Cover Page for Statistical Analysis Plan

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Official title of study:	An investigational trial comparing the efficacy and safety of once weekly NNC0148-0287 C (insulin 287) versus once daily insulin glargine, both in combination with metformin, with or without DPP-4 inhibitors, in insulin naïve subjects with type 2 diabetes mellitus
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16.1.9 Documentation of statistical methods

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Statistical analysis plan ..... Link

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Statistical Analysis Plan

Trial ID: NN1436-4383

An investigational trial comparing the efficacy and safety of once weekly NNC0148-0287 C (insulin 287) versus once daily insulin glargine, both in combination with metformin, with or without DPP-4 inhibitors, in insulin naïve subjects with type 2 diabetes mellitus

Author

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List of abbreviations

AE	adverse event
ANOVA	analysis of variance
CI	confidence interval
CRF	case report form
DPP4i	dipeptidyl peptidase-4 inhibitor
ECG	electrocardiogram
eCRF	electronic case report form
FAS	full analysis set
FGM	flash glucose monitoring
FPG	fasting plasma glucose
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IGlar	insulin glargine
IWRS	interactive web response system
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measurement
PK	pharmacokinetics
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
SD	standard deviation
SMPG	self-measured plasma glucose
T2DM	type 2 diabetes mellitus

1 Introduction

1.1 Trial information

This is a 26-week, randomised, double-blind, double-dummy, active-controlled, parallel-group, stratified, multicentre, multinational trial with 2 arms comparing the efficacy and safety of treatment with insulin 287 once weekly versus insulin glargine (IGlar) once daily in insulin-naïve subjects with type 2 diabetes mellitus (T2DM) inadequately controlled on metformin with or without dipeptidyl peptidase-4 inhibitors (DDP4i).

Subjects will be randomised in a 1:1 manner to receive once weekly insulin 287 and once daily placebo or once weekly placebo and once daily IGlar. The randomisation of subjects will be stratified based on use of DPP4i.

The total duration for the individual subject will be approximately 33 weeks. The trial includes a 2-week screening period, followed by a 26-week randomised treatment period and a 5-week follow-up period.

The overall trial design and visit schedule are outlined in the trial diagram Figure 1-1 and trial flowchart (protocol section 2), respectively.

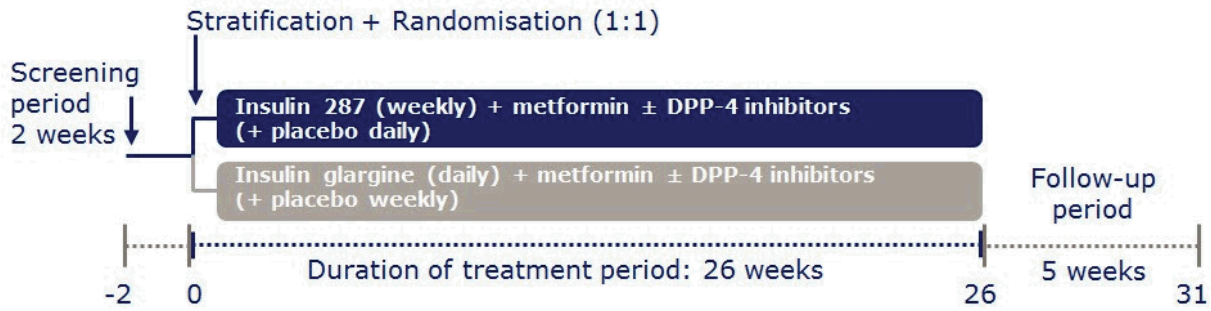

Figure 1-1 Trial design

The primary objective is to investigate the effect on glycaemic control after 26 weeks treatment of once weekly insulin 287 versus once daily IGlar both in combination with metformin with or without DPP4i in insulin-naïve T2DM subjects inadequately treated with metformin with or without DPP4i.

The secondary objective is to investigate the safety and tolerability during 26 weeks of treatment with once weekly insulin 287 versus once daily IGlar both in combination with metformin with or without DPP4i in insulin-naïve subjects with T2DM inadequately treated with metformin with or without DPP4i.

The exploratory objectives are

- To investigate the pharmacokinetics (PK) of insulin 287 using population PK during 26 weeks of treatment in insulin-naïve subjects with T2DM inadequately treated with metformin with or without DPP4i
- To investigate the effect on glycaemic control (using [redacted] FreeStyle Libre Pro) of insulin 287 and IGlar during 26 weeks of treatment in insulin naïve subjects with T2DM inadequately treated with metformin with or without DPP4i

Subjects who prematurely discontinue trial product permanently or withdraw from the trial will be asked to attend the end of treatment visit (V28) as soon as possible and the follow-up visits (FU1 and FU2) after 2 and 5 weeks, respectively. In case of premature trial product discontinuation, once the follow-up visits are completed the subject should be contacted by phone every 4 weeks and finally come in for the discontinuation follow-up visit (V28A) 26 weeks after randomisation.

For further details on handling of subjects who prematurely discontinue trial product permanently or withdraw from the trial and the trial in general, please see the trial protocol.

1.2 Scope of the statistical analysis plan

This statistical analysis plan (SAP) is based on the protocol *An investigational trial comparing the efficacy and safety of once weekly NNC0148-0287 C (insulin 287) versus once daily insulin glargine, both in combination with metformin, with or without DPP-4 inhibitors, in insulin naïve subjects with type 2 diabetes mellitus*, version 1.0 (dated 25 June 2018). Most of the statistical analyses and derivations of endpoints presented in this SAP are identical to those described in the protocol; some have been updated or added for technical or clinical reasons, but mostly the SAP contains clarifications for derivations, calculations of endpoints, and analyses. The changes to the statistical considerations proposed in this SAP and the reasons for the changes are described in section 3.

