

## Cover Page for Statistical Analysis Plan

Sponsor name:	Novo Nordisk A/S
NCT number	NCT04770532
Sponsor trial ID:	NN1436-4478
Official title of study:	A 26-week trial comparing the effect and safety of once weekly insulin icodex and once daily insulin degludec, both with or without non-insulin anti-diabetic drugs, in subjects with type 2 diabetes treated with basal insulin (ONWARDS 2)
Document date*:	02 March 2021

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

## Statistical Analysis Plan

**NN1436-4478**

**A 26-week trial comparing the effect and safety of once weekly insulin icodec and once daily insulin degludec, both with or without non-insulin anti-diabetic drugs, in subjects with type 2 diabetes treated with basal insulin**

**ONWARDS 2**

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

### Author

Insulin & Devices

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## Version history

This Statistical Analysis Plan (SAP) for trial NN1436-4478 is based on the protocol version 2.0 dated 30-NOV-2020.

**Table 1 SAP Version History Summary**

<b>SAP Version</b>	<b>Approval Date</b>	<b>Change</b>	<b>Rationale</b>
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
3.0	See approval date in the electronic document management system	Addition of personal CGM device use as a factor in statistical analyses	Based on FDA suggestion

## 1 Introduction

This statistical analysis plan (SAP) is based on the protocol: *A 26-week trial comparing the effect and safety of once weekly insulin icodex and once daily insulin degludec, both with or without non-insulin anti-diabetic drugs, in subjects with type 2 diabetes treated with basal insulin, 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 icodex, with or without non-insulin anti-diabetic drugs, in subjects with T2D treated with basal insulin. This includes comparing the difference in change from baseline in HbA<sub>1c</sub> between insulin icodex and insulin degludec after 26 weeks of treatment to a non-inferiority limit of 0.3%.

##### 1.1.1.2 Secondary objective

To compare safety, and patient reported outcomes (PROs) with once weekly insulin icodex versus once daily insulin degludec, both with or without non-insulin anti-diabetic drugs, in subjects with T2D treated with basal insulin.

##### 1.1.1.3 Estimand

The estimand is the ‘treatment policy estimand’ defined as the treatment difference between insulin icodex and insulin degludec of the change in HbA<sub>1c</sub> 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 <sub>1c</sub>	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 endpoints

Endpoint title	Time frame	Unit
Change in fasting plasma glucose (FPG)	From baseline week 0 (V2) to week 26 (V28)	mmol/L
Time in target-range 3.9–10.0 mmol/L (70–180 mg/dL)*	From week 22 (V24) to week 26 (V28)	% of readings
Change in DTSQs (Diabetes Treatment Satisfaction Questionnaire) in total treatment satisfaction	From baseline week 0 (V2) to week 26 (V28)	Score 0-36 6 items scored on a scale of 0 to 6. The higher the score the greater the satisfaction with treatment

\* using continuous glucose monitoring (CGM) system, Dexcom G6

#### 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
Time spent < 3.0 mmol/L (54 mg/dL)*	From week 22 (V24) to week 26 (V28)	% of readings
Time spent > 10 mmol/L (180 mg/dL)*	From week 22 (V24) to week 26 (V28)	% of readings
Mean weekly insulin dose	From week 24 (V26) to week 26 (V28)	U
Change in body weight	From baseline week 0 (V2) to week 26 (V28)	kg

\* using continuous glucose monitoring (CGM) system, Dexcom G6

### 1.1.2.3 Exploratory endpoints

Endpoint title	Time frame	Unit
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

## 1.2 Trial design

This is a 26-week randomised, open label, active-controlled, parallel-group, multicentre, multinational, treat-to-target trial with two treatment arms. The trial investigates the effect on glycaemic control, safety and electronic PROs of treatment with once weekly insulin iicodec compared to once daily insulin degludec, both with or without non-insulin anti-diabetic drugs, in basal insulin treated subjects with inadequately controlled T2D on once or twice daily insulin.

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](#) and trial flowchart (protocol section [1.2](#)), respectively.

**Figure 1 Trial design**



For further details see protocol section [4.1](#).

