Cover Page for Statistical Analysis Plan

Sponsor name:	Novo Nordisk A/S
NCT number	NCT04795531
Sponsor trial ID:	NN1436-4479
Official title of study:	A 26-week double blinded, multiregional, trial comparing the effect and safety of once weekly insulin icodec and once daily insulin degludec 100 units/mL, both in combination with non-insulin anti-diabetic drugs, in insulin naïve subjects with type 2 diabetes (ONWARDS 3)
Document date*:	20 January 2021

*Document date refers to the date on which the document was most recently updated.

Statistical Analysis Plan

NN1436-4479

A 26-week double blinded, multiregional, trial comparing the effect and safety of once weekly insulin icodec and once daily insulin degludec 100 units/mL, both in combination with non-insulin anti-diabetic drugs, in insulin naïve subjects with type 2 diabetes.

ONWARDS 3

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

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Version history

This Statistical Analysis Plan (SAP) for trial NN1436-4479 is based on the protocol version 2.0 dated 30-NOV-2020.

Table 1 SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1.0	See approval date in the electronic document management system	Not Applicable	Original version
2.0	See approval date in the electronic document management system	Method for imputing missing data using completing comparator subjects changed to imputing from baseline values within own arm when baseline values are available	Based on FDA recommendation

1 Introduction

This statistical analysis plan (SAP) is based on the protocol: *A 26-week double blinded, multiregional, trial comparing the effect and safety of once weekly insulin icodec and once daily insulin degludec 100 units/mL, both in combination with non-insulin anti-diabetic drugs, in insulin naïve subjects with type 2 diabetes*, version 2.0 (dated 30-NOV-2020). Most of the statistical analyses and derivations of endpoints presented in this SAP are identical to those described in the protocol, but some have been updated or added for technical or clinical reasons. The SAP also contains specifications of additional derivations and analyses. The changes to the protocol-planned statistical analyses and the reasons for these changes are described in Appendix 2, section 6.2.

1.1 Objectives and endpoints

1.1.1 Primary, secondary and exploratory objective and estimand

1.1.1.1 Primary objective

To demonstrate the effect on glycaemic control of once weekly insulin icodec in combination with non-insulin anti-diabetic drugs in insulin-naïve subjects with T2D. This includes comparing the difference in change from baseline in HbA_{1c} between insulin icodec and insulin degludec after 26 weeks of treatment to a non-inferiority limit of 0.3%.

1.1.1.2 Secondary objective

To compare parameters of safety with once weekly insulin icodec versus once daily insulin degludec, both in combination with non-insulin anti-diabetic drugs in insulin-naïve subjects with T2D.

1.1.1.3 Estimand

The estimand is the 'treatment policy estimand' defined as the treatment difference between insulin icodec and insulin degludec of the change in HbA_{1c} from baseline to week 26 for all randomised subjects, irrespective of adherence to randomised treatment and changes to anti-diabetic background medication. The following intercurrent events will be handled by the treatment policy strategy: initiation of bolus insulin treatment for more than 2 weeks, discontinuation of randomised insulin treatment, and withdrawal from the trial (measurements collected after these intercurrent events are used in the primary analysis).

1.1.2 Primary, secondary and exploratory endpoints

1.1.2.1 Primary endpoint

Endpoint title	Time frame	Unit
Change in HbA_{1c}	From baseline week 0 (V2) to week 26 (V28)	%-point

1.1.2.2 Secondary endpoints

1.1.2.2.1 Confirmatory secondary endpoints

Not applicable for this trial.

1.1.2.2.2 Supportive secondary endpoints

Secondary efficacy endpoint

Endpoint title	Time frame	Unit
Change in fasting plasma glucose (FPG)	From baseline week 0 (V2) to week 26 (V28)	mmol/L

Secondary safety endpoints

Endpoint title	Time frame	Unit
Number of severe hypoglycaemic episodes (level 3)	From baseline week 0 (V2) to week 31 (V30)	Number of episodes
Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter)	From baseline week 0 (V2) to week 31 (V30)	Number of episodes
Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) or severe hypoglycaemic episodes (level 3)	From baseline week 0 (V2) to week 31 (V30)	Number of episodes
Number of severe hypoglycaemic episodes (level 3)	From baseline week 0 (V2) to week 26 (V28)	Number of episodes
Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter)	From baseline week 0 (V2) to week 26 (V28)	Number of episodes
Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) or severe hypoglycaemic episodes (level 3)	From baseline week 0 (V2) to week 26 (V28)	Number of episodes
Change in body weight	From baseline week 0 (V2) to week 26 (V28)	Kg
Mean weekly insulin dose	From week 24 (P26) to week 26 (V28)	U

1.1.2.3 Exploratory endpoints

Not applicable for this trial.

