIM-D	Treatment Related Impact Measure - Diabetes
T-T-T	treat-to-target
TZD	thiazolidinedione
U	Unit

1 Introduction

1.1 Trial information

This is a 26 week, 2:1 randomised, controlled, open label, two-arm, parallel-group, T-T-T trial comparing efficacy and safety of IDegAsp and BIAsp 30 both ± metformin, BID in subjects with type 2 diabetes inadequately controlled on OD or BID premix/selfmix or basal insulin ± metformin.

Total trial duration for the individual subject will be approximately 31 weeks including screening and follow-up. Subjects will attend weekly visits/phone contacts throughout the trial as schematically described in the protocol

At visit 2 randomisation will be carried out in a 2:1 manner using an IWRS to randomise subjects into the treatment groups: IDegAsp BID or BIAsp 30 BID both in combination with or without metformin.

1.2 Scope of the statistical analysis plan

This SAP is based on the statistical analyses in the protocol 'A trial comparing efficacy and safety of insulin degludec/insulin aspart and BIAsp 30 in subjects with type 2 diabetes', version 4.0, 31 May 2017. This SAP includes the definition of last observed value (LOV), leaves out the mean PG at baseline as covariate in the analysis for the 2-point profiles, and clarifies the convergence to mmol/mol of of a very low HbA1c measured in %.

Changes to the statistical methods proposed in the SAP and the reason for the change must be reported in the clinical trial report (CTR).

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). The primary efficacy analysis will be repeated on the Per Protocol (PP) analysis set in accordance with the Committee for Proprietary Medicinal Products (CPMP) Points to Consider[1].

Secondary confirmatory and supportive 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.

The primary objective of this trial is to confirm efficacy of the investigational product in terms of glycaemic control as assessed by HbA_{1c}. If efficacy of the investigational product can be confirmed as assessed by comparing the mean HbA_{1c} treatment difference to a non-inferiority limit of 0.4%, the trial also aims to show superiority of the investigational product over the comparator for a number of confirmatory secondary endpoints. 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 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.

In addition, if non-inferiority can be confirmed and the 95% confidence interval for the mean HbA_{1c} treatment difference not only lies entirely below 0.4% but also below zero this will be considered as evidence of superiority of the investigational product over the comparator in terms of change from baseline in HbA_{1c} after 26 weeks of treatment.

Only endpoints derived after 26 weeks of treatment will be analysed statistically. Missing values will be imputed using the Last Observation Carried Forward (LOCF) method. LOCF has been a standard approach in diabetes trials for many years, and was used as the primary analysis in all 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 degludec LOCF has generally provided similar results to alternative methods 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. All endpoints will be summarised descriptively at each visit by treatment and in total using observed data. After 26 weeks of treatment, descriptive statistics will be presented based both on observed and Last Observed Value (LOV) data, which corresponds to 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 summarised by the geometric mean, CV, median, minimum and maximum value.

LOCF imputed data will be used as the basis for plotting data if not otherwise specified.

Presentation of results from a statistical analysis will include the estimated mean treatment effects (least-squares means [LSMeans]) for absolute values and change from baseline if applicable. Estimated mean treatment differences (or 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 and the confirmatory secondary endpoints for which formal statistical testing will be performed. The other endpoints are considered supportive and explorative in nature and no p-values will be presented.

For endpoints measured over time mean values will be plotted to explore the trajectory over time. For survival endpoints, Kaplan-Meier plots are presented for each treatment. Data collected before randomisation will only be summarised descriptively.

2.1 Sample size calculation

The primary objective of this trial is to confirm efficacy of IDegAsp BID ± metformin in terms of glycaemic control.

This is done by showing that:

IDegAsp BID ± metformin is non-inferior to BIAsp 30 BID ± metformin in terms of glucose lowering effect as assessed by change from baseline in HbA_{1c} after 26 weeks of treatment using a non-inferiority margin of 0.4% (absolute). Sample size is determined based on this primary objective.

Throughout this section of the protocol the term "investigational product" will be used as a synonym for IDegAsp BID and the term "comparator" will be used as a synonym for BIAsp 30 BID.