## 2 Statistical hypotheses

The primary hypothesis to be tested is that insulin iicodec is non-inferior to insulin degludec in terms of change from baseline to week 26 in HbA<sub>1c</sub>.

Formally, let D be the treatment difference 'insulin iicodec' minus 'insulin degludec' of the change in HbA<sub>1c</sub> from baseline to week 26. The null-hypothesis will be tested against the alternative hypothesis of non-inferiority as given by

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

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.<sup>1</sup> 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 iicodec relative to treatment with a basal insulin analogue
- It represents less than 50% of a suitably conservative estimate of insulin degludec's treatment effect on HbA<sub>1c</sub> in a placebo-controlled trial in a basal insulin treated population; The treatment effect of degludec versus placebo in a basal insulin treated population is unknown but in a similar progressed T2D population of subjects already treated with liraglutide, degludec was shown to be superior to placebo (estimated treatment difference: -0.92%-point [-1.00; -0.75] 95%CI).<sup>2</sup>

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 icodex is superior to insulin degludec in terms of change from baseline to week 26 in HbA<sub>1c</sub>.

Formally, let D be the mean treatment difference ‘insulin icodex’ minus ‘insulin degludec’ of the change in HbA<sub>1c</sub> from baseline to week 26. The null-hypothesis of insulin icodex not superior will be tested against the alternative hypothesis of superiority as given by

$$H_0: D \geq 0\% \text{ against } H_A: D < 0\%$$

### 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: All subjects randomised. Subjects will be analysed according to the randomised treatment.
Safety analysis set	All subjects randomly assigned to trial treatment 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 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 and statistical analyses being based on full analysis set unless otherwise specified.

## 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.

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

- Treatment: Once weekly insulin icodex, insulin degludec
- Region: Asia, Europe, North America, Africa
- Personal CGM device use: yes, no

The regions will be defined as follows:

- Asia: Japan, South Korea
- Europe: Bulgaria, Germany, Poland, Portugal, Ukraine
- North America: United States
- Africa: South Africa

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.

All endpoints based on CGM measurements will be summarised and analysed using the full analysis set and the 'in-trial' period and will be derived the following way. The percentage of time spent in a given glycaemic range will be calculated as 100 times the number of recorded measurements in the given glycaemic range, divided by the total number of recorded measurements. Following international consensus criteria it will be required that at least 70% of the planned CGM measurements during the last four weeks of treatment are available for endpoint data to be included in the analysis.<sup>3</sup>

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<sub>1c</sub> 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 using all HbA<sub>1c</sub> measurements obtained at the week 26 visit, especially including measurements from subjects discontinuing their randomised treatment or initiating treatment with bolus insulin for more than 2 weeks. Missing HbA<sub>1c</sub> values at the week 26 visit (regardless of treatment completion status) will be imputed from trial participants, who have discontinued their randomised treatment or initiated treatment with bolus insulin 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<sub>1c</sub>.
- Second, for subjects who discontinued their randomised treatment or initiated treatment with bolus insulin for more than 2 weeks at any time prior to the week 26 visit and have an HbA<sub>1c</sub> measurement at the week 26 visit, the change in HbA<sub>1c</sub> from last available planned on-treatment without initiation of treatment with bolus insulin for more than 2 weeks (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<sub>1c</sub> values for the change from LAOT-WOB to the week 26 visit and subsequently the missing HbA<sub>1c</sub> 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, personal CGM device use (yes/no) and randomised treatment as fixed factors, and baseline HbA<sub>1c</sub> 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.<sup>4</sup>

This analysis has the underlying assumption that subjects with missing data behave similarly as subjects that discontinue randomised treatment or initiate treatment with bolus insulin 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. 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<sub>1c</sub> will be considered confirmed if the 95% CI is strictly below zero.

Missing HbA<sub>1c</sub> at week 26 will be summarised by subject's treatment completion 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<sub>1c</sub> 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  $\Delta_i$  to the imputed HbA<sub>1c</sub> values before analysing the data. The value of  $\Delta_i$  will be varied independently in the two treatment arms. The non-inferiority margin of 0.3% will be among the  $\Delta_i$  values investigated. The plausibility of the values of  $\Delta_i$  where the conclusions 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 as follows:

- First, an ANCOVA model with region, personal CGM device 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 completed data sets, the endpoint will be analysed using an ANCOVA model with region, personal CGM device 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.