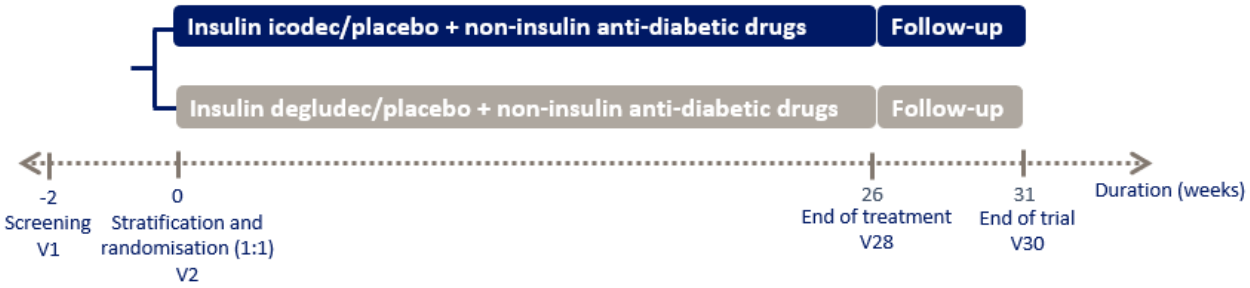
1.2 Trial design

This is a 26-week randomised, stratified, double blinded, double dummy, active-controlled, parallel-group, multicentre, multiregional, treat-to-target trial with two treatment arms. The trial investigates the effect on glycaemic control and safety of treatment with once weekly insulin icodec compared to once daily insulin degludec, both in combination with non-insulin anti diabetic drugs, in insulin naïve subjects with inadequately controlled T2D on non-insulin anti-diabetic drugs in need for insulin initiation.

The trial duration is approximately 33 weeks, consisting of 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 Figure 1-1 and trial flowchart (see protocol section 1.2), respectively.

Figure 1-1 Trial design



For further details see protocol section 4.1.

2 Statistical hypotheses

The primary hypothesis to be tested is that insulin icodec is non-inferior to insulin degludec in terms of change from baseline to week 26 in HbA_{1c}.

Formally, let D be the treatment difference 'insulin icodec' minus 'insulin degludec' of the change in HbA_{1c} from baseline to week 26. The null-hypothesis will be tested against the alternative hypothesis of non-inferiority as given by

$$H0: D \geq 0.30\% \text{ against } HA: D < 0.30\%$$

The non-inferiority margin of 0.3%-point is chosen based on the recommendation in the FDA guidance for industry on developing drugs for treatment of diabetes.[1] Also, this margin is considered to provide sufficient assay sensitivity based on the below considerations:

- The margin does not represent an unacceptable loss of efficacy with insulin icodec relative to treatment with a basal insulin analogue
- It represents less than 50% of a suitably conservative estimate of insulin glargine's treatment effect on HbA_{1c} in a placebo-controlled trial (-0.85%-point $[-1.04; -0.66]_{95\%CI}$ versus placebo) in insulin-naïve subjects, which demonstrated insulin glargine's superiority.[2]
- Other basal insulin analogues have previously been shown to yield similar reductions in HbA_{1c} compared to insulin glargine. As only insulin glargine (not insulin degludec) has been compared to placebo in previous trials, the above-mentioned insulin glargine results are used as reference for consideration of the margin.

The following describe the secondary confirmatory hypothesis. In order to control the overall Type I error at a 5% level, two sided, a hierarchical testing procedure will be used. If non-inferiority in glycaemic control is concluded in the primary analysis, confirmatory testing proceeds to the following hypothesis:

- Insulin icodec is superior to insulin degludec in terms of change from baseline to week 26 in HbA_{1c}

Formally, let D be the mean treatment difference 'insulin icodec' minus 'insulin degludec' of the change in HbA_{1c} from baseline to week 26. The null-hypothesis of insulin icodec not superior will be tested against the alternative hypothesis of superiority as given by

$$H0: D \geq 0\% \text{ against } HA: D < 0\%$$

3 Sample size determination

See protocol section 9.2.

4 Analysis sets

The following populations are defined:

Population	Description
Randomised	All subjects randomised.
Full analysis set	Full analysis set (FAS): All subjects randomised excluding the Chinese extension cohort. Subjects will be analysed according to the randomised treatment.
Safety analysis set	All subjects randomly assigned to trial treatment excluding the Chinese extension cohort and who take at least 1 dose of trial product. Subjects are analysed according to the treatment they actually received.
Chinese extension cohort	All Chinese subjects randomised after the respective planned recruitment period.
Extended full analysis set	Extended full analysis set (EFAS): All subjects randomised including the Chinese extension cohort. Subjects will be analysed according to the randomised treatment.
Extended safety analysis set	Extended safety analysis set (ESAS): All subjects randomly assigned to trial treatment including the Chinese extension cohort and who take at least 1 dose of trial product. Subjects are analysed according to the treatment they actually received.

