Cover Page for Statistical Analysis Plan

Sponsor name:	Novo Nordisk A/S
NCT number	NCT04848480
Sponsor trial ID:	NN1436-4625
Official title of study:	Efficacy and Safety of Once Weekly Insulin Icodec Compared to Once Daily Insulin Degludec 100 Units/mL, Both in Combination With Insulin Aspart, in Adults With Type 1 Diabetes. A 26-week, Randomised, Multicentre, Open-label, Active-controlled, Parallel Group, Two Armed, Treat-to-target Trial Investigating the Effect on Glycaemic Control and Safety of Treatment With Once Weekly Insulin Icodec Compared to Once Daily Insulin Degludec, Both in Combination With Insulin Aspart in Adults With Type 1 Diabetes, With a 26-week Extension Investigating Long Term Safety
Document date*	15 April 2021

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

Note: The date in the header of Page 2 is the date of compilation of the documents and not of an update to content.

16.1.9 Documentation of statistical methods

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Statistical Analysis Plan

NN1436-4625

Efficacy and safety of once weekly insulin icodec compared to once daily insulin degludec 100 units/mL, both in combination with insulin aspart, in adults with type 1 diabetes. ONWARDS 6

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

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Insulin & Devices

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Version history

This Statistical Analysis Plan (SAP) for trial NN1436-4625 is based on the protocol version 4.0 dated 14-APR-2021.

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

1 Introduction

This statistical analysis plan (SAP) is based on the protocol: *Efficacy and safety of once weekly insulin icodec compared to once daily insulin degludec 100 units/mL, both in combination with insulin aspart, in adults with type 1 diabetes*, version 4.0 (dated 14-APR-2021). 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 confirm the effect on glycaemic control of once weekly insulin icodec in combination with insulin aspart, in subjects with T1D. This includes comparing the difference in change from baseline in HbA_{1c} between once weekly insulin icodec and once daily insulin degludec both in combination with insulin aspart after 26 weeks of treatment to a non-inferiority limit of 0.3%.

1.1.1.2 Secondary objective

To compare the safety and patient reported outcomes of once weekly insulin icodec versus once daily insulin degludec, both in combination with insulin aspart, in subjects with T1D.

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: 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) to week 26	%-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) to week 26	mmol/L
Time in range 3.9-10.0 mmol/L (70-180 mg/dL)*	From week 22 to week 26	% of readings
Change in DTSQs (Diabetes Treatment Satisfaction Questionnaire) in total treatment satisfaction	From baseline (week 0) to week 26	Score 0-36 6 items scored on a scale of 0 to 6. The higher the score the greater the satisfaction with treatment
Change in HbA_{1c}	From baseline (week 0) to week 52	%-point

* 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) to week 26	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) to week 26	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) to week 26	Number of episodes
Number of severe hypoglycaemic episodes (level 3)	From baseline (week 0) to week 57	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) to week 57	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) to week 57	Number of episodes
Number of nocturnal 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) to week 26	Number of episodes

Number of nocturnal 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) to week 57	Number of episodes
Time spent < 3.0 mmol/L (54 mg/dL)*	From week 22 to week 26	% of readings
Time spent > 10 mmol/L (180 mg/dL)*	From week 22 to week 26	% of readings
Mean total weekly insulin dose	From week 24 to week 26	U
Mean total weekly insulin dose	From week 50 to week 52	U
Change in body weight	From baseline (week 0) to week 26	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) to week 52	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) to week 52	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) to week 52	Number of episodes
Number of nocturnal 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) to week 52	Number of episodes

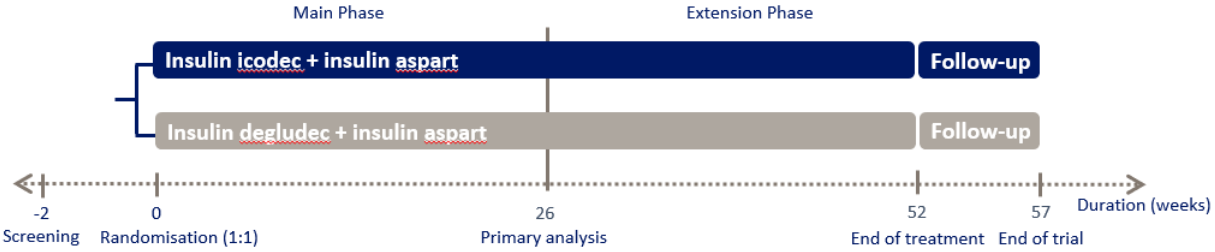
1.2 Trial design

This is a 26-week, randomised, multicentre, multinational, open-label, active-controlled, parallel group, two-armed, treat-to-target trial investigating the effect on glycaemic control and safety of treatment with once weekly insulin icodec compared to once daily insulin degludec, both in combination with insulin aspart in subjects with T1D, with a 26-week extension phase. The first 26 weeks of the trial constitute the main phase, after which the primary analysis is planned. The focus of the 26-week extension phase is to evaluate long-term safety and provide long-term exposure data.