The non-inferiority margin of 0.4% (absolute) was chosen in accordance with the FDA guidance[2]. Let D be the mean treatment difference for change in HbA_{1c} (investigational product minus comparator). The null-hypothesis will be tested against the alternative hypothesis of non-inferiority as given by

H_0: $D > 0.4\%$ against H_A: $D \leq 0.4\%$

Operationally the null-hypothesis will be rejected and non-inferiority considered confirmed if the upper bound of the two-sided 95% confidence interval for the mean HbA_{1c} treatment difference is below or equal to 0.4%. This is equivalent to using a one-sided test of size 2.5%.

Sample size is determined using a t-statistic under the assumption of a one-sided test of size 2.5% and a zero mean treatment difference (i.e. D=0%). Based on experience from previous phase 3 trials in subjects with type 2 diabetes treated with insulin an estimate for the standard deviation (SD) of 1.3% for HbA_{1c} will be used in the sample size calculation (Table 2–1). The sample size calculation is done using SAS 9.3.

Table 2–1 Specifications assumed for sample size calculation

Statistical test	One sided Significance Level	Non-inferiority Margin	SD	Mean Difference	Randomisation Scheme	Required Power
two-group t test	2.5%	0.4% (absolute)	1.3%	0.0%	2:1	87%

Table 2–2 Sensitivity of sample size (integers) to variations in SD and power

#subjects in total	SD=1.1	SD=1.2	SD=1.3	SD=1.4
Power = 80%	270	321	375	435
Power = 85%	309	366	429	498
Power = 87%	327	390	456	528
Power = 90%	360	429	504	582

From Table 2–2 it is seen that the primary objective will be met with at least 87% power with 456 subjects assuming a SD of 1.3%.

As this is a non-inferiority trial sample size will be determined such that the anticipated power is at least 87% in the evaluation of the PP analysis set. In previous phase 3 trials in type 2 diabetes treated with insulin 5-25% of the randomised subjects were excluded from the PP analysis set. The number of excluded subjects was dependent on the trial design. In this trial an estimate of 15% will be used and sample size is ceiled in the FAS to have integer sample size for each group that adheres exactly to the group allocation weights (2:1). Hence the total number of subject to be randomised must be 537 subjects in order to have at least 87% power in the evaluation of the PP analysis set (**Error! Reference source not found.**).

Table 2–3 Anticipated number of subjects in FAS and PP analysis set

	IDegAsp BID	BIAsp 30 BID	Total
Number of subjects in the FAS	358	179	537
Number of subjects in the PP	304	152	456

Definition of analysis sets

2.2 Definition of analysis sets

- 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".
- The Per-Protocol analysis set will consist of 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_{1c} at screening or randomisation
  - Have at least one non-missing HbA_{1c} after 12 weeks of exposure
  - Have at least 12 weeks of exposure

Subjects will contribute to the evaluation "as treated".

Safety Analysis Set: 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".

Randomised subjects who are lost to follow up and where no exposure information of the investigational product or its comparator is available after randomisation will be handled as unexposed. The OADs that the subjects are included on and will stay on throughout the trial are concomitant medications and regarded as non-investigational products.

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 e.g. classification of anti-diabetic treatment not foreseen in the protocol, will be documented before database lock.

2.3 Primary endpoint

The primary endpoint is change from baseline in HbA_{1c} (%) after 26 weeks of treatment

2.3.1 Statistical analysis

Change from baseline in HbA_{1c} after 26 weeks of treatments will be analysed using an Analysis of Variance (ANOVA) method with treatment, anti-diabetic therapy at screening and sex as fixed factors, and age and baseline HbA_{1c} as covariates. The anti-diabetic therapy at screening is a factor with the following four levels:

- Basal insulin regimen without metformin
- Basal insulin regimen with metformin
- Premix/self-mix regimen without metformin

- Premix/self-mix regimen with metformin

The model will be fitted using FAS and from this model the relevant treatment differences will be estimated.