In exceptional cases, subjects or observations may be eliminated from the full analysis set. In such case the reasons for their exclusion will be documented before unblinding. The subjects and observations excluded from analysis sets, and the reason for this, will be described in the clinical trial report.

The following periods will be considered for the data collected:

In-trial period

The in-trial period starts at randomisation 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 as above.

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

On-treatment 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 end of trial visit (V30)
- The last date on trial product + 5 weeks for once daily insulin and + 6 weeks for once weekly insulin (corresponding to 5 weeks after the end of the dosing interval for both treatment arms)
- The end-date for the in-trial observation period

The on-treatment period represents the time period in which a subject is considered exposed to trial product.

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

All efficacy endpoints will be summarised and analysed using the full analysis set (FAS) and the 'in-trial' period. Safety endpoints will be evaluated using the on-treatment period with descriptive statistics being based on the safety analysis set (SAS) and statistical analyses being based on the FAS unless otherwise specified.

If China does not reach recruitment target of 100 Chinese subjects within the planned recruitment period all efficacy endpoints will in addition be summarised and analysed using the extended full analysis set (EFAS) and the 'in-trial' period, and safety endpoints will be evaluated using the on-treatment period with descriptive statistics being based on the extended safety analysis set (ESAS) and statistical analyses being based on the EFAS unless otherwise specified. These results will be presented in the extension part report.

5 Statistical analyses

5.1 General considerations

Presentation of results from a statistical analysis will include the estimated mean treatment difference (or ratio) presented together with the two-sided 95% confidence interval and the corresponding two-sided p-value. For the extension part analyses p-values will not be included (see also section 5.8).

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

- Treatment: Once weekly insulin icodec, insulin degludec
- Region: Asia, Europe, North America, South America,
- SU or glinide use: yes, no

The regions will be defined as follows:

- Asia: China, Taiwan
- Europe: Austria, Denmark, France, Czech Republic
- North America: Canada, United States
- South America: Argentina, Brazil, Mexico

Baseline is defined as information collected at week 0 (V2). In case a measurement is not available at week 0 (V2) the most recent measurement prior to week 0 (V2) will be used as baseline.

The number 541024 will be used as the seed for all imputations.

5.2 Subject disposition

Subject disposition will be summarised descriptively.

5.3 Primary endpoint analysis

5.3.1 Definition of endpoints

The primary endpoint is change in HbA_{1c} from baseline to week 26. See also Appendix 3, section 6.3.

5.3.2 Main analytical approach

The 'treatment policy' estimand, will be estimated based on the Full Analysis Set (FAS) using all HbA_{1c} measurements obtained at the week 26 visit, especially including measurements from subjects discontinuing their randomised treatment or initiating bolus insulin treatment for more than 2 weeks. Missing HbA_{1c} at the week 26 visit (regardless of treatment completion status) will be imputed from trial participants, who have discontinued their randomised treatment or initiated bolus insulin treatment for more than 2 weeks prior to the week 26 visit and have a measurement at the week 26 visit in the following way:

- First, one thousand (1000) copies of the dataset will be generated for HbA_{1c}.

- Second, for subjects who discontinued their randomised treatment or initiated bolus insulin treatment for more than 2 weeks at any time prior to the week 26 visit and have an HbA_{1c} measurement at the week 26 visit, the change in HbA_{1c} from last available planned on-treatment without initiation of more than 2 weeks bolus insulin treatment (LAOT-WOB) value to the week 26 visit will be analysed for each dataset copy using an analysis of covariance (ANCOVA) model with randomised treatment as fixed factor and LAOT-WOB value and the time point (study day) of this assessment as covariates. The estimated parameters, and their variances, from the model will be used to impute missing HbA_{1c} values for the change from LAOT-WOB to the week 26 visit and subsequently the missing HbA_{1c} value at the week 26 visit.

- For each of the complete data sets, the primary endpoint will be analysed using an ANCOVA model with region, SU or glinide use (yes/no), and randomised treatment as fixed factors, and baseline HbA_{1c} as a covariate. The estimates and standard deviations for the 1000 data sets will be pooled to one estimate and associated standard deviation using Rubin's rule.[3]

This analysis has the underlying assumption that subjects with missing data behave similarly as subjects that discontinue randomised treatment or initiate bolus insulin treatment for more than 2 weeks.

In case the amount of data for the described imputation model (see second step above) is insufficient for meaningful imputation, the first alternative will be the following:

- to simplify the imputation model by removing the following two covariates from the model: LAOT-WOB value and the time point (study day) of this assessment.

If the amount of data for this reduced model is still insufficient for meaningful imputation, the following imputation strategy will be applied instead:

- missing values at week 26 will be imputed with baseline value adding a random error term. The baseline value will be included as a covariate. This imputation method also includes measurements collected after intercurrent events, but is otherwise similar to the imputation method for endpoints where there is no data collection after premature treatment discontinuation as described for change in FPG (see section 5.4.1.1).