#### ***Time in target range 3.9-10.0 mmol/L (70-180 mg/dL), from week 22 (V24) to week 26 (V28)***

Missing time in target range 3.9-10.0 mmol/L (70-180 mg/dL) (TIR) from week 22 to week 26 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 the 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 as follows:

- First, one thousand (1000) copies of the dataset will be generated for TIR.
- Second, for each dataset copy, an analysis of variance (ANOVA) model will be fitted to TIR 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 completed data sets, the endpoint will be analysed using an ANOVA model with region, personal CGM device 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 DTSQs (Diabetes Treatment Satisfaction Questionnaire) in total treatment satisfaction from baseline week 0 (V2) to week 26 (V28)***

The change in DTSQs in total treatment satisfaction from baseline to week 26 will be analysed using the same model as specified for change in FPG, but the corresponding baseline value will be used as a covariate.

##### **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, personal CGM device 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.

For the definition and classification of hypoglycaemic episodes refer to Protocol Appendix 7 (Protocol Section [10.7](#)).

#### ***Time spent < 3.0 mmol/L (54 mg/dL) and time spent > 10 mmol/L (180 mg/dL) from week 22 (V24) to week 26 (V28)***

Time spent < 3.0 mmol/L (54 mg/dL) (below range) and time spent > 10 mmol/L (180 mg/dL) (above range) from week 22 to week 26 will be analysed separately in a similar manner as 'time in target range 3.9-10.0 mmol/L (70-180 mg/dL)' if deemed appropriate, i.e. if data can be considered normally distributed. However, if a large number of subjects have 0% time spent below range or above range, then an alternative analysis will be performed, where time spent below or above range will be analysed separately using a negative binomial model on the number of recorded measurements below and above range, respectively, with a log-link function and the logarithm of the total number of recorded measurements as an offset. The model will include randomised treatment, personal CGM device use (yes/no) and region as factors.

#### ***Mean weekly insulin dose from week 24 (V26) to week 26 (V28)***

Mean weekly insulin dose during the last 2 weeks of treatment (from week 24 to 26) will be log-transformed and analysed using the same model as specified for change in FPG, but with using the log-transformed weekly insulin dose at screening as a covariate. The imputation will also be done on log-transformed values, i.e., missing values will be imputed by the log-transformed baseline value adding a random error term. The random error term will be normally distributed with a standard deviation set equal to the estimated residual standard deviation of an ANCOVA analysis on the log-transformed LAOT-WOB values.

#### ***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

### *Hypoglycaemic episodes*

The following hypoglycaemic endpoints will be analysed separately using the same method as described for supportive secondary hypoglycaemic endpoints (see section [5.4.1.2](#)), substituting the on-treatment period with the period from week 0 to week 26 and the follow-up 2 visit (V30) with time of discontinuation:

- 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).

## 5.6 Other safety analyses

All safety analyses will be made on the safety analysis set. 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*

Nocturnal hypoglycaemic episodes: episodes occurring between 00:01 and 05:59 both inclusive.

The following nocturnal hypoglycaemic assessments will be analysed separately using the same method described for the supportive secondary hypoglycaemic endpoints (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)

The following nocturnal hypoglycaemic assessments will be analysed separately using the same method described for the supportive secondary hypoglycaemic endpoints, substituting the on-treatment period with the period from week 0 to week 26, and substituting the time of follow-up 2 visit (V30) with time of discontinuation:

- 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 icodex antibodies

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

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

The correlation between anti-insulin icodex antibodies titres and actual weekly basal insulin dose, HbA<sub>1c</sub>, and change from baseline in HbA<sub>1c</sub>, 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 icodex antibodies titres at follow-up and each of the following assessments:

- actual weekly basal insulin dose from week 24 to 26
- HbA<sub>1c</sub> at week 26
- change from baseline in HbA<sub>1c</sub> 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 icodex antibodies will also be summarised. "Treatment-induced" anti-insulin icodex antibodies is defined as cases in which subjects switch from negative anti-insulin icodex antibodies at baseline to positive anti-insulin icodex antibodies during trial. "Treatment-boosted" anti-insulin icodex antibodies is defined as cases in which subjects, who have positive anti-insulin icodex antibodies at baseline, experience that anti-insulin icodex 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 HbA<sub>1c</sub> target