The trial duration is approximately 59 weeks, consisting of a 2-week screening period, followed by an initial 26-week randomised treatment period, a 26-week extension phase and a 5-week follow-up period. Primary analysis is planned after the initial 26-week main phase. The overall trial design

and visit schedule are outlined in Figure 1 and trial flowchart (see 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 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 ≥0.30% against HA: D <0.30%

The non-inferiority margin of 0.3%-point is chosen based on the recommendation of health authority guidance for industry on developing drugs for treatment of diabetes.[1,2] Furthermore:

- 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 30% of a suitably conservative estimate of insulin degludec´s treatment effect on HbA_{1c} in a placebo-controlled trial in a T1D population; The treatment effect of degludec versus placebo in a T1D population is unknown but in a 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] $_{95\%CI}$).

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 one 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 (V56).
- 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.

Main-on-treatment period

The main-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 date of the on-treatment period
- Week 26 (V28).

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

All efficacy endpoints will be summarised and analysed using the full analysis set and the 'in-trial' period. Safety endpoints will be evaluated using both the main-on-treatment and the on-treatment period with descriptive statistics being based on the safety analysis set and statistical analyses being based on the 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 icodec, insulin degludec
- Screening HbA_{1c} < 8%: yes, no
- Pre-trial basal insulin treatment: twice daily or insulin glargine U300: yes or no
- Region: Asia, Europe, North America

The regions will be defined as follows:

- Asia: India, Japan
- Europe: Austria, Netherlands, Germany, Turkey, Italy, Russia, Spain, United Kingdom
- North America: United States, Canada

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.[3]

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. 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 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 having discontinued their randomised treatment prior to the week 26 visit and have a HbA_{1c} visit measurement at the week 26 visit, the change in HbA_{1c} from last available planned on-treatment (LAOT) value to the week 26 visit will be analysed for each dataset copy using an ANCOVA model with randomised treatment as fixed factor and LAOT 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 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, screening HbA_{1c} < 8% (yes/no), pre-trial basal insulin treatment and randomised treatment as fixed factors, and baseline HbA_{1c} as 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.[4]

This analysis has the underlying assumption that subjects with missing data behave similarly as subjects that discontinue randomised treatment.

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 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).

Missing HbA_{1c} 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_{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 Δi to the imputed HbA_{1c} values before analysing the data. The value of Δi will be varied independently in the two treatment arms. The non-inferiority margin of 0.3% will be among the Δi values investigated. The plausibility of the values of Δi where the conclusion of the primary analysis change will be evaluated to assess the robustness of the primary analysis result.

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 values. Specifically, the imputations and analyses will be carried out as follows:

- First, an ANCOVA model with region, screening HbA_{1c} < 8% (yes/no), pre-trial basal insulin treatment and randomised treatment as fixed factors, and a baseline value as a covariate will be fitted to the LAOT value.
- 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 1000 times.
- For each of the complete data sets, the endpoint will be analysed using an ANCOVA model with region, screening HbA_{1c} < 8% (yes/no), pre-trial basal insulin treatment and randomised treatment as fixed factors, and a baseline value as a covariate.
- The estimates and SDs for the 1000 data sets will be pooled to one estimate and associated SD 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 - i.e., data will be imputed based on the assumption that, subjects with missing endpoint data will behave like subjects completing insulin degludec treatment. Specifically, the imputations and analyses will be carried out as follows:

- First, one thousand (1000) copies of the dataset will be generated for TIR.
- Second, for each dataset copy, an ANCOVA model will be fitted to TIR values for subjects who completed their randomised treatment 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 ANCOVA model with region, screening HbA_{1c} < 8% (yes/no), pre-trial basal insulin treatment and randomised treatment as fixed factors. The estimates and SDs for the 1000 data sets will be pooled to one estimate and associated SD 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.

Change in HbA_{1c} from baseline week 0 (V2) to week 52 (V54)

The change in HbA_{1c} from baseline to week 52 will be analysed similar to the primary endpoint specified above.

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 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).
- Number of nocturnal 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 subjects who discontinued their randomised treatment, the number of episodes in the missing period (time of follow-up 2 visit (V56) to planned end of the main-on-treatment period) will be imputed using a multiple imputation technique, assuming that the event rate pre-follow-up 2 visit (V56) follows the respective treatment groups rate whilst post-follow-up 2 visit (V56) event rate is the rate of the comparator 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, screening HbA_{1c} < 8% (yes/no), pre-trial basal insulin treatment and randomised treatment as fixed factors and the logarithm of the main-on-treatment period as offset.
- Second, based on the estimated parameters for the comparator 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 SDs for the 1000 data sets will be pooled to one estimate and associated SD using Rubin's rule.