If non-inferiority is confirmed, i.e. if the 95% CI is strictly below 0.3%, then the primary endpoint will further be tested for superiority. Superiority for change in HbA_{1c} will be considered confirmed if the 95% CI is strictly below zero.

Missing HbA_{1c} at week 26 will be summarised by subject status.

5.3.3 Sensitivity analysis

The following sensitivity analysis evaluating the robustness of the assumptions about the missing data will be carried out:

For the primary endpoint, a two-dimensional tipping point analysis will be performed where subjects having imputed HbA_{1c} measurement at the week 26 visit are assumed to have a worse outcome in the insulin icodec arm and a better outcome in the insulin degludec arm compared to what was imputed in the primary analysis. This is done by adding or subtracting values Δ_i to the imputed HbA_{1c} values before analysing the data. The value of Δ_i will be varied independently in the two treatment arms. The non-inferiority margin of 0.3% will be among the Δ_i values investigated. The plausibility of the values of Δ_i where the conclusion of the non-inferiority or superiority change will be evaluated to assess the robustness of the results.

5.4 Secondary endpoints analysis

5.4.1 Supportive secondary endpoints

Supportive secondary endpoints will be evaluated in the framework of the primary estimand.

5.4.1.1 Efficacy endpoints

Change in fasting plasma glucose (FPG) from baseline week 0 (V2) to week 26 (V28)

Missing FPG values at the week 26 visit (regardless of treatment completion status) for both treatment arms will be imputed with baseline value adding a random error term. The random error term is normally distributed with a standard deviation set equal to the estimated residual standard deviation of an ANCOVA analysis on the LAOT-WOB values. Specifically, the imputations and analyses will be carried out as follows:

- First, an ANCOVA model with region, SU or glinide use (yes/no), and randomised treatment as fixed factors, and a baseline value as a covariate will be fitted to the LAOT-WOB values.
- Second, the estimated residual standard deviation, *s*, from this model will be used to impute missing values by the baseline value, adding a random normally distributed term with mean 0 and standard deviation *s*. This will be done a 1000 times.
- For each of the complete data sets, the endpoint will be analysed using an ANCOVA model with region, SU or glinide use (yes/no), and randomised treatment as fixed factors, and a baseline value as a covariate. The estimates and standard deviations for the 1000 data sets will be pooled to one estimate and associated standard deviation using Rubin's rule.

5.4.1.2 Safety endpoints

Hypoglycaemic episodes

The following hypoglycaemic endpoints will be analysed separately using the method described below:

- Number of severe hypoglycaemic episodes (level 3) from baseline week 0 (V2) to week 31 (V30)
- Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) from baseline week 0 (V2) to week 31 (V30)
- Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) or severe hypoglycaemic episodes (level 3) from baseline week 0 (V2) to week 31 (V30)

For subjects who discontinued their randomised treatment, the number of episodes in the missing period (time of follow-up 2 visit (V30) to planned end of the on-treatment period) will be imputed using a multiple imputation technique, assuming that the event rate pre follow-up 2 visit (V30) follows the respective treatment groups rate whilst post follow-up 2 visit (V30) event rate is the rate of the insulin degludec group. The imputation will be done as follows:

- First, a Bayes negative binomial model with log-link function will be fitted to the event rate data to obtain the posterior distribution of model parameters. The model will include region, SU or glinide use (yes/no), and randomised treatment as fixed factors and the logarithm of the on-treatment period as offset.
- Second, based on the estimated parameters for the insulin degludec group in this model, the number of episodes in the missing period will be imputed for subjects who discontinued their randomised treatment. Multiple copies (1000 copies) of a complete data set will be generated by sampling from the estimated distribution.

- For each of the complete data sets, the number of episodes will be analysed using a negative binomial model with log-link, fixed factors and offset as described in step 1. The estimates and standard deviations for the 1000 data sets will be pooled to one estimate and associated standard deviation using Rubin's rule.

The following hypoglycaemic endpoints will be analysed separately using the method described above, substituting the on-treatment period with the period from week 0 to week 26, and substituting 'follow up 2 visit (V30)' with 'discontinuation of treatment':

- Number of severe hypoglycaemic episodes (level 3) from baseline week 0 (V2) to week 26 (V28)
- Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) from baseline week 0 (V2) to week 26 (V28)
- Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) or severe hypoglycaemic episodes (level 3) from baseline week 0 (V2) to week 26 (V28).

For the definition and classification of hypoglycaemic episodes refer to the protocol Appendix 7 (protocol section 10.7).