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 i0f the p-value for the one-sided test of

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

is less than or equal to 2.5%, where D is the mean treatment difference (investigational product minus comparator)

If non-inferiority is confirmed the superiority of the investigational product over comparator in change from baseline HbA1c (%) after 26 weeks of treatment will be investigated. Superiority will be considered confirmed if the upper bound of the two-sided 95% confidence interval, which is calculated using the FAS, is below 0%. The PP analysis is considered supportive here.

The HbA1c analyses will be carried out in both standard unit (%) and converted unit (mmol/mol), but the results given in % are considered confirmatory. Subjects with HbA1c < 4.1 % (i.e. LLOQ) will get a converted value of LLOQ/2=10.6565 mmol/mol instead of the negative value that would have resulted from using the standard formula 10.93*value(%)-23.5.

2.3.2 Sensitivity analysis

The primary efficacy analysis will be repeated on the PP analysis set and the set of all completed subjects as sensitivity analyses.

The following sensitivity analyses will be performed using the FAS only.

All observed HbA_{1c} measurements available post randomisation at scheduled measurement times will also be analysed in a linear mixed model using an unstructured residual covariance matrix (if possible), and with treatment, time, interaction between treatment and time, anti-diabetic treatment at screening and sex as fixed effects and age and baseline HbA_{1c} as covariates.

This approach relies on the assumption that data are missing at random (MAR) according to the taxonomy defined by Rubin.[3] The results will be compared to the results of the LOCF method for dealing with missing data. Any marked difference concerning treatment differences between the MAR and LOCF approach will be commented upon in the CTR.

Change in HbA_{1c} from baseline will also be analysed using a model with only treatment as fixed factor and baseline HbA_{1c} as covariate to assess the sensitivity of the results to inclusion/exclusion of fixed factors and covariates.

2.4 Secondary endpoints

2.4.1 Confirmatory secondary endpoints

Provided that non-inferiority is confirmed for the primary endpoint, a number of confirmatory secondary endpoints will be tested to confirm superiority of the investigational product over the comparator.

The confirmatory secondary endpoints are given below together with the direction of the test for superiority. The order of the endpoints defines the testing sequence.

1. Change from baseline in FPG after 26 weeks of treatment (analysed at central laboratory)
   - Superiority is considered confirmed if the 95% confidence interval for the treatment difference (investigational product minus comparator) is entirely below zero
2. Number of treatment emergent nocturnal confirmed hypoglycaemic episodes
   - Superiority is considered confirmed if the 95% confidence interval for the relative risk (investigational product / comparator) is entirely below one
3. Number of treatment emergent confirmed hypoglycaemic episodes
   - Superiority is considered confirmed if the 95% confidence interval for the relative risk (investigational product / comparator) is entirely below one
4. Change from baseline in body weight after 26 weeks of treatment
   - Superiority is considered confirmed if the 95% confidence interval for the treatment difference (investigational product minus comparator) is entirely below zero
5. Responder without hypoglycaemic episodes (HbA_{1c} <7.0% after 26 weeks of treatment and no confirmed episodes during the last 12 weeks of treatment or within 7 days after the last randomised treatment including only subjects exposed for at least 12 weeks)
   - Superiority is considered confirmed if the 95% confidence interval for the odds ratio (investigational product / comparator) is entirely above one

Change from baseline in FPG
Change from baseline in FPG after 26 weeks of treatment will be analysed using an ANOVA method with treatment, anti-diabetic therapy at screening and sex as fixed factors, and age and baseline FPG as covariates.

Number of treatment emergent confirmed hypoglycaemic episodes
A hypoglycaemic episode is defined as treatment emergent if the onset of the episode is on or after the first day of exposure to randomised treatment and no later than 7 days after the last day of randomised treatment.

The number of confirmed hypoglycaemic episodes 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, anti-diabetic therapy at screening and sex as fixed factors, and age as covariate.

Number of treatment emergent nocturnal confirmed hypoglycaemic episodes

A hypoglycaemic episode that has time of onset between 00:01 and 05:59 a.m. (both included) will be considered nocturnal.