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

- Achievement of HbA<sub>1c</sub><7.0% after 26 weeks (yes/no)
- Achievement of HbA<sub>1c</sub><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<sub>1c</sub><7.0% after 26 weeks without severe hypoglycaemic episodes (level 3) during the prior 12 weeks (yes/no)
- Achievement of HbA<sub>1c</sub>≤6.5% after 26 weeks (yes/no)
- Achievement of HbA<sub>1c</sub>≤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<sub>1c</sub>≤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<sub>1c</sub> 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, personal CGM device use (yes/no) and randomised treatment as fixed factors, and baseline HbA<sub>1c</sub> 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 icodex 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 icodex.

The population PK analysis will be performed by Quantitative Clinical Pharmacology, Novo Nordisk. A more technical and detailed elaboration of the population PK analysis will be given in a modelling analysis plan, which will be prepared before database lock. In brief, a previously developed PK model for insulin icodex 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 modelling analysis plan.

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 icodex serum concentration data will be tabulated in the bioanalytical report.

### **5.8 Interim analyses**

Not applicable for this trial.

#### **5.8.1 Data monitoring committee**

Not applicable for this trial.

### **5.9 Reporting of the main part of the trial**

Not applicable for this trial.

## 6 Supporting documentation

### 6.1 Appendix 1: List of abbreviations

AE	Adverse event
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
BG	Blood glucose
CGM	Continuous glucose monitoring
CI	Confidence interval
DTSQ	Diabetes Treatment Satisfaction Questionnaire
FDA	Food and Drug Administration
FPG	Fasting plasma glucose
PK	Pharmacokinetics
PRO	Patient reported outcome
SAE	Serious adverse event
SAP	Statistical analysis plan
SMPG	Self-measured plasma glucose
T2D	Type 2 Diabetes
TIR	Time in range

## 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 [5.1](#) 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, 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 meaningful 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 for change in FPG, change in DTSQs in total treatment satisfaction and mean weekly insulin dose has been changed from imputing missing data using completing comparator subjects to imputing from baseline values within own arm.

In section [5.4.1.2](#) description of the alternative analysis for time spent < 3.0 mmol/L and time spent > 10.0 mmol/L has been added, in case of many subjects with 0% time spent.

In section [5.5](#) description of analyses of exploratory endpoints has been added.

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.

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

Type	Title	Time frame	Unit	Details
Primary endpoint	Change in HbA <sub>1c</sub>	From baseline week 0 (V2) to week 26 (V28)	%-point	The HbA <sub>1c</sub> value at baseline week 0 subtracted from the HbA <sub>1c</sub> 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	Time in target-range 3.9–10.0 mmol/L (70-180 mg/dL)	From week 22 (V24) to week 26 (V28)	% of readings	Calculated as 100 times the number of recorded measurements in the given glycaemic range, divided by the total number of recorded measurements. Following international consensus criteria, it will be required that at least 70% of the planned CGM measurements during the last four weeks of treatment are available for endpoint data to be included in the analysis.
Supportive secondary endpoint	Change in DTSQs (Diabetes Treatment Satisfaction Questionnaire) in total treatment satisfaction	From baseline week 0 (V2) to week 26 (V28)	Score 0-36 6 items scored on a scale of 0 to 6. The higher the score the greater the satisfaction with treatment	The DTSQs score in total treatment satisfaction at baseline week 0 subtracted from the DTSQs score in total treatment satisfaction 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.