2 Statistical considerations

2.1 Sample size determination

The primary estimand is defined as the treatment difference in change in HbA_{1c} from baseline to week 26 between once weekly insulin 287 and once daily IGlar for all randomised subjects, if all subjects had adhered to treatment and did not receive ancillary treatment. This is a "hypothetical" estimand. This estimand aims to reflect the treatment effect for subjects that are actually able to take the drug during the intended treatment period. With the aim of evaluating proof of concept this estimand is considered relevant.

The sample size is determined such that the width of the two-sided 95% confidence interval (CI) for the treatment difference assuming normally distributed data in change from baseline to 26 weeks in HbA_{1c} is 0.5%-point. The standard deviation (SD) is expected to be 1.0%-point for all treatment

arms based on observations with IGlar in insulin naïve T2DM trials (NN1250-3579, NN1250-3643 and NN1250-3672). A total of 246 subjects with 123 in each treatment arm will ensure the required width of the 95% CI. The required width of the confidence interval is independent of the choice of estimand and sensitivity analyses since all randomised subjects will contribute to all analyses. The SD is assumed to be 1.0 based on observations from finalised clinical trials with IGlar in insulin naïve T2DM subjects. Since the assumed SD of 1 is to the conservative side it is assumed that the SD will not be further increased by the choice of estimand.

Table 2-1 displays sample sizes for various alternative standard deviations and widths of the 95% CI.

Table 2-1 Sample size for various standard deviations and widths of the confidence interval

	Width of the 95% CI		
SD	0.40	0.50	0.60
0.9	312	200	140
1.0	386	**246**	172
1.1	466	298	208

Sample size is computed for 1:1 randomisation. SD: standard deviation.

2.2 Definition of analysis sets

The following analysis sets are defined in accordance with the International Council for Harmonisation (ICH)-E9 guidance[1].

- 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".
- 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".

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 sponsor study group. The subjects or observations to be excluded, and the reasons for their exclusion must

be documented and signed by those responsible before database lock. The subjects and observations excluded from analysis sets, and the reason for this, will be described in the clinical trial report.

2.3 Definition of trial periods

The in-trial period starts at randomisation (as registered in IWRS) and ends at the date of:

- The last direct subject-site contact
- Withdrawal for subjects who withdraw their informed consent
- The last subject-investigator contact as defined by the investigator for subjects who are lost to follow-up (i.e. possibly an unscheduled phone visit)
- Death for subjects who die before any of the above

For subjects not randomised but exposed to trial product, the in-trial period starts at the date of first dose of trial product. The end date is as defined above.

Baseline assessments are always included in the in-trial observation period.

For adjudicated events it is the event adjudication committee (EAC) determined onset date that determines if the event belongs to the in-trial period.

The on-treatment period starts at the date of first dose of trial product as recorded on the eCRF, and ends at the first date of any of the following:

- The follow-up visit (FU2)
- The last date on trial product + 5 weeks for once daily insulin and + 6 weeks for once weekly insulin
- The end-date for the in-trial observation period

Baseline assessments are always included in the on-treatment observation period.

For adjudicated events it is the EAC determined onset date that determines if the event belongs to the on-treatment period.

The on-treatment without ancillary treatment starts at the date of first dose of trial product as recorded on the eCRF and ends at the first date of any of the following:

- The last dose of trial product + 5 weeks for once daily insulin and + 6 weeks for once weekly insulin
- Initiation of any diabetes treatment other than trial products and metformin +/- DPP4i
- Increasing the dose of metformin or DPP4i
- The end date of the on-treatment period if no ancillary treatment was initiated

The following will *not* be considered ancillary treatment:

- If a subject decreases the dose of background medication, or if a subject for a few days takes another antidiabetic drug other than randomised treatment or increases the dose of background medication due to reasons not related to the effect of randomised treatment, e.g.,
  - if antidiabetic treatment is given for an SAE
  - if a subject is hospitalised and it is against hospital policy to use trial products
  - if metformin or DPP4i is re-initiated after a few days without due to an AE or if removed entirely due to financial reasons
  - if a temperature deviation leaves trial product unavailable for distribution and administration
  - if a subject forgot trial medication while going on vacation and had to use other antidiabetic treatment while away
- Antidiabetic drugs initiated after end of treatment visit

Baseline assessments are always included in the on-treatment without ancillary treatment period.

The 'on-treatment without ancillary treatment' observation period will be the primary observation period for efficacy evaluations. Safety will be evaluated based the 'on-treatment' observation periods unless otherwise specified.

Periods considered as the titration period, the maintenance period, and the baseline to end of treatment period are used for certain hypoglycaemia tabulations. The titration period starts at the date of first dose of active trial product as recorded on the eCRF and ends on the date of week 16 visit (V18) minus 1 day, the end of study date, the end of treatment visit date (V28), or the end of active treatment date, whichever comes first. The maintenance period starts at the date of week 16 visit (V18) and ends on the end of treatment visit date (V28), the end of study date, or the end of active treatment date, whichever comes first. The maintenance period only exists if the end date for the titration period corresponds to the start date of the maintenance period. The baseline to end of treatment visit period starts at the date of first dose of active trial product as recorded on the eCRF and ends on the end of treatment visit date (V28) or the end of study date, whichever comes first.