The number of treatment emergent nocturnal confirmed hypoglycaemic episodes 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, anti-diabetic therapy at screening and sex as fixed factors and age as covariate.

Change from baseline in body weight

Body weight is assessed at trial site. Change from baseline in body weight after 26 weeks of treatment will be analysed using an ANOVA method with treatment, anti-diabetic therapy at screening and sex as fixed factors, and age and baseline body weight as covariates.

Responder without hypoglycaemic episodes

Responder without hypoglycaemic episodes is a dichotomous endpoint (responder/non-responder) that is defined based on whether a subject has met the ADA HbA_{1c} target (< 7%) after 26 weeks of treatment without treatment emergent confirmed hypoglycaemic episodes during the last 12 weeks of treatment or within 7 days after last randomised treatment. The endpoint will only be defined for subjects that have been exposed to the investigational product or its comparator for at least 12 weeks.

Responder analysis will be based on a logistic regression model using treatment, anti-diabetic therapy at screening and sex as fixed factors, and age and baseline HbA_{1c} as covariates.

2.4.2 Supportive secondary endpoints

2.4.2.1 Efficacy

The timing of assessments is outlined in the trial flow chart.

HbA_{1c} responder endpoints

Two dichotomous endpoints (responder/non-responder) will be defined based on whether a subject has met the ADA HbA_{1c} target ($HbA_{1c} < 7.0\%$) and the International Diabetes Federation (IDF) HbA_{1c} target ($HbA_{1c} \leq 6.5\%$) after 26 weeks of treatment.

Additional dichotomous endpoints will be defined based on whether those treatment targets after 26 weeks of treatment are achieved without hypoglycaemic episodes in the last 12 weeks of treatment or within 7 days after last randomised treatment considering confirmed episodes and severe episodes only. These endpoints will only be defined for subjects that have been exposed for at least 12 weeks.

The responder endpoints will be analysed separately based on a logistic regression model using treatment, anti-diabetic therapy at screening and sex as fixed factors, and age and baseline HbA_{1c} as covariates.

Self measured plasma glucose

Self-measured plasma glucose will be measured in terms of the 9-point profiles (SMPG) and glucose measurements used for insulin dose adjustments.

9-point profile (SMPG) after 26 weeks of treatment

A 9-point profile (SMPG) will include measurements before and 90 minutes after start of breakfast, lunch and main evening meal, measurements prior to bedtime and at 4 a.m., and one before breakfast the following day.

The endpoints from the 9-point profiles (SMPG) will be:

- 9-point profile (SMPG)
- Mean of the 9-point profile (SMPG)
- Fluctuation in the 9-point profile (SMPG)
- Prandial plasma glucose (PG) increments

The mean of 9-point profile (SMPG) is defined as the area under the profile divided by the measurement time and is calculated using the trapezoidal method. The fluctuation in the 9-point profile (SMPG) is defined as

$$\frac{1}{T}\int_0^T \left| PG(t) - \overline{PG} \right| dt$$

,

where T, PG(t) and $\overline{PG}$ denotes the length of the profile, the PG value at time t and the mean of the profile, respectively.

Prandial PG increment for each meal will be derived from the 9-point profile (SMPG) as the difference between PG values available 90 minutes after meal and before meal. Mean prandial PG increment over all meals will be derived as the mean of all available meal increments.

A mixed effect model will be fitted to the 9-point profile (SMPG) data. The model will include treatment, time, interaction between treatment and time, anti-diabetic therapy at screening and sex as fixed factors, age and the values from the profile at baseline as covariates and subject as random effect. From the model, mean profile by treatment and relevant treatment differences will be estimated and explored.

Mean and fluctuation in the 9-point profile (SMPG) and prandial PG increment endpoints will be analysed separately using an ANOVA method with treatment, anti-diabetic therapy at screening and sex as fixed factors, and age and the relevant baseline value as covariates. Fluctuation in the 9-point profile (SMPG) will be logarithm transformed before analysed.