Type	Title	Time frame	Unit	Details
Supportive secondary endpoint	Time spent < 3.0 mmol/L (54 mg/dL)	From week 22 (V24) to week 26 (V28)	% of readings	Calculated as 100 times the number of recorded measurements below 3.0 mmol/L (54 mg/dL) divided by the total number of recorded measurements. Following international consensus criteria, it will be required that at least 70% of the planned CGM measurements during the last four weeks of treatment are available for endpoint data to be included in the analysis.
Supportive secondary endpoint	Time spent > 10 mmol/L (180 mg/dL)	From week 22 (V24) to week 26 (V28)	% of readings	Calculated as 100 times the number of recorded measurements above 10 mmol/L (180 mg/dL) divided by the total number of recorded measurements. Following international consensus criteria, it will be required that at least 70% of the planned CGM measurements during the last four weeks of treatment are available for endpoint data to be included in the analysis.
Supportive secondary endpoint	Mean weekly insulin dose	From week 24 (V26) to week 26 (V28)	U	The mean of weekly insulin doses during the two weeks.
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.
Exploratory 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.
Exploratory 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.
Exploratory 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.
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.
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.

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) 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)	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)	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)	Number of episodes	Nocturnal hypoglycaemic episodes: episodes occurring between 00:01 and 05:59 both inclusive.
Derivation	Achievement of HbA <sub>1c</sub> <7.0% after 26 weeks (yes/no)	Week 26 (V28)	Count of subject	<p>Dichotomous outcome variable:  <i>Yes</i>: subject achieved HbA<sub>1c</sub> &lt; 7.0% after 26 weeks</p> <p><i>No</i>: subject did not achieve HbA<sub>1c</sub> &lt; 7.0% after 26 weeks</p>
Derivation	Achievement of HbA <sub>1c</sub> <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	<p>Dichotomous outcome variable:  <i>Yes</i>: subject achieved HbA<sub>1c</sub> &lt; 7.0% after 26 weeks without severe or clinically significant hypoglycaemic episodes during the prior 12 weeks</p> <p><i>No</i>: subject did not achieve HbA<sub>1c</sub> &lt; 7.0% after 26 weeks <u>or</u> subject had a severe or clinically significant hypoglycaemic episode during the prior 12 weeks <u>or</u> subject discontinued randomised treatment prematurely</p>
Derivation	Achievement of HbA <sub>1c</sub> <7.0% after 26 weeks without severe hypoglycaemic episodes (level 3) during the prior 12 weeks (yes/no)	Week 26 (V28)	Count of subject	<p>Dichotomous outcome variable:  <i>Yes</i>: subject achieved HbA<sub>1c</sub> &lt; 7.0% after 26 weeks without severe hypoglycaemic episodes during the prior 12 weeks</p> <p><i>No</i>: subject did not achieve HbA<sub>1c</sub> &lt; 7.0% after 26 weeks <u>or</u> subject had a severe hypoglycaemic episode during the prior 12 weeks <u>or</u> subject discontinued randomised treatment prematurely</p>

Type	Title	Time frame	Unit	Details
Derivation	Achievement of HbA <sub>1c</sub> ≤6.5% after 26 weeks (yes/no)	Week 26 (V28)	Count of subject	<p>Dichotomous outcome variable:  <i>Yes</i>: subject achieved HbA<sub>1c</sub>≤6.5% after 26 weeks</p> <p><i>No</i>: subject did not achieve HbA<sub>1c</sub>≤6.5% after 26 weeks</p>
Derivation	Achievement of HbA <sub>1c</sub> ≤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	<p>Dichotomous outcome variable:  <i>Yes</i>: subject achieved HbA<sub>1c</sub>≤6.5% after 26 weeks without severe or clinically significant hypoglycaemic episodes during the prior 12 weeks</p> <p><i>No</i>: subject did not achieve HbA<sub>1c</sub>≤6.5% after 26 weeks <b>or</b> subject had a severe or clinically significant hypoglycaemic episode during the prior 12 weeks <b>or</b> subject discontinued randomised treatment prematurely</p>
Derivation	Achievement of HbA <sub>1c</sub> ≤6.5% after 26 weeks without severe hypoglycaemic episodes (level 3) during the prior 12 weeks (yes/no)	Week 26 (V28)	Count of subject	<p>Dichotomous outcome variable:  <i>Yes</i>: subject achieved HbA<sub>1c</sub>≤6.5% after 26 weeks without severe hypoglycaemic episodes during the prior 12 weeks</p> <p><i>No</i>: subject did not achieve HbA<sub>1c</sub>≤6.5% after 26 weeks <b>or</b> subject had a severe hypoglycaemic episode during the prior 12 weeks <b>or</b> subject discontinued randomised treatment prematurely</p>

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