Cover Page for Statistical Analysis Plan

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Statistical Analysis Plan

NN1436-4481

Effectiveness and safety of once weekly insulin icodec used with DoseGuide versus once daily basal insulin analogues in an insulin naïve type 2 diabetes population in a clinical practice setting

ONWARDS 5

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

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Author

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Insulin & Devices

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Version history

This Statistical Analysis Plan (SAP) for trial NN1436-4481 is based on the protocol version 2.0 dated 23-NOV-2020.

Table 1 SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1.0	See approval date in the electronic document management system	Not Applicable	Original version
2.0	See approval date in the electronic document management system	Addition of summaries and analyses of hypoglycaemic episodes identified using an alternative definition based on SMPG measurements	To supplement the protocol-defined analyses due to the difference in the collection of hypoglycaemic episodes between the two arms

1 Introduction

This statistical analysis plan (SAP) is based on the protocol: *Effectiveness and safety of once weekly insulin icodec used with DoseGuide versus once daily basal insulin analogues in an insulin naïve type 2 diabetes population in a clinical practice setting*, version 2.0 (dated 23-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 effectiveness on glycaemic control of once weekly insulin icodec used with DoseGuide in combination with non-insulin anti-diabetic drugs in insulin naïve subjects with T2D in a clinical practice setting. This includes comparing the difference in change from baseline in HbA_{1c} between insulin icodec used with DoseGuide and once daily basal insulin analogues after 52 weeks of treatment to a non-inferiority limit of 0.3%.

1.1.1.2 Secondary objective

To compare effect on safety and patient reported outcomes related to treatment satisfaction and compliance of once weekly insulin icodec used with DoseGuide versus once daily basal insulin analogues both in combination with any non-insulin antidiabetic drugs in insulin-naïve subjects with T2D in a clinical practice setting.

1.1.1.3 Estimand

The estimand is the 'treatment policy estimand' defined as the treatment difference between insulin icodec used with DoseGuide and basal insulin analogues of the change in HbA_{1c} from baseline to week 52 for all randomised subjects, irrespective of adherence to randomised treatment and changes to antidiabetic background medication. The following intercurrent events will be handled by the treatment policy strategy: discontinuation of investigational medical products, and withdrawal from the trial (measurements collected after these intercurrent events are used in the primary analysis). This estimand aims to reflect effectiveness of the treatment on a population level in clinical practice.

1.1.2 Primary, secondary and exploratory endpoints

1.1.2.1 Primary endpoint

Endpoint title	Time frame	Unit
Change in HbA_{1c}	From baseline week 0 (V2) to week 52 (V6)	%-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 effectiveness endpoints

Endpoint title	Time frame	Unit
Time from baseline to treatment discontinuation or intensification	From baseline week 0 (V2) to week 52 (V6)	Days
Change in DTSQs (Diabetes Treatment Satisfaction Questionnaire) in total treatment satisfaction	From baseline week 0 (V2) to week 52 (V6)	Score of 0-36. 6 items scored on a scale of 0 to 6. The higher the score the greater the satisfaction with treatment.
Trim-D (Treatment Related Impact Measure for Diabetes) compliance domain	At end of treatment week 52 (V6)	Score of 4-20. 4 items scored on a scale of 1 to 5 Transformed to a 0-100 scale with higher scores corresponding to better compliance.

Secondary safety endpoints

Endpoint title	Time frame	Unit
Number of severe hypoglycaemic episodes (level 3)	From baseline week 0 (V2) to week 57 (V8)	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 57 (V8)	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 57 (V8)	Number of episodes