2.4 Statistical analyses

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

All efficacy endpoints will be summarised using the full analysis set (FAS) and the 'on-treatment without ancillary treatment' observation period, albeit the primary endpoint will also be summarised using the 'in-trial' observation period. Safety endpoints will be summarised using the safety analysis set (SAS) and the 'on-treatment' observation period unless otherwise specified. All statistical analyses of efficacy and safety endpoints will be based on the FAS unless otherwise specified.

Endpoints are summarised by arithmetic mean, SD, median, and minimum and maximum value. Selected endpoints, e.g. endpoints that are analysed log-transformed, will be reported with geometric mean and coefficient of variation in place of mean and SD. For measurements over time, mean values will be plotted to explore the trajectory over time for selected endpoints. 'On-treatment without ancillary treatment' observed data will be used as the basis for plotting efficacy data while 'on-treatment' observed data will be used as the basis for plotting safety data if not otherwise specified. Mean profile for HbA_{1c} will be plotted by time of treatment discontinuation and treatment in order to investigate discontinuation patterns. Data obtained after treatment discontinuation or initiation of ancillary treatment will be included using different plot symbols. In addition, selected endpoints will be summarised by mean cumulative function plots, dot plots, box plots, and plots of the mean change from baseline over time. For HbA_{1c}, additional summary tables and mean plots based on 'in-trial' data will also be prepared.

In accordance with guidance[2], endpoints will be assessed at frequent visits and also on subjects who discontinue treatment. If an assessment has been made both at screening and randomisation, 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.

End of treatment assessments for withdrawn or prematurely discontinued subjects are reallocated to the nearest planned visit where the assessments were supposed to be taken, if this scheduled visit is at most 7 days apart and no assessment already exists at this visit. For prematurely discontinued subjects, the discontinuation follow-up visit (V28A) 26 weeks after randomisation is reallocated to the end of treatment visit (V28) after performing the previous reallocation.

Laboratory values below the lower limit of quantification (LLOQ) will be set to ½LLOQ.

Presentation of results from a statistical analysis will include the estimated mean treatment effects using least square mean (LSMean) for absolute values, and change from baseline where applicable. The LSMean is either obtained by Rubin's rule weighing together LSMeans from multiple imputation estimations or obtained directly from estimation of a parameterised statistical model. In addition, estimated mean treatment difference (or ratio) will be presented together with the two-sided 95% confidence interval and corresponding two-sided p-value.

In the statistical models, explanatory factors will be coded as follows:

- Treatment: Once weekly insulin 287, Once daily IGlar
- DPP4i has 2 levels (yes and no)
- Region has 2 levels (Europe and North America)
- Visit: Planned visits for actual endpoint according to flowchart

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

2.4.1 Primary endpoint

The primary endpoint is change from baseline to week 26 in HbA_{1c}.

Primary estimand

For the primary endpoint, the primary estimand is defined as the "hypothetical" estimand[3].

The treatment difference between once weekly insulin 287 versus once daily IGlar in change from baseline to week 26 in HbA_{1c} for all randomised subjects if all subjects had adhered to treatment and did not initiate ancillary treatment in subjects with T2DM inadequately treated with metformin with or without DPP4i.

The primary estimand will be estimated based on the FAS. This estimand aims to reflect the treatment effect for subjects that are actually able to take the drug during the intended treatment period. With the aim of evaluating proof of concept, this estimand is considered relevant i.e. a de jure estimand addressing efficacy.

Subjects may start ancillary treatment during the trial. Hence, data obtained after occurrence of intercurrent event such as initiation of ancillary treatment and discontinuation of randomised treatment will not be included in the estimation of the primary estimand.

To estimate this estimand, change from baseline in HbA_{1c} after 26 weeks will be analysed with the linear mixed model for repeated measurement (MMRM) method with an unstructured covariance matrix. All post baseline HbA_{1c} measurements obtained on planned visits while the subject continues the randomised treatment and does not initiate ancillary treatment will contribute to the analysis. Hence, data obtained after initiation of ancillary treatment or discontinuation of randomised treatment will not be included in the estimation of the primary estimand. For definition of ancillary treatment, please see protocol section 7.7. For concomitant diabetes medication not considered to be ancillary treatment, please see section 2.3 above. This analysis has the underlying assumption that the missing data mechanism is 'missing at random'. The model will include use of DPP4i (yes/no), region, treatment and visit as fixed factors and baseline HbA_{1c} as covariate. Interactions between visit and all factors and covariates will also be included in the model. The estimated mean treatment difference and the confidence interval will be presented together with the corresponding two-sided p-value. In the following, this MMRM method will be referred to as the standard MMRM method.

Secondary estimand

The secondary estimand for the primary endpoint is the "treatment policy" estimand.

The secondary estimand is defined as the treatment difference between once weekly insulin 287 versus once daily IGlar in change from baseline to week 26 in HbA_{1c} for all randomised subjects, regardless of the treatment actually received in subjects with T2DM inadequately treated with

metformin with or without DPP4i. This estimand aims to reflect the treatment effect for all subjects regardless of treatment adherence, i.e. a de facto estimand addressing effectiveness.

This will be estimated using all HbA_{1c} measurements obtained at week 26, also including measurements from subjects discontinuing their randomised treatment or initiating ancillary treatment. Missing HbA_{1c} measurements at week 26 will be imputed from trial participants who are from the same randomised group, who have discontinued their randomised treatment and have an HbA_{1c} measurement at week 26.