The following hypoglycaemic endpoints will be analysed separately using the method described above, substituting the main-on-treatment period with the on-treatment period:

- Number of severe hypoglycaemic episodes (level 3), from baseline week 0 (V2) to week 57 (V56).
- 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 57 (V56).
- 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 57 (V56).
- Number of nocturnal 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 57 (V56). Nocturnal hypoglycaemic episodes are hypoglycaemic episodes occurring between 00:01 and 05:59 both inclusive.

For the definition and classification of hypoglycaemic episodes refer to the 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, 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 offset. The model will include region, screening HbA_{1c} < 8% (yes/no), pre-trial basal insulin treatment and randomised treatment as factors.

Mean total weekly insulin dose from week 24 (V26) to week 26 (V28) and mean total weekly insulin dose from week 50 (V52) to week 52 (V54)

Mean weekly insulin dose during the last 2 weeks of treatment (from week 50 to week 52) and during the last 2 weeks in the main part (from week 24 to 26) will be log-transformed and analysed separately using the same statistical model as specified for change in FPG. Pre-trial (baseline) total weekly insulin dose will be log-transformed and included as a covariate in the model. 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 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 main-on-treatment period with the period from week 0 to week 52 and the follow-up 2 (V56) with time of discontinuation:

- Number of severe hypoglycaemic episodes (level 3) from week 0 (V2) to week 52 (V54)
- Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) from week 0 (V2) to week 52 (V54)
- 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 week 0 (V2) to week 52 (V54)
- Number of nocturnal clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) or severe hypoglycaemic episodes (level 3) from week 0 (V2) to week 52 (V54).

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 main-on-treatment and 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 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 severe hypoglycaemic episodes (level 3) from baseline week 0 (V2) to week 57 (V56)
- 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 57 (V56)
- Number of nocturnal severe hypoglycaemic episodes (level 3) from baseline week 0 (V2) to week 52 (V54)

- 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 52 (V54)

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 57 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 50 to 52
- HbA_{1c} at week 52
- change from baseline in HbA_{1c} at week 52
- 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 52 and week 57 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, personal CGM device 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 Insulin dose

Total weekly insulin dose, as well as weekly basal dose and weekly bolus dose will be summarised separately by treatment and week.

Mean weekly basal insulin dose from week 24 to week 26, and mean weekly bolus insulin dose from week 24 to week 26 will be summarised and analysed separately using the same model as specified for the mean total weekly insulin dose, but with the corresponding log-transformed weekly insulin dose as a covariate.

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

5.7.3 Assessments collected at week 52

Assessments collected at week 52, if not already described, will be summarised and analysed in the similar way as at week 26.

5.8 Interim analyses

The trial does not include a formal interim analysis. However, the reporting will be split into a main phase and an extension phase, where the results of the main phase can be reported possibly before LPLV. Subjects will provide consent for the full length of the trial. To preserve trial integrity during the extension phase, dissemination of results from the main phase will, during the extension phase, initially be limited to communication internally and with regulatory authorities.

5.8.1 Data monitoring committee

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. 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
BG	Blood glucose
CGM	Continuous glucose monitoring
CI	Confidence interval
FDA	Food and Drug Administration
FPG	Fasting plasma glucose
PK	Pharmacokinetics
SAE	Serious adverse event
SAP	Statistical analysis plan
SMPG	Self-measured plasma glucose
T1D	Type 1 Diabetes
T2D	Type 2 Diabetes
TIR	Time in range

6.2 Appendix 2: Changes to protocol-planned analyses

In section 4 the sentence about subjects not randomised but exposed to trial product was added.

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 has 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 5.4.1.2 the description of the alternative analysis for time spent < 3.0 mmol/L and time spent > 10.0 mmol/L has been corrected because stratification factors were missing. Clarifying information was added to the description of the analysis of total weekly insulin dose and body weight.

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_{1c}	From baseline (week 0) to week 26	%-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) to week 26	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 to week 26	% 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) to week 26	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	Change in HbA_{1c}	From baseline (week 0) to week 52	%-point	The HbA_{1c} value at baseline week 0 subtracted from the HbA_{1c} value at week 52.
Supportive secondary endpoint	Number of severe hypoglycaemic episodes (level 3)	From baseline (week 0) to week 26	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) to week 26	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) to week 26	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) to week 57	Number of episodes	The count of all severe hypoglycaemic episodes (level 3) within the time frame.