1.1.2.3 Exploratory endpoints

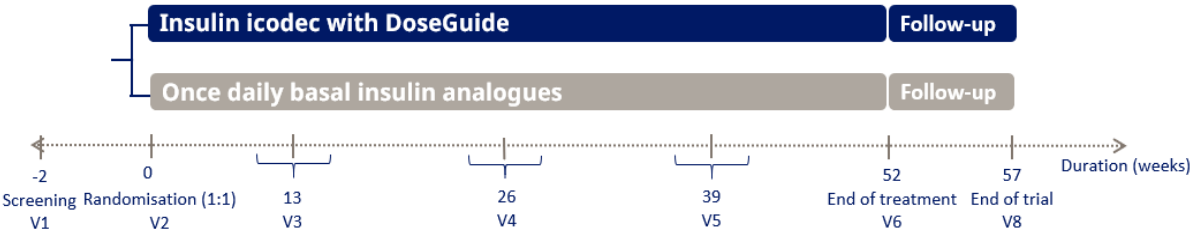
Endpoint title	Time frame	Unit
Number of severe hypoglycaemic episodes (level 3)	From baseline week 0 (V2) to week 52 (V6)	Number of episodes
Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter)	From baseline week 0 (V2) to week 52 (V6)	Number 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 52 (V6)	Number of episodes

1.2 Trial design

This is a 52-week, randomised, open label, parallel-group, active-controlled, multi-centre, multi-national trial with real world elements comparing insulin icodec used with DoseGuide versus once daily basal insulin analogues among insulin naïve T2D subjects in which insulin initiation is needed.

The trial duration is approximately 59 weeks, consisting of a 2-week screening period, followed by a 52-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 icodec used with DoseGuide is non-inferior to once daily basal insulin analogues in terms of change from baseline to week 52 in HbA_{1c}.

Formally, let D be the treatment difference 'insulin icodec used with DoseGuide' minus 'basal insulin analogues' of the change in HbA_{1c} from baseline to week 52. The null-hypothesis will be tested against the alternative hypothesis of non-inferiority as given by

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

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

- The margin does not represent an unacceptable loss of effectiveness with insulin icodec relative to treatment with a basal insulin analogue
- It represents less than 50% of a suitably conservative estimate of insulin glargine's treatment effect on HbA_{1c} in a placebo-controlled trial in insulin naïve subjects (-0.85%-point $[-1.04; -0.66]_{95\%CI}$ versus placebo), which demonstrated insulin glargine's superiority.[2]

- Other basal insulin analogues have previously been shown to yield similar reductions in HbA_{1c} compared to insulin glargine.

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

- Insulin icodec used with DoseGuide is superior to once daily basal insulin analogues in terms of change in HbA1c from baseline to week 52

Formally, let D be the mean treatment difference 'insulin icodec used with DoseGuide' minus 'basal insulin analogues' of the change in HbA_{1c} from baseline to week 52. The null-hypothesis of insulin icodec used with DoseGuide not superior will be tested against the alternative hypothesis of superiority as given by:

$$H0: D \geq 0.0\% \text{ against } HA: D < 0.0\%$$

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 (V8)
- 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 effectiveness 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 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 used with DoseGuide, basal insulin analogues
- Region: Europe, North America

The regions will be defined as follows:

- Europe: Germany, Greece, Hungary, Poland, Serbia, Turkey
- North America: Canada, United States

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

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

5.2 Subject disposition

Subject disposition will be summarised descriptively.

5.3 Primary endpoint analysis

5.3.1 Definition of endpoints

The primary endpoint is change in HbA_{1c} from baseline to week 52. 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_{1c} measurements obtained at the week 52 visit, especially including measurements from subjects discontinuing their randomised treatment. Missing HbA_{1c} at the week 52 visit (regardless of treatment completion status) will be imputed from trial participants, who have discontinued their randomised treatment prior to the week 52 visit and have a measurement at the week 52 visit in the following way:

- First, one thousand (1000) copies of the dataset will be generated for HbA_{1c}.
- Second, for subjects who discontinued their randomised treatment at any time prior to the week 52 visit and have an HbA_{1c} measurement at the week 52 visit, the change in HbA_{1c} from last available planned on-treatment (LAOT) value to the week 52 visit will be analysed for each dataset copy using an analysis of covariance (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 52 visit and subsequently the missing HbA_{1c} value at the week 52 visit.
- For each of the complete data sets, the primary endpoint will be analysed using an ANCOVA model with region and randomised treatment as fixed factors, and baseline HbA_{1c} as a covariate. The estimates and standard deviations for the 1000 data sets will be pooled to one estimate and associated standard deviation using Rubin's rule[3].