This will be done as follows:

- First, one thousand (1000) copies of the dataset will be generated.
- Second, for each dataset copy, and each treatment group, an analysis of variance (ANOVA) model with baseline HbA_{1c} value as a covariate will be fitted to the week 26 value based on subjects having discontinued their randomised treatment and have an HbA_{1c} measurement at week 26. The estimated parameters, and their variances, from the model will be used to impute missing values at week 26 in the same treatment group. The factors region and use of DPP4i are not considered in this step assuming the number of subjects to impute from will be low and that may lead the model to not meet the convergence criteria.
- For each of the complete data sets, the change from baseline in HbA_{1c} after 26 weeks will be analysed using an analysis of covariance model with use of DPP4i (yes/no), region and treatment as fixed factor, and baseline HbA_{1c} as covariate. The estimates and standard deviations for the 1000 data sets will be pooled to one estimate and associated SD using Rubin's rule.

If less than 3 subjects have discontinued their randomised treatment and have an HbA_{1c} measurement at week 26 in any of the treatment groups, then the second step above will be carried out combining the two treatment arms and including treatment as factor in the model.

The estimated mean treatment difference and the confidence interval will be presented together with the corresponding two-sided p-value.

Sensitivity analysis

The following sensitivity analysis of the assumptions about the missing data will be carried out: for the primary estimand, a tipping point like type of analysis will be performed where subjects from the Insulin 287 arm having no HbA_{1c} measurement at week 26 are assumed to have a worse outcome compared to what was imputed in the primary analysis. This is done by adding a value Δi to the imputed HbA_{1c} values in the Insulin 287 arm before analysing the data. The imputation is implemented as a multiple imputation in two steps. In the first step, intermittent missing HbA_{1c} values are imputed (1000 copies) for each treatment separately using a Markov Chain Monte Carlo method in order to obtain a monotone missing data pattern. In the second step, sequential multiple imputation of HbA_{1c} values at week 4, 8, 12, 16, 20 and 26 for each dataset copy and each treatment

group is fitted using an analysis of covariance model with use of DPP4i (yes/no) and region as fixed factors, and baseline HbA_{1c} and earlier HbA_{1c} as covariates. For each of the complete data set, a penalty is added to the imputed HbA_{1c} values in the insulin 287 arm after which change from baseline in HbA_{1c} after 26 weeks is derived and analysed using an analysis of covariance model with use of DPP4i (yes/no), region and treatment as fixed factor, and baseline HbA_{1c} as covariate. For each penalty, the estimates and standard deviations for the 1000 data sets will be pooled to one estimate and associated SD using Rubin's rule. The resulting estimated treatment differences and 95% CIs will be plotted as function of Δi to evaluate the robustness of the primary analysis results.

2.4.2 Secondary endpoints

2.4.3 Confirmatory secondary endpoints

Not applicable for this trial.

2.4.3.1 Supportive secondary endpoints

The supportive secondary endpoints will be addressed in terms of the framework of the primary estimand only.

Efficacy endpoints

- Change from baseline to week 26 in fasting plasma glucose
- 9-point profile (individual SMPG values) at week 26
- Change from baseline to week 26 in mean of the 9-point profile, defined as the area under the profile divided by measurement time
- Fluctuations of the 9-point profile (defined as the integrated absolute distance from the mean profile value divided by measurement time) at week 26
- Fasting C-peptide at week 26
- Change from baseline to week 26 in body weight
- Weekly dose of insulin 287 and weekly dose of IGlar from visit 26 to visit 28

FPG and body weight – change from baseline after 26 weeks

Change from baseline in FPG and body weight will be analysed using the standard MMRM method with relevant baseline as the covariate.

Fasting C-peptide

Fasting C-peptide will be logarithmically transformed and analysed using the standard MMRM method but including relevant log-transformed baseline as the covariate.

SMPG 9-point profile

The following endpoints will be derived from self-measured plasma glucose,

1. 9-point profile (individual SMPG values) at week 26
2. Change from baseline to week 26 in mean of the 9-point profile, defined as the area under the profile divided by measurement time
3. Fluctuations of the 9-point profile (defined as the integrated absolute distance from the mean profile value divided by measurement time) at week 26

A linear mixed effect model will be fitted to the 9-point SMPG profile data at week 26. The model will include treatment, region, use of DPP4i, time, the interaction between treatment and time, the interaction between region and time, and the interaction between use of DPP4i and time as fixed factors and subject as random effect.

Change from baseline in mean of the 9-point profile, and fluctuation in 9-point profiles after 26 weeks will be analysed separately using the standard MMRM method with relevant baseline as the covariate. Fluctuation in the 9-point profile will be logarithmically transformed before analysed. Baseline fluctuation in the 9-point profile also will be log-transformed in the model.

Insulin dose

Insulin 287 dose and IGlar dose will be summarised by week.

Weekly dose from visit 26 to visit 28, i.e. the average weekly dose during the last two weeks of treatment, will be logarithmically transformed and analysed based on standard MMRM method but not including baseline as a covariate.

Safety endpoints

Number of treatment emergent adverse events from baseline to week 31

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

The treatment emergent period represents the period where subjects are considered exposed to trial product, i.e. it coincides with the on-treatment period as defined in section 2.2.

A treatment emergent adverse event is defined as an event that has onset date (or increase in severity) during the on-treatment observation period. These will therefore be referred to as 'on-treatment AEs' hereafter.