Mean weekly insulin dose from week 24 (P26) to week 26 (V28)

Missing mean weekly insulin dose during the last 2 weeks of treatment (from week 24 to 26) will be analysed log-transformed. Missing mean weekly insulin doses during the last 2 weeks of treatment (from week 24 to 26) (regardless of treatment completion status) will be imputed from trial participants who are from the insulin degludec group, and who have completed and adhered to their randomised insulin treatment without initiation of bolus insulin treatment for more than 2 weeks at any time prior to the week 26 visit – i.e., data will be imputed based on the assumption that subjects with missing endpoint data will behave like subjects completing insulin degludec treatment without initiation of bolus insulin treatment for more than 2 weeks at any time prior to the week 26 visit. Specifically, the imputations and analyses will be carried out as follows:

- First, one thousand (1000) copies of the dataset will be generated for mean weekly insulin dose.
- Second, for each dataset copy, an analysis of variance (ANOVA) model will be fitted to mean weekly insulin dose values for subjects who completed their randomised treatment without initiation of bolus insulin treatment for more than 2 weeks at any time prior to the week 26 visit in the insulin degludec group. The estimated mean, and variances, from the model will be used to impute missing values in both treatment groups.
- For each of the complete data sets, the endpoint will be analysed using an ANOVA model with region, SU or glinide use (yes/no), and randomised treatment as fixed factors. The estimates and standard deviations for the 1000 data sets will be pooled to one estimate and associated standard deviation using Rubin's rule.

Change in body weight from baseline week 0 (V2) to week 26 (V28)

Change in body weight from week 0 to week 26 will be analysed based on the in-trial period using the same statistical model as specified for the primary endpoint, but with the corresponding baseline value as a covariate.

5.5 Exploratory endpoints analysis

Not applicable for this trial.

5.6 Other safety analyses

All safety analyses will be made on the safety analysis set and the extension safety analysis set (ESAS), if applicable. The standard safety assessments (SAEs, AEs, safety laboratory parameters, vital signs, etc.) will be reported descriptively based on the on-treatment period; including any notable changes of clinical interest in laboratory parameters. In addition, SAEs will be reported descriptively based on the in-trial period.

5.6.1 Nocturnal hypoglycaemic episodes

Nocturnal hypoglycaemic episodes are hypoglycaemic episodes occurring between 00:01 and 05:59 both inclusive. The following nocturnal hypoglycaemic derivations will each be analysed separately using the same method as described for the corresponding supportive secondary hypoglycaemic endpoint (see section 5.4.1.2).

- Number of nocturnal severe hypoglycaemic episodes (level 3) from baseline week 0 (V2) to week 31 (V30)
- Number of nocturnal clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) from baseline week 0 (V2) to week 31 (V30)
- Number of nocturnal clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) or severe nocturnal hypoglycaemic episodes (level 3) from baseline week 0 (V2) to week 31 (V30)
- Number of nocturnal severe hypoglycaemic episodes (level 3) from baseline week 0 (V2) to week 26 (V28)
- Number of nocturnal clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) from baseline week 0 (V2) to week 26 (V28)
- Number of nocturnal clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) or severe nocturnal hypoglycaemic episodes (level 3) from baseline week 0 (V2) to week 26 (V28).

5.6.2 Anti-insulin icodec antibodies

Antibodies will be evaluated based on the in-trial period. The following will be summarised by visit:

- Anti-insulin icodec antibodies status (positive / negative)
- Anti-insulin icodec antibodies cross-reactivity to endogenous insulin status (positive / negative)
- Anti-insulin icodec antibodies titres and change from baseline in anti-insulin icodec antibody titres

The correlation between anti-insulin icodec antibodies 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 icodec antibodies titres at follow-up and each of the following assessments:

- actual weekly basal insulin dose from week 24 to week 26
- HbA_{1c} at week 26
- change from baseline in HbA_{1c} at week 26
- level 2 and level 3 combined hypoglycaemic episodes during the on-treatment period

will be derived with the corresponding p-value for test of no correlation.

A shift table from baseline to week 26 and week 31 for cross-reactivity anti-insulin antibody status will be prepared.

Number and percentage of subjects with "treatment-induced" and "treatment-boosted" anti-insulin icodec antibodies will also be summarised. "Treatment-induced" anti-insulin icodec antibodies is defined as cases in which subjects switch from negative anti-insulin icodec antibodies at baseline to positive anti-insulin icodec antibodies during trial. "Treatment-boosted" anti-insulin icodec antibodies is defined as cases in which subjects, who have positive anti-insulin icodec antibodies at baseline, experience that anti-insulin icodec antibodies titres increase by at least two 2-fold dilution steps during trial.

5.6.3 Record selection

A re-test at any visit is defined as repeating the same laboratory assessment using new sample material. A re-test may be taken if a subject shows up in a non-fasting state for a laboratory assessment that is to be taken in a fasting condition or when sample material is lost or damaged.

In case of multiple eligible assessments at same planned time point (where only one was planned) only the first value will be selected.