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

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 52 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 DTSQs in total treatment satisfaction (see section 5.4.1.1).

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

Missing HbA_{1c} at week 52 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 52 visit are assumed to have a worse outcome in the insulin icodec used with DoseGuide arm and a better outcome in the basal insulin analogues arm compared to what was imputed in the primary analysis. This is done by adding or subtracting values Δ_i to the imputed HbA_{1c} values before analysing the data. The value of Δ_i will be varied independently in the two treatment arms. The non-inferiority margin of 0.3% will be among the Δi values investigated. The plausibility of the values of Δ_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 Effectiveness endpoints

Time from baseline to treatment discontinuation or intensification (from baseline week 0 (V2) to week 52 (V6))

Time from baseline to treatment discontinuation or intensification will be analysed using a stratified log-rank test where randomised treatment will be included as strata in the model. Subjects lost to follow-up or withdrawing from trial before the completion of the treatment period will contribute to the analysis as discontinuing treatment at the time of the end of the in-trial period if the time of discontinuation is unknown. Cumulative incidence function by randomised treatment will be presented together with estimated and relative risks (risk ratio) at week 26 and week 52. The 25%, 50% (median) and 75% percentiles based on the cumulative incidence function will also be presented.

Additionally, time from baseline to treatment discontinuation or intensification will be analysed using a stratified log-rank test with randomised treatment and region included as strata in the model. Cumulative incidence function by strata from the model, together with the 25%, 50% (median) and 75% percentiles based on the cumulative incidence function will be presented. Estimated risks at week 26 and week 52 will also be shown.

Change in DTSQs (Diabetes Treatment Satisfaction Questionnaire) in total treatment satisfaction from baseline week 0 (V2) to week 52 (V6)

Missing DTSQs scores in total treatment satisfaction at the week 52 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 will be carried as follows:

- First, an ANCOVA model with region and randomised treatment as fixed factors, and a baseline value as a covariate will be fitted to the LAOT values.
- Second, the estimated residual standard deviation, *s*, from this model will be used to impute missing values by the baseline value, adding a random normally distributed term with mean 0 and standard deviation *s*. This will be done a 1000 times.
- For each of the complete data sets, the endpoint will be analysed using an ANCOVA model with region 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.

Trim-D (Treatment Related Impact Measure for Diabetes) compliance domain at week 52 (V6)

Missing Trim-D compliance domain scores at week 52 visit (regardless of treatment completion status) will be imputed from trial participants who are from the basal insulin analogues 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 the treatment with basal insulin analogues. Specifically, the imputations will be carried as follows:

- First, one thousand (1000) copies of the dataset will be generated for the Trim-D compliance domain scores.
- Second, for each dataset copy, an analysis of variance (ANOVA) model will be fitted to Trim-D compliance domain scores for subjects who completed their randomised treatment in the basal insulin analogues group. The estimated mean, and variances, from the model will be used to impute missing values in both treatment groups.
- For each of the complete data sets, the endpoint will be analysed using an ANOVA model with region 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.

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 57 (V8)
- 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 (V8)

- 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 (V8)

For subjects who discontinued their randomised treatment, the number of episodes in the missing period (time of follow-up 2 (V8) 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 (V8) follows the respective treatment groups rate whilst post follow-up 2 (V8) event rate is the rate of the basal insulin analogues 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 and randomised treatment as fixed factors and the logarithm of the on-treatment period as offset.
- Second, based on the estimated parameters for the basal insulin analogues 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.

For the definition and classification of hypoglycaemic episodes refer to Protocol Appendix 8 (Protocol Section 10.8).