On-treatment AEs are summarised descriptively 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 on-treatment AEs and of serious on-treatment AEs 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 treatment discontinuation.

Furthermore, summary tables based on system organ class and preferred terms are made for the on-treatment period for:

- All AEs
- Serious AEs
- AEs possibly or probably related to trial product
- Severe AEs
- AEs reported by safety areas of interest
- AEs 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

A listing for AEs occurring outside of the on-treatment period, i.e. with onset date before the first day of exposure to randomised treatment and AEs collected after the on-treatment period, will be presented.

Additional summaries will be displayed for SAEs, including events collected after premature treatment discontinuation ("in-trial" summary).

Summary of number of on-treatment injection site reactions will be presented as an overview including all AEs, serious AEs, AEs by severity and AEs by relation to treatment. Furthermore, summary table of injection site reaction based on system organ class and preferred terms will be made.

Number of hypoglycaemic episodes

The definition and classification of hypoglycaemic episodes are outlined in Table 2-2. For further details, please refer to Appendix 8 in the protocol. Data on hypoglycaemic episodes are presented in terms of the number of subjects with at least one episode (N), the percentage of subjects with at least one episode (%), the number of episodes (E) and the event rate per 100 years of exposure (R). The summaries are made for all and nocturnal (between 00:01 and 05.59 both inclusive) episodes respectively.

Table 2-2 Classification of hypoglycaemia

Level	Glycaemic criteria	Description
Hypoglycaemia alert value (level 1)	< 3.9 mmol/L (70 mg/dL) and ≥ 3.0 mmol/L (54 mg/dL)	Sufficiently low for treatment with fast-acting carbohydrate and dose adjustment of glucose-lowering therapy

Level	Glycaemic criteria	Description
Clinically significant hypoglycaemia (level 2)	< 3.0 mmol/L (54 mg/dL)	Sufficiently low to indicate serious clinically important hypoglycaemia
Severe hypoglycaemia (level 3)	No specific glucose threshold	Hypoglycaemia associated with severe cognitive impairment requiring external assistance for recovery

Number of hypoglycaemic episodes, whenever analysed statistically, will be analysed by a negative binomial regression model with treatment, region and use of DPP4i (yes/no) as fixed factors and the log of time period for which the hypoglycaemic episodes are considered as an offset. In the following, this model will be referred to as the standard negative binomial regression model.

Level 1 hypoglycaemic episodes, level 2 and level 3 combined hypoglycaemic episodes, level 2 hypoglycaemic episodes, and level 3 hypoglycaemic episodes from baseline to end of treatment visit will be summarised and analysed separately by the standard negative binomial regression model to the extent data allows.

The above summaries will be repeated for the on-treatment period, the titration period and the maintenance period. The statistical analysis will be repeated for the following to the extent data allows,

1. Number of level 2 and level 3 combined hypoglycaemic episodes during the on-treatment period
2. Number of level 2 and level 3 combined hypoglycaemic episodes during the titration period
3. Number of level 2 and level 3 combined hypoglycaemic episodes during the maintenance period
4. Number of level 2 hypoglycaemic episodes during the on-treatment period
5. Number of level 2 hypoglycaemic episodes during the titration period
6. Number of level 2 hypoglycaemic episodes during the maintenance period
7. Number of level 3 hypoglycaemic episodes during the on-treatment period
8. Number of level 3 hypoglycaemic episodes during the titration period
9. Number of level 3 hypoglycaemic episodes during the maintenance period

The number of nocturnal level 2 and level 3 combined hypoglycaemic episodes and number of level 2 hypoglycaemic episodes, and number of level 3 hypoglycaemic episodes:

- from baseline to end of treatment visit
- during the on-treatment period
- during the titration period
- during the maintenance period

will be analysed similarly to the extent data allows.

Antibodies from baseline to week 31

The following is to be prepared for both insulin 287 and insulin glargine. Anti-insulin antibody level, anti-insulin antibody titres and change from baseline in anti-insulin antibody titres will be summarised and tabulated. For anti-insulin antibody level, mean plots by treatment week will be prepared. The correlation between anti-insulin antibody titres and actual weekly basal insulin dose, HbA_{1c}, and change from baseline in HbA_{1c}, respectively, will be illustrated using mean plots by treatment week for quartiles of peak post baseline to week 31 titre values. The Spearman's rank correlation coefficient between change in anti-insulin antibody titres at follow-up to actual weekly basal insulin dose during week 25 and week 26, HbA_{1c} at week 26, change from baseline in HbA_{1c} at week 26, and level 2 and level 3 combined hypoglycaemic episodes during the on-treatment period, respectively, will be derived and displayed in a table with the corresponding p-value for test of no correlation. Anti-insulin antibody status will be tabulated by visit, and anti-insulin antibody cross-reactivity to endogenous insulin status will be tabulated by visit for subjects positive for anti-insulin antibodies. Shift table from baseline to week 26 and follow-up for cross-reactivity anti-insulin antibody status will be prepared.

2.4.3.2 Exploratory endpoints

- Insulin 287 concentrations, evaluated in a population PK analysis
- Time in range 3.9-7.8 mmol/L (70–140 mg/dL) measured by flash glucose monitoring (FGM) ([redacted] Free Style Libre Pro) during the last 2 weeks of treatment (week 25 and 26). The percentage of time spent in glycaemic range will be calculated as 100 times the number of recorded measurements in glycaemic range 3.9-7.8 mmol/L (70-140 mg/dL) divided by the total number of recorded measurements. It will be analysed using the standard MMRM method but not including baseline as a covariate.