2-point profile (SMPG) values used for dose adjustment

The endpoints from the SMPG measurements obtained throughout the trial for dose adjustment will be:

- Mean PG before meals (breakfast and main evening meal) after 26 weeks of treatment
- Responder for PG titration targets
- Time from randomisation (measured in weeks) to achieve titration targets
- Within-subject variability as measured by CV% after 26 weeks of treatment

The mean PG value before a meal will be calculated at each visit using the available data and separately for breakfast and main evening meal.

The mean before meal PG values after 26 weeks of treatment will be analysed separately, using an ANOVA method with treatment, anti-diabetic therapy at screening and sex as fixed factors, and age as covariates.

From the mean before meal PG value, a dichotomous endpoint (responder/non-responder) will be derived for each meal that shows if a subject has achieved the titration target at each visit.

For each target a survival endpoint will be derived as the time from randomisation to the date a subject achieves the titration target for the first time.

The two survival endpoints will be analysed separately in a Cox proportional hazards model including treatment, anti-diabetic therapy at screening and sex as fixed factors and age as covariate. An analysis will also be performed for the time to all titration targets are met. Subjects that are lost

for follow up without meeting the target and subjects that never meet the target during treatment will be censored at the last day of treatment.

The logarithm transformed SMPG values available before breakfast and main evening meal, will be analysed separately as repeated measures in a linear mixed model with treatment, anti-diabetic therapy at screening and sex as fixed factors, age as covariate and subject as random factor. The model will assume independent within- and between-subject errors with variances depending on treatment. Within-subject variability as measured by CV% for a treatment can be calculated from the corresponding residual variance σ^2 as $CV\,\% = 100\sqrt{\left(\exp\left(\sigma^2\right)-1\right)}$. The confidence interval for the CV ratio between treatments will be calculated using the delta method.

2.4.3 Safety

Adverse Events

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

When reporting the trial results the EAC evaluation will be employed. All discrepancies between EAC and the investigators' classification of the CV events will be listed by event.

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 7 days after the last day of randomised treatment.

TEAEs are summarised descriptively whereas AE's not defined as treatment emergent are presented in listings. The summaries of TEAEs are made displaying the number of subjects with at least one event, the percentage of subjects with at least one event, the number of events and the event rate per 100 years. These summaries are done by seriousness, severity, relation to insulin treatment, relation to device, withdrawal due to AEs and outcome.

Furthermore summary tables based on system organ class and preferred terms 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 arm or by at least 5% of all subjects

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 A/S to classify an episode according to the confirmed hypoglycaemia definition and the ADA definition (severe, documented symptomatic, asymptomatic, probable symptomatic and relative) as further detailed in the protocol.

A hypoglycaemic episode is defined as treatment emergent if the onset of the episode is on or after the first day of exposure to randomised treatment and no later than 7 days after the last day of randomised treatment. A hypoglycaemic episode that has time of onset between 00:01 and 05:59 a.m. (both included) is considered to be nocturnal.

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, confirmed hypoglycaemic episodes in the maintenance period, nocturnal confirmed hypoglycaemic episodes, nocturnal confirmed hypoglycaemic episodes in the maintenance period and the ADA classification of hypoglycaemia.

The number of treatment emergent severe, confirmed, confirmed in the maintenance period, nocturnal confirmed hypoglycaemic episodes and nocturnal confirmed in the maintenance period will be analysed using a negative binomial regression model with a log-link function and the logarithm of the time period for which a hypoglycaemic episode is considered treatment emergent as offset. The model will include treatment, anti-diabetic therapy at screening and sex as fixed factors, and age as covariate. If the number of severe or nocturnal confirmed hypoglycaemic episodes is too small for statistical analysis, then these analyses may not be performed.

Fundoscopy/fundus photography

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

ECG

- ECG 12-lead findings will be summarised descriptively including summaries of the change from baseline.

Physical examination

- Physical examination should include:
- head, ears, eyes, nose, throat, neck
- respiratory system

- CV system
- gastrointestinal system incl. mouth
- musculoskeletal system
- central and peripheral nervous system
- skin

The physical examination measurements and their change from baseline will be summarised descriptively.