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 52 and the follow-up 2 visit (V8) with time of discontinuation:

- Number of severe hypoglycaemic episodes (level 3) from baseline week 0 (V2) to week 52 (V6)
- 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 52 (V6)
- 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 52 (V6).

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 57 (V8)
- 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 (V8)
- 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 57 (V8)

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 52, and substituting the time of follow-up 2 visit (V8) with time of discontinuation:

- Number of nocturnal severe hypoglycaemic episodes (level 3) from baseline week 0 (V2) to week 52 (V6)
- 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 (V6)
- 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 52 (V6).

5.6.2 Hypoglycaemic episodes based on SMPG measurements

Alternative definition will be used to identify hypoglycaemic episodes based on SMPG measurements instead of reporting by subject. Hypoglycaemic episodes will be derived by applying the blood glucose thresholds for hypoglycaemia alert value (level 1) (<3.9 mmol/L (70 mg/dL)) and clinically significant hypoglycaemia (level 2) (<3.0 mmol/L (54 mg/dL)) directly to SMPG data. The SMPG measurements related to severe hypoglycaemic episodes (level 3) will not be used in the derivation of hypoglycaemia alert value episodes (level 1) or clinically significant hypoglycaemic episodes (level 2). The definition of severe hypoglycaemia (level 3) will not change.

The following derivations will be summarised descriptively based on the on-treatment period:

- Number of hypoglycaemia alert value (level 1) (<3.9 mmol/L (70 mg/dL), confirmed by BG meter) based on SMPG measurements
- Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) based on SMPG measurements
- Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) based on SMPG measurements or severe hypoglycaemic episodes (level 3)

All statistical analyses of the number of clinically significant hypoglycaemic episodes (level 2) and the number of clinically significant hypoglycaemic episodes (level 2) or severe hypoglycaemic episodes (level 3) described in sections 5.4.1.2, 5.5 and 5.6.1 will be repeated for the hypoglycaemic episodes based on SMPG measurements. This will include analyses for the period from baseline week 0 (V2) to week 52 (V6) and the period from baseline week 0 (V2) to week 57 (V8), together with the analyses of corresponding nocturnal hypoglycaemic episodes for both periods.

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 e.g. 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 Body weight

Change in body weight from week 0 to week 52 will be analysed using the same statistical model as specified for the primary endpoint, but with the corresponding baseline value as a covariate.

5.7.1.2 Achievement of HbA_{1c} target

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

- Achievement of HbA_{1c}<7.0% after 52 weeks (yes/no)
- 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)
- Achievement of HbA_{1c}<7.0% after 52 weeks without severe hypoglycaemic episodes (level 3) during the prior 12 weeks (yes/no)
- Achievement of HbA_{1c}≤6.5% after 52 weeks (yes/no)
- 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)
- Achievement of HbA_{1c}≤6.5% after 52 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 52 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 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.

5.7.1.3 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.

5.7.1.4 Antidiabetic background medication

Subjects experiencing changes to non-insulin antidiabetic background medication during the trial lasting more than 2 weeks will be summarised descriptively by treatment including number and proportion of subjects.

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

5.7.1.5 Insulin dose

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

Mean weekly insulin dose from two weeks before week 52 (two weeks before V6) to week 52 (V6) will be summarised by treatment, and log-transformed and analysed using the same statistical model as specified for Trim-D compliance domain.

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.

5.8 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
CI	Confidence interval
DTSQ	Diabetes Treatment Satisfaction Questionnaire
FDA	Food and Drug Administration
SAE	Serious adverse event
SAP	Statistical analysis plan
SMPG	Self-measured plasma glucose
T2D	Type 2 Diabetes
Trim-D	Treatment Related Impact Measure for Diabetes

6.2 Appendix 2: Changes to protocol-planned analyses

6.2.1 Changes prior to first patient first visit

In section 2 'unacceptable loss of efficacy' was replaced with 'unacceptable loss of effectiveness' to align with the trial objective.

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. 'Efficacy endpoints' was replaced with 'effectiveness endpoints' to align with the endpoints section.