Since the data accuracy may vary during the first 24 hours after sensor fitting, the FGM data from the 1st day (24h) of each sensor period will be excluded from analysis. Following the international consensus criteria[4], it will be required that at least 70% of the planned FGM measurements during the last 2 weeks of treatment is available for endpoint data to be included in the analysis.

2.4.4 Other analyses

Other efficacy tabulations:

HbA_{1c} responders after 26 weeks

Dichotomous outcome (responder=yes/non-responder=no) will be defined based on whether a subject has met a specific level of $HbA_{1c} < 7.0\%$ after 26 weeks. Analysis of this responder outcome will be based on a logistic regression model with treatment, region and use of DPP4i as fixed factors and baseline HbA_{1c} as covariate.

Missing HbA_{1c} (according to the primary estimand) are imputed by the standard MMRM method before applying the specific responder criterion.

HbA_{1c} responders with minimal weight gain after 26 weeks

Responder will be defined as:

- HbA_{1c} < 7.0% and change from baseline in body weight < 3%

Analysis of this responder outcome will be based on a logistic regression model with treatment, region and use of DPP4i as fixed factors and baseline HbA_{1c} and baseline body weight as covariates.

Missing HbA_{1c} and body weight (according to the framework of the primary estimand) are imputed by the standard MMRM method before applying the specific responder criterion.

HbA_{1c} responders after 26 weeks without severe or clinically significant hypoglycaemic episodes during the last 12 weeks of treatment

Responder will be defined as:

- HbA_{1c} < 7.0% and without severe or clinically significant hypoglycaemic episodes during the last 12 weeks of treatment

Analysis of this responder outcome will be based on a logistic regression model with treatment, region and use of DPP4i as fixed factors and baseline HbA_{1c} as covariate.

Missing HbA_{1c} (according to the primary estimand) are imputed by the standard MMRM method before applying the specific responder criterion. Subjects with less than 12 weeks of treatment without ancillary treatment will conservatively be set to being non-responder.

HbA_{1c} responders after 26 weeks without severe hypoglycaemic episodes during the last 12 weeks of treatment

Responder will be defined as:

- HbA_{1c} < 7.0% and without severe hypoglycaemic episodes during the last 12 weeks of treatment

Analysis of this responder outcome will be based on a logistic regression model with treatment, region and use of DPP4i as fixed factors and baseline HbA_{1c} as covariate.

Missing HbA_{1c} (according to the primary estimand) are imputed by the standard MMRM method before applying the specific responder criterion. Subjects with less than 12 weeks of treatment without ancillary treatment will conservatively be set to being non-responder.

HbA_{1c} responders with minimal weight gain after 26 weeks and without severe or clinically significant hypoglycaemic episodes during the last 12 weeks of treatment

Responder will be defined as:

- HbA_{1c} < 7.0% without severe or clinically significant hypoglycaemic episodes during the last 12 weeks of treatment, and change from baseline in body weight < 3%

Analysis of this responder outcome will be based on a logistic regression model with treatment, region and use of DPP4i as fixed factors and baseline HbA_{1c} and body weight as covariates.

Missing HbA_{1c} and body weight (according to the framework of the primary estimand) are imputed by the standard MMRM method before applying the specific responder criterion. Subjects with less than 12 weeks of treatment without ancillary treatment will conservatively be set to being non-responder.

HbA_{1c} responders with minimal weight gain after 26 weeks and without severe hypoglycaemic episodes during the last 12 weeks of treatment

Responder will be defined as:

- HbA_{1c} < 7.0% without severe hypoglycaemic episodes during the last 12 weeks of treatment, and change from baseline in body weight < 3%

Analysis of this responder outcome will be based on a logistic regression model with treatment, region and use of DPP4i as fixed factors and baseline HbA_{1c} and body weight as covariates.

Missing HbA_{1c} and body weight (according to the framework of the primary estimand) are imputed by the standard MMRM method before applying the specific responder criterion. Subjects with less than 12 weeks of treatment without ancillary treatment will conservatively be set to being non-responder.

Similar analyses as defined above will be carried out for responder targets replacing HbA_{1c} <7.0% with HbA_{1c} ≤6.5%.

FPG responders after 26 weeks

Dichotomous outcome (responder=yes/non-responder=no) will be defined based on whether a subject has met a specific target level of FPG ≤ 7.2 mmol/L (130 mg/dL) after 26 weeks. Analysis of this responder outcome will be based on a logistic regression model with treatment, region and use of DPP4i as fixed factors and baseline FPG as covariate.

Missing FPG (according to the framework of the primary estimand) are imputed by the standard MMRM method before applying the specific responder criterion.

Similar analyses as defined above will be carried out for responder targets replacing FPG ≤ 7.2 mmol/L (130 mg/dL) with FPG ≤ 6 mmol/L (108 mg/dL).

Other safety tabulations:

Clinical evaluation (ECG, eye examination and physical examination) change from baseline after 26 weeks

Eye examination (fundoscopy/fundus photography) and 12-lead ECG findings will be summarised descriptively, including:

- Summaries for each visit
- Shift tables from baseline to after 26 weeks

Laboratory assessment (Biochemistry and Haematology) - change from baseline after 26 weeks

All laboratory parameters will be summarised descriptively including:

- Summaries by visit
- Box plots by time since randomisation

Lipids and vital signs

Lipids and vital signs will be summarised by treatment.