Type	Title	Time frame	Unit	Details
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) to week 57	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) to week 57	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 nocturnal 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) to week 26	Number of episodes	Nocturnal hypoglycaemic episodes: episodes occurring between 00:01 and 05:59 both inclusive.
Supportive secondary endpoint	Number of nocturnal 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) to week 57	Number of episodes	Nocturnal hypoglycaemic episodes: episodes occurring between 00:01 and 05:59 both inclusive.
Supportive secondary endpoint	Time spent < 3.0 mmol/L (54 mg/dL)	From week 22 to week 26	% 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.

Type	Title	Time frame	Unit	Details
Supportive secondary endpoint	Time spent > 10 mmol/L (180 mg/dL)	From week 22 to week 26	% 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 to week 26	U	The mean of weekly insulin doses during the two weeks.
Supportive secondary endpoint	Mean weekly insulin dose	From week 50 to week 52	U	The mean of weekly insulin doses during the two weeks.
Supportive secondary endpoint	Change in body weight	From baseline (week 0) to week 26	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) to week 52	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) to week 52	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) to week 52	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.
Exploratory endpoint	Number of nocturnal 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) to week 52	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) to week 26	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) to week 26	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) to week 57	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) to week 57	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) to week 52	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) to week 52	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	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	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
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	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

Type	Title	Time frame	Unit	Details
				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	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	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	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
Assessment	Mean weekly basal insulin dose	From week 24 to week 26	U	The mean of weekly insulin doses during the two weeks.
Assessment	Mean weekly bolus insulin dose	From week 24 to week 26	U	The mean of weekly insulin doses during the two weeks.
Assessment	Change in fasting plasma glucose (FPG)	From baseline (week 0) to week 52	mmol/L	The FPG value at baseline week 0 subtracted from the FPG value at week 52

Type	Title	Time frame	Unit	Details
Assessment	Time in target-range 3.9–10.0 mmol/L (70-180 mg/dL)	From week 48 to week 52	% 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.
Assessment	Change in DTSQs (Diabetes Treatment Satisfaction Questionnaire) in total treatment satisfaction	From baseline (week 0) to week 52	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 52.
Assessment	Time spent < 3.0 mmol/L (54 mg/dL)	From week 48 to week 52	% 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.
Assessment	Time spent > 10 mmol/L (180 mg/dL)	From week 48 to week 52	% 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.
Assessment	Change in body weight	From baseline (week 0) to week 52	Kg	The body weight value at baseline week 0 subtracted from the body weight value at week 52.
Assessment	Mean weekly basal insulin dose	From week 50 to week 52	U	The mean of weekly insulin doses during the two weeks.
Assessment	Mean weekly bolus insulin dose	From week 50 to week 52	U	The mean of weekly insulin doses during the two weeks.
Derivation	Achievement of HbA_{1c}<7.0% after 52 weeks (yes/no)	Week 52	Count of subject	Dichotomous outcome variable: *Yes*: subject achieved HbA_{1c} < 7.0% after 52 weeks *No*: subject did not achieve HbA_{1c} < 7.0% after 52 weeks

Type	Title	Time frame	Unit	Details
Derivation	Achievement of HbA_{1c}<7.0% after 52 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 52	Count of subject	Dichotomous outcome variable: *Yes*: subject achieved HbA_{1c} < 7.0% after 52 weeks without severe or clinically significant hypoglycaemic episodes during the prior 12 weeks *No*: subject did not achieve HbA_{1c} < 7.0% after 52 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}<7.0% after 52 weeks without severe hypoglycaemic episodes (level 3) during the prior 12 weeks (yes/no)	Week 52	Count of subject	Dichotomous outcome variable: *Yes*: subject achieved HbA_{1c} < 7.0% after 52 weeks without severe hypoglycaemic episodes during the prior 12 weeks *No*: subject did not achieve HbA_{1c} < 7.0% after 52 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 52 weeks (yes/no)	Week 52	Count of subject	Dichotomous outcome variable: *Yes*: subject achieved HbA_{1c} ≤6.5% after 52 weeks *No*: subject did not achieve HbA_{1c} ≤6.5% after 52 weeks
Derivation	Achievement of HbA_{1c}≤6.5% after 52 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 52	Count of subject	Dichotomous outcome variable: *Yes*: subject achieved HbA_{1c} ≤6.5% after 52 weeks without severe or clinically significant hypoglycaemic episodes during the prior 12 weeks *No*: subject did not achieve HbA_{1c} ≤6.5% after 52 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 52 weeks without severe hypoglycaemic episodes (level 3) during the prior 12 weeks (yes/no)	Week 52	Count of subject	Dichotomous outcome variable: *Yes*: subject achieved HbA_{1c} ≤6.5% after 52 weeks without severe hypoglycaemic episodes during the prior 12 weeks

Type	Title	Time frame	Unit	Details
				No: subject did not achieve $HbA_{1c} \leq 6.5\%$ after 52 weeks **or** subject had a severe hypoglycaemic episode during the prior 12 weeks **or** subject discontinued randomised treatment prematurely

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