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 section 5.4.1.1 additional analyses of time from baseline to treatment discontinuation or intensification have been added. Moreover, based on recommendations from FDA, the method for imputing missing data for change in DTSQs in total treatment satisfaction has been changed from imputing missing data using completing comparator subjects to imputing from baseline values within own arm.

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.

6.2.2 Changes after first patient first visit but before the database lock

Section 5.6.2 has been added with additional summaries and analyses of hypoglycaemic episodes identified using an alternative definition based on SMPG measurements.

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

Type	Title	Time frame	Unit	Details
Primary endpoint	Change in HbA_{1c}	From baseline week 0 (V2) to week 52 (V6)	%-point	The HbA_{1c} value at baseline week 0 subtracted from the HbA_{1c} value at week 52.
Supportive secondary endpoint	Time from baseline to treatment discontinuation or intensification	From baseline week 0 (V2) to week 52 (V6)	Days	Time from baseline to treatment discontinuation or intensification.
Supportive secondary endpoint	Change in DTSQs (Diabetes Treatment Satisfaction Questionnaire) in total treatment satisfaction	From baseline week 0 (V2) to week 52 (V6)	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.
Supportive secondary endpoint	Trim-D (Treatment Related Impact Measure for Diabetes) compliance domain	At end of treatment week 52 (V6)	Score of 4-20. 4 items scored on a scale of 1 to 5 Transformed to a 0-100 scale with higher scores corresponding to better compliance.	The Trim-D compliance domain score at week 52.
Supportive secondary endpoint	Number of severe hypoglycaemic episodes (level 3)	From baseline week 0 (V2) to week 57 (V8)	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 57 (V8)	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 57 (V8)	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 severe hypoglycaemic episodes (level 3)	From baseline week 0 (V2) to week 52 (V6)	Number of episodes	The count of all severe hypoglycaemic episodes (level 3) within the time frame.

Type	Title	Time frame	Unit	Details
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 52 (V6)	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 52 (V6)	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 57 (V8)	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 57 (V8)	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 57 (V8)	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 52 (V6)	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 52 (V6)	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 52 (V6)	Number of episodes	Nocturnal hypoglycaemic episodes: episodes occurring between 00:01 and 05:59 both inclusive.
Assessment	Change in body weight	From baseline week 0 (V2) to week 52 (V6)	Kg	The body weight value at baseline week 0 subtracted from the body weight value at week 52.

Type	Title	Time frame	Unit	Details
Derivation	Achievement of HbA_{1c}<7.0% after 52 weeks (yes/no)	Week 52 (V6)	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
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 (V6)	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 (V6)	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 (V6)	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 (V6)	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 (V6)	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
Assessment	Mean weekly insulin dose	From two weeks before week 52 (two weeks before V6) to week 52 (V6)	U	The mean of weekly insulin doses during the two weeks.
Derivation	Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) based on SMPG measurements	From baseline week 0 (V2) to week 57 (V8)	Number of episodes	The count of all clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL) confirmed by BG meter) identified based on SMPG measurements within the time frame.
Derivation	Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) based on SMPG measurements or nocturnal severe hypoglycaemic episodes (level 3)	From baseline week 0 (V2) to week 57 (V8)	Number of episodes	The count of all clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) identified based on SMPG measurements or severe hypoglycaemic episodes (level 3) within the time frame.
Derivation	Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) based on SMPG measurements	From baseline week 0 (V2) to week 52 (V6)	Number of episodes	The count of all clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL) confirmed by BG meter) identified based on SMPG measurements within the time frame.
Derivation	Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) based on SMPG measurements or nocturnal severe hypoglycaemic episodes (level 3)	From baseline week 0 (V2) to week 52 (V6)	Number of episodes	The count of all clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) identified based on SMPG measurements or severe hypoglycaemic episodes (level 3) within the time frame.
Derivation	Number of nocturnal clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) based on SMPG measurements	From baseline week 