Other exploratory tabulations:

Time in range measured by FGM ([redacted] Free Style Libre Pro) during the last two weeks of treatment (week 25 and 26) will be analysed using the standard MMRM method but not including baseline as a covariate for the following time in range,

- Time in range 3.9–6.0 mmol/L (70-108 mg/dL)
- Time in range 3.9–10.0 mmol/L (70-180 mg/dL)
- Time spent < 3.0 mmol/L (54 mg/dL)
- Time spent < 3.9 mmol/L (70 mg/dL)
- Time spent > 10.0 mmol/L (180 mg/dL)
- Time spent > 13.9 mmol/L (250 mg/dL)

Within subject variability as measured by CV% during the last two weeks of treatment (week 25 and 26) will be logarithmically transformed and analysed using an analysis of covariance model with treatment, region and use of DPP4i as fixed factors. Within subject variability will be calculated as the sample CV% of the recorded measurements.

For population PK analysis refer section 2.5.

2.5 Pharmacokinetic and/or pharmacodynamic modelling

Insulin 287 serum concentration data will be used for a population PK analysis. The objective of the population PK analysis is to evaluate the effects of pre-specified covariates on serum concentrations of insulin 287.

The population PK analysis will be performed by Quantitative Clinical Pharmacology, Novo Nordisk A/S. A more technical and detailed elaboration of the population PK analysis will be given in a modelling analysis plan (MAP), which will be prepared before Database Lock (DBL). In brief, a previously developed PK model for insulin 287 will be applied. The absorption rate constant (Ka) in the model will be fixed, and the apparent clearance (CL/F) and the apparent volume of distribution (V/F) will be re-estimated. The covariates of interest will be incorporated into the PK model using criteria which will be specified in the MAP.

The population PK analysis will be reported in a separate modelling report, which will not be a part of the clinical trial report. The individual insulin 287 serum concentration data will be tabulated in the bioanalytical report (BAR).

2.6 Additional sensitivity analyses

Seven subjects used an incorrect type of syringe for once daily IGlar or once daily placebo during varying time of the treatment period which led to administration of 2.5 times the prescribed dose of once daily IGlar or once daily placebo.

One of the seven subjects experienced level 1 hypoglycaemic episodes while on the incorrect type of syringe. If the subject who experienced level 1 hypoglycaemic episodes while on the incorrect type of syringe turns out to be randomised to IGlar after randomisation code break, a sensitivity analysis will be carried out by repeating the supportive statistical analysis for level 1 hypoglycaemic episodes from baseline to end of treatment visit but excluding this subject.

An increased dose of IGlar can potentially affect the development of anti-glargine antibodies. If any if the seven subjects turn out to be randomised to IGlar after randomisation code break, those who turn out to be randomised to IGlar will be excluded from an additional summary table of the change from baseline in anti-insulin glargine antibody titres by visit and an additional correlation analysis of the Pearson's correlation coefficients.

3 Changes to the statistical analyses planned in the protocol

Sample size determination

Because of recruitment issues, it was decided to not round number of subjects to be randomised from 246 to 250. Hence, the corresponding sentence has been deleted, and information about the number in each arm is included based on 246 subjects to be randomised.

The sample size for width of 95% CI of 0.40 and SD of 1.0 should have been 386 instead of the reported 384, as per sample size calculation. The number has been updated. However, this would not have affected the choice of sample size.

Definition of trial periods

A subsection including definition of trial periods has been added. The wording of the on-treatment period and the in-trial period have been updated with more details. Furthermore, a definition of the on-treatment without ancillary treatment period has been included to conceptualize the trial period described in the description of the primary estimand. A high-level description of what period will be of main interest for efficacy and safety evaluations has been included. Finally, the titration period, the maintenance period, and the baseline to end of treatment visit period have also been defined in more detail.

Ancillary treatment definition has been updated to reflect that only a dose increase of the background medication can be considered as ancillary treatment whereas the previous definition comprised any dose change. This is to reflect that ancillary treatment is considered as something extra on top of randomised treatment or the already taken background medication.

Statistical analyses

A summary with details on what analysis set and trial period to base summaries and analyses of efficacy and safety endpoints on have been included for easy reference. To align with what period summaries of efficacy and safety endpoints are to be based upon, efficacy data will be plotted for the on-treatment without ancillary treatment period and safety data will be plotted for the on-treatment period.

Selected endpoints will not be summarised by empirical distribution plots. Hence, this has been deleted. Furthermore, only selected endpoints will have mean values plotted over time. Mean cumulative function plots and dot plots, however, will be used to summarise selected endpoints, which is why these have been added to the list of plot types. Furthermore, it has been specified that the additional plots for HbA_{1c} for 'in-trial' data are mean plots.

End of treatment assessments for withdrawn or prematurely discontinued subjects may be reallocated, as has been described.

Primary estimand

It had been specified that all post baseline HbA_{1c} measurements obtained on planned visits while the subject continues the randomised treatment will contribute to the analysis. However, this needed to be updated to while the subject continues the randomised treatment and does not initiate ancillary treatment in order to align with the primary estimand.

Reference to definition of ancillary treatment has been included together with reference to descriptive text on what concomitant diabetes medication is not to be considered ancillary treatment.

Secondary estimand

The analysis and imputation descriptions have been clarified for alignment with the secondary estimand.

Sensitivity analysis

A multiple imputation model mimicking the primary analysis has been specified for the tipping point analysis.

Efficacy endpoints

Change from baseline to week 26 in mean of the 9-point profile had been defined as the area under the profile while it should have been defined as the area under the profile divided by measurement time, which has been updated.