5.7 Other analyses

5.7.1 Other derivations and assessments

5.7.1.1 Achievement of HbA1c target

The following derivations will be analysed separately using the method described below:

- Achievement of HbA_{1c}<7.0% after 26 weeks (yes/no)
- Achievement of HbA_{1c}<7.0% after 26 weeks without severe (level 3) or clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) during the prior 12 weeks (yes/no)
- Achievement of HbA_{1c}<7.0% after 26 weeks without severe hypoglycaemic episodes (level 3) during the prior 12 weeks (yes/no)
- Achievement of HbA_{1c}≤6.5% after 26 weeks (yes/no)
- Achievement of HbA_{1c}≤6.5% after 26 weeks without severe (level 3) or clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) during the prior 12 weeks (yes/no)
- Achievement of HbA_{1c}≤6.5% after 26 weeks without severe hypoglycaemic episodes (level 3) during the prior 12 weeks (yes/no)

See Appendix 3, section 6.3 for further details.

Missing HbA_{1c} data at 26 weeks will be imputed in the same way as for the primary analysis (step 1 and 2 in section 5.3.2) before deriving the dichotomous outcome. Subjects who discontinue randomised treatment prematurely will have the dichotomous outcome also evaluating hypoglycaemia set to 'no'. For each of the 1000 complete data sets, the endpoint will be analysed using a logistic regression model with region, SU or glinide use (yes/no), and randomised treatment as fixed factors, and baseline HbA_{1c} value as a covariate. The estimates and standard deviations for the 1000 data sets will be pooled to one estimate and associated standard deviation using Rubin's rule.

5.7.1.2 Self-measured plasma glucose (SMPG)

Mean fasting SMPG used for dose adjustment will be summarised by visit and treatment. Furthermore number and percentage of subjects achieving mean fasting SMPG used for dose adjustment within range (4.4–7.2 mmol/l) will be presented by visit and treatment.

5.7.1.3 Antidiabetic background medication

Subjects experiencing changes to antidiabetic background medication during the trial lasting more than 2 weeks will be summarised descriptively by treatment including number and proportion of subjects. Subjects will be further divided into two subgroups:

- subjects with changes to bolus treatment for more than 2 weeks
- subjects with changes to other antidiabetic background medication for more than 2 weeks

Changes to antidiabetic background medication are considered to be both initiation / discontinuation of antidiabetic background medication and increase / decrease in dose level of antidiabetic background medication.

5.7.1.4 Insulin dose

Weekly actual insulin doses will be summarised by treatment and week.

Flexibility of up to +/-3 days is allowed for the dosing of the weekly trial drug. Number of subjects utilizing this flexibility together with the number of times they have utilized it and the number of days they have deviated from the weekly dosing will be summarised.

5.7.2 Pharmacokinetic modelling

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

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 DBL. In brief, a previously developed PK model for insulin icodec 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 part of the clinical trial report. The individual insulin icodec serum concentration data will be tabulated in the bioanalytical report.

5.8 Interim analyses

The trial does not include a formal interim analysis. However, the potential split of the trial into a main and an extension part offers the opportunity of reporting results before LSLV. Main part is defined to end at time of LSLV for subjects recruited within the planned recruitment period. The main part analysis will include a minimum of 580 randomised subjects and will include data from all non-Chinese subjects and data from Chinese subjects that have been recruited within the planned recruitment period and have achieved end of trial. No data from the remaining Chinese subjects will be included in the main part evaluation and the randomisation code for these subjects will not be revealed at time of DBL for the main part. So, blinding of randomised treatment for these subjects will be maintained ensuring that trial integrity is preserved.

If 100 Chinese subjects cannot be recruited within the planned recruitment period, there will also be an extension part of the trial. The extension part will include all randomised subjects and is defined to end at the time of LSLV for the entire Chinese cohort. A second reporting of the trial based on the extension part will take place when LSLV for the entire Chinese cohort has been reached.

Confirmation of glycaemic control of insulin icodec will be based on the results from the analysis of the main part of the trial. The data from the extension part will be considered supportive only and is intended for the Chinese NDA.

The type 1 error rate will be maintained at 5%, as no statistical inference from the entire trial population will be drawn at the time of the extension part analysis. For the extension part similar analyses and data presentations as for the main part will be conducted and reported. Confidence intervals will be presented if relevant, but no p-values will be included in the extension part analyses.

5.8.1 Data monitoring committee

This section is not applicable for this trial.

5.9 Reporting of the main part of the trial

A database lock is planned shortly after last subject last visit of the main part of the trial. The results from this main part will thereafter be reported. In case 100 Chinese subjects cannot be recruited within the planned recruitment period the complete trial will be reported after database lock of the extension part.