Vital signs

Vital signs include diastolic blood pressure, systolic blood pressure and pulse findings will be summarised descriptively including summaries of the change from baseline.

Laboratory safety parameters

The following laboratory assessments are performed:

- haematology (haemoglobin, leucocytes, thrombocytes, haematocrit, differential counts and erythrocytes)
- biochemistry (creatinine, total protein, ALT, AST, AP, sodium, potassium, albumin, total bilirubin)
- lipid profile (LDL, HDL, triglycerides and total cholesterol)
- urinary albumin-to-creatinine ratio assess in spot urine
- urine by sticks (tests for blood, protein and ketones)

Insulin antibodies

Individual laboratory values will be compared to their relevant reference range (when existing) and flagged as being below or above the range. Change from baseline will be summarised descriptively.

Change from baseline in lipid endpoints after 26 weeks of treatment will be analysed separately using an ANOVA method with treatment, anti-diabetic therapy at screening and sex as fixed factors, and age and baseline value as covariates.

Insulin degludec specific antibodies, insulin aspart specific antibodies, and cross-reacting antibodies will be illustrated using descriptive statistics and graphs.

Insulin dose

Prescribed and actual insulin dose per day and separately for morning and evening dose will be recorded. The respective insulin doses will be summarised descriptively according to regimen as dose in units and units/kg per week.

Body weight

In addition to the confirmatory statistical analysis after 26 weeks of treatment, body weight will summarised descriptively including summaries of the change from baseline.

Other assessments

The results from the blood pregnancy test will be presented in listings using the Safety Analysis Set.

2.5 Interim analysis

No interim analyses or other analyses of unblinded data will be performed before the database is locked

2.6 Health economics and/or patient reported outcomes

The following questionnaires will be used to compare PROs and costs associated with hypoglycaemia between treatments:

- SF-36[4,5]
- TRIM-D[6] and TRIM-D Device[6]
- Device Specific Questionnaires I and II[7]

For the questionnaires , SF-36 and TRIM-D the change in score (total score if appropriate) from baseline will be analysed separately using an ANOVA method with treatment, anti-diabetic therapy at screening and sex as fixed factors, and age and the relevant baseline value as covariates.

For the device questionnaire TRIM-D Device , which is not assessed at baseline, the score (total score if appropriate) will be analysed using an ANOVA method with treatment, anti-diabetic therapy at screening and sex as fixed factors, and age as covariate.

For Device Specific Questionnaires I and II, since there are no validated scoring algorithms, formal statistical analysis will not be conducted and only descriptive statistics will be presented.

3 Changes to the statistical analyses planned in the protocol

There were 2 minor changes to the statistical analyses planned in the protocol as described below:

- The mean PG at baseline as covariate in the analysis for the 2-point SMPG profiles was not included since the 2-point SMPG was not collected until visit 3.
- Last Observed Value (LOV) was defined to summarise efficacy data and replace LOCF in summary table.

4 References

1. EMEA-Committee for Proprietary Medicinal Products. CPMP/EWP/482/99 - Points to consider on switching between superiority and non-inferiority. 27-2-2000.
2. Food and Drug Administration. Food and Drug Administration, Code of Federal Regulations, Guidance for Industry, Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention. Draft Guidance. 2008.
3. Rubin DB. Inference and missing data. Biometrika 1976; 63(3):581-592.
4. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992; 30(6):473-483.
5. Ware JE, Kosinski M, Dewey JE. How to Score Version Two of the SF-36 Health Survey. Lincoln, RI: QualityMetric Incorporated, 2002.
6. Brod M, Skovlund SE, Wittrup-Jensen KU. Measuring the impact of diabetes through patient report of treatment satisfaction, productivity and symptom experience. Qual Life Res 2006; 15(3):481-491.
7. Niskanen L, Jensen LE, Rastam J, Nygaard-Pedersen L, Erichsen K, Vora JP. Randomized, multinational, open-label, 2-period, crossover comparison of biphasic insulin aspart 30 and biphasic insulin lispro 25 and pen devices in adult patients with type 2 diabetes mellitus. Clin Ther 2004; 26(4):531-540.