For fluctuation, timing of endpoint has been included to align with description of the other endpoints.

For fasting C-peptide, it has been clarified that it is fasting C-peptide at week 26 and not change from baseline to week 26 that is to be analysed.

Daily dose of IGlar has been updated to weekly dose of IGlar and dose at week 26 has been updated to dose during the last two weeks of treatment; endpoint description is now aligned with wording in protocol section 4.3.2.2 and the wording of analysis hereof.

Fasting C-peptide

Analysis description of fasting C-peptide has been included in its own subsection and wording is updated to reflect that fasting C-peptide should be analysed on log-scale.

SMPG 9-point profile

Change from baseline to week 26 in mean of the 9-point profile had been defined as the area under the profile while it should have been defined as the area under the profile divided by measurement time, which has been updated.

Insulin doses

Endpoint description has been updated to make the description clearer and to align wording with that of other endpoints.

Number of treatment emergent adverse events from baseline to week 31

The on-treatment period corresponds to the treatment emergent period and the treatment emergent terminology will not be used in any outputs. Hence, redundant text has been deleted with reference to the description of the on-treatment period. Consequently, treatment emergent AEs are referred to as on-treatment AEs.

Summaries of on-treatment AEs, including on-treatment injection site reactions, leading to withdrawal from trial will not be produced as the end of trial form does not contain the information. Furthermore, summary of on-treatment injection site reactions leading to treatment discontinuation will not be produced; the information is contained in an overall summary of on-treatment AEs leading to treatment discontinuation.

Summary tables based on system organ class and preferred terms are not to be made for moderate and mild on-treatment AEs or for on-treatment AEs with preferred term that are experienced by at least 1% of the subjects in any treatment arm or by at least 1% of all subjects. Consequently, this text has been deleted.

Text describing listing for AEs occurring outside of the on-treatment period has been rephrased and redundant text has been deleted.

Number of hypoglycaemic episodes

Details as to what hypoglycaemic episodes will be summarised and analysed have been provided, and the time period considered for each analysis have been made unambiguous with time periods now corresponding to the defined trial periods.

Antibodies from baseline to week 31

All outputs for antibody data are described in more detail in this section whereas the section under ‘other safety tabulations’ has been deleted to make the description clear even though not all outputs in the updated section are relevant for the supportive secondary safety endpoints. Similar outputs are to be made for both insulin 287 and insulin glargine. Anti-insulin antibody %B/T level will be summarised and tabulated, but not change in anti-insulin antibody %B/T level. Correlation plots are illustrated using mean plots instead of scatter plots. Pearson’s correlation coefficient has been replaced by Spearman’s rank correlation coefficient due to the discrete nature of the titre values. The correlation coefficients are only to be derived for titre not %B/T level and should also be derived for correlation to the level 2 and level 3 combined hypoglycaemic episodes during the on-treatment period while correlation to insulin dose has been updated to specify the dose during last two weeks of treatment to align with the dose endpoint. Finally, positive/negative summaries have been defined in more detail.

Exploratory endpoints

Time in range should be summarised based on percentage of time spent in range, not time unit as specified in protocol section 4.3.3. Furthermore, it has been specified that at least 70% of the planned FGM measurements within a sensor period need to be available to derive time in range within period.

Other efficacy tabulations

It has been clarified that missing values for whatever reason are imputed, not only missing values due to subject discontinuing treatment or initiating ancillary treatment, but still according to the primary estimand.

In the responder outcome defined as HbA_{1c} responders with minimal weight gain after 26 weeks and without clinically significant hypoglycaemic episodes during the last 12 weeks of treatment, severe hypoglycaemic episodes should have been included alongside clinically significant hypoglycaemic episodes. This has been updated and the endpoint now corresponds to a similar endpoint without minimal weight gain.

Definition of minimal weight gain after 26 weeks should have said change from baseline in body weight $< 3\%$ instead of $\leq 3\%$, which has now been updated. In description of FPG responder, target should have said ≤ 7.2 mmol/L instead of < 7.2 mmol/L, which has now been updated.

Other safety tabulations

For laboratory assessment, no shift table from baseline to after 26 weeks, proportion of subjects with measurement outside reference range by treatment and week, and listings of individual values outside reference ranges (abnormal values) will be produced after end of text reduction.

Similar to the exploratory endpoint of time in target-range, the exploratory tabulations of other time in range are to be based on the last two weeks of treatment, which has now been specified

It is not feasible to analyse FGM data as repeated measures in a linear mixed model. The analysis has been updated to analysis of covariance of the logarithmically transformed within subject CV for the last two weeks of treatments.

Additional sensitivity analyses

Additional sensitivity analyses have been added to explore impact of serious breach on potentially affected hypoglycaemic episodes data and antibody data.

4 References

1. Little RJA, Rubin DB. Statistical analysis with missing data: New York: John Wiley & Sons. 1987.
2. National Academy of Sciences (NAS). The Prevention and Treatment of Missing Data in Clinical Trials. Washington D.C.: The National Academies Press. 2010.
3. Mallinckrodt CH, Lin Q, Lipkovich I, Molenberghs G. A structured approach to choosing estimands and estimators in longitudinal clinical trials. Pharm Stat. 2012;11(6):456-61.
4. Danne T, Nimri R, Battelino T, Bergenstal RM, Close KL, DeVries JH, et al. International Consensus on Use of Continuous Glucose Monitoring. Diabetes Care. 2017;40(12):1631-40.