6 Supporting documentation

6.1 Appendix 1: List of abbreviations

AE	Adverse event
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
BG	Blood glucose
CI	Confidence interval
EFAS	Extended full analysis set
ESAS	Extended safety analysis set
FAS	Full analysis set
FDA	Food and Drug Administration
FPG	Fasting plasma glucose
MAP	Modelling analysis plan
PK	Pharmacokinetics
SAP	Statistical analysis plan
SAS	Safety analysis set
SMPG	Self-measured plasma glucose
SU	Sulfonylureas
T2D	Type 2 Diabetes

6.2 Appendix 2: Changes to protocol-planned analyses

In section 4 the sentence "Baseline assessments are always included in the in-trial observation period." has been added to the definition of the in-trial period, and the sentence "Baseline assessments are always included in the on-treatment observation period." has been added to the definition of the on-treatment period to clarify that the baseline assessments should always be included.

In section 5.4.1.2 the following changes have been made:

1. In the described analysis method "discontinuation" has been replaced with "follow-up 2 visit (V30)". For subjects who discontinue their randomised treatment, hypoglycaemic episodes are collected until follow-up 2 visit (V30), and this data should be included as supportive secondary endpoints will be evaluated in the framework of the primary estimand.

2. For the 3 hypoglycaemic endpoints based on the period week 0 (V2) to week 26 (V28) further specifications for the analysis method were needed:

    - the on-treatment period in the described analysis method should be replaced with the period from week 0 to week 26.

    - 'follow-up 2 visit (V30)' should be replaced with 'discontinuation of treatment', since the analysis of these endpoints should consider only hypoglycaemic episodes occurring while subjects are being treated with icodec or degludec, and hence hypoglycaemic episodes occurring during follow-up should not be included.

3. For supportive secondary endpoints with time frame starting at week 0 (V2) the word "baseline" has been added in front of week 0 (V2) in the headers to align with section 3.2 in the protocol.

In section 5.1 the baseline definition has been updated to clarify that week 0 (V2) is considered as baseline and if not available the most recent measurement prior to week 0 (V2) will be used as baseline. In this section additional information on the extension part analyses and the seed number for the imputations have also been included.

In section 5.3.2 description of alternative imputation strategies in case of insufficient amount of data for imputation has been added.

In section 5.3.3 it has been added that the sensitivity analysis will also be done for the superiority evaluation.

In sections 5.4.1.1 and 5.4.1.2, based on recommendations from FDA, the method for imputing missing data has been changed from imputing missing data using completing comparator subjects to imputing from baseline values within own arm. The following analyses are affected:

- second alternative approach for endpoints with data collection after premature treatment discontinuation (change in HbA1c and body weight),
- change in FPG.

Besides that, additional derivations and assessments have been added to section 5.6 and 5.7 along with further details on data reporting and presentation. Also further elaborations on extension part reporting have been added to section 5.8.

6.3 Appendix 3: Definition and calculation of endpoints, assessments and derivations

Type	Title	Time frame	Unit	Details
Primary endpoint	Change in HbA_{1c}	From baseline week 0 (V2) to week 26 (V28)	%-point	The HbA_{1c} value at baseline week 0 subtracted from the HbA_{1c} value at week 26.
Supportive secondary endpoint	Change in fasting plasma glucose (FPG)	From baseline week 0 (V2) to week 26 (V28)	mmol/L	The FPG value at baseline week 0 subtracted from the FPG value at week 26.
Supportive secondary endpoint	Number of severe hypoglycaemic episodes (level 3)	From baseline week 0 (V2) to week 31 (V30)	Number of episodes	The count of all severe hypoglycaemic episodes (level 3) within the time frame.
Supportive secondary endpoint	Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter)	From baseline week 0 (V2) to week 31 (V30)	Number of episodes	The count of all clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL) confirmed by BG meter) within the time frame.
Supportive secondary endpoint	Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) or severe hypoglycaemic episodes (level 3)	From baseline week 0 (V2) to week 31 (V30)	Number of episodes	The count of all clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) or severe hypoglycaemic episodes (level 3) within the time frame.
Supportive secondary endpoint	Number of severe hypoglycaemic episodes (level 3)	From baseline week 0 (V2) to week 26 (V28)	Number of episodes	The count of all severe hypoglycaemic episodes (level 3) within the time frame.
Supportive secondary endpoint	Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter)	From baseline week 0 (V2) to week 26 (V28)	Number of episodes	The count of all clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL) confirmed by BG meter) within the time frame.
Supportive secondary endpoint	Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) or severe hypoglycaemic episodes (level 3)	From baseline week 0 (V2) to week 26 (V28)	Number of episodes	The count of all clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) or severe hypoglycaemic episodes (level 3) within the time frame.
Supportive secondary endpoint	Change in body weight	From baseline week 0 (V2) to week 26 (V28)	Kg	The body weight value at baseline week 0 subtracted from the body weight value at week 26.
Supportive secondary endpoint	Mean weekly insulin dose	From week 24 (P26) to week 26 (V28)	U	The mean of weekly insulin doses during the two weeks.
Derivation	Number of nocturnal severe hypoglycaemic episodes (level 3)	From baseline week 0 (V2) to week 31 (V30)	Number of episodes	Nocturnal hypoglycaemic episodes: episodes occurring between 00:01 and 05:59 both inclusive.

Type	Title	Time frame	Unit	Details
Derivation	Number of nocturnal clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter)	From baseline week 0 (V2) to week 31 (V30)	Number of episodes	Nocturnal hypoglycaemic episodes: episodes occurring between 00:01 and 05:59 both inclusive.
Derivation	Number of nocturnal clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) or nocturnal severe hypoglycaemic episodes (level 3)	From baseline week 0 (V2) to week 31 (V30)	Number of episodes	Nocturnal hypoglycaemic episodes: episodes occurring between 00:01 and 05:59 both inclusive.
Derivation	Number of nocturnal severe hypoglycaemic episodes (level 3)	From baseline week 0 (V2) to week 26 (V28) end of treatment visit	Number of episodes	Nocturnal hypoglycaemic episodes: episodes occurring between 00:01 and 05:59 both inclusive.
Derivation	Number of nocturnal clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter)	From baseline week 0 (V2) to week 26 (V28) end of treatment visit	Number of episodes	Nocturnal hypoglycaemic episodes: episodes occurring between 00:01 and 05:59 both inclusive.
Derivation	Number of nocturnal clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) or nocturnal severe hypoglycaemic episodes (level 3)	From baseline week 0 (V2) to week 26 (V28) end of treatment visit	Number of episodes	Nocturnal hypoglycaemic episodes: episodes occurring between 00:01 and 05:59 both inclusive.
Derivation	Achievement of HbA_{1c}<7.0% after 26 weeks (yes/no)	Week 26 (V28)	Count of subject	Dichotomous outcome variable: *Yes*: subject achieved HbA_{1c} < 7.0% after 26 weeks *No*: subject did not achieve HbA_{1c} < 7.0% after 26 weeks
Derivation	Achievement of HbA_{1c}<7.0% after 26 weeks without severe (level 3) or clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) during the prior 12 weeks (yes/no)	Week 26 (V28)	Count of subject	Dichotomous outcome variable: *Yes*: subject achieved HbA_{1c} < 7.0% after 26 weeks without severe or clinically significant hypoglycaemic episodes during the prior 12 weeks *No*: subject did not achieve HbA_{1c} < 7.0% after 26 weeks **or** subject had a severe or clinically significant hypoglycaemic episode during the prior 12 weeks **or** subject discontinued randomised treatment prematurely

Type	Title	Time frame	Unit	Details
Derivation	Achievement of HbA_{1c}<7.0% after 26 weeks without severe hypoglycaemic episodes (level 3) during the prior 12 weeks (yes/no)	Week 26 (V28)	Count of subject	Dichotomous outcome variable: *Yes*: subject achieved HbA_{1c} < 7.0% after 26 weeks without severe hypoglycaemic episodes during the prior 12 weeks *No*: subject did not achieve HbA_{1c} < 7.0% after 26 weeks **or** subject had a severe hypoglycaemic episode during the prior 12 weeks **or** subject discontinued randomised treatment prematurely
Derivation	Achievement of HbA_{1c}≤6.5% after 26 weeks (yes/no)	Week 26 (V28)	Count of subject	Dichotomous outcome variable: *Yes*: subject achieved HbA_{1c} ≤6.5% after 26 weeks *No*: subject did not achieve HbA_{1c} ≤6.5% after 26 weeks
Derivation	Achievement of HbA_{1c}≤6.5% after 26 weeks without severe (level 3) or clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) during the prior 12 weeks (yes/no)	Week 26 (V28)	Count of subject	Dichotomous outcome variable: *Yes*: subject achieved HbA_{1c} ≤6.5% after 26 weeks without severe or clinically significant hypoglycaemic episodes during the prior 12 weeks *No*: subject did not achieve HbA_{1c} ≤6.5% after 26 weeks **or** subject had a severe or clinically significant hypoglycaemic episode during the prior 12 weeks **or** subject discontinued randomised treatment prematurely
Derivation	Achievement of HbA_{1c}≤6.5% after 26 weeks without severe hypoglycaemic episodes (level 3) during the prior 12 weeks (yes/no)	Week 26 (V28)	Count of subject	Dichotomous outcome variable: *Yes*: subject achieved HbA_{1c} ≤6.5% after 26 weeks without severe hypoglycaemic episodes during the prior 12 weeks *No*: subject did not achieve HbA_{1c} ≤6.5% after 26 weeks **or** subject had a severe hypoglycaemic episode during the prior 12 weeks **or** subject discontinued randomised treatment prematurely

7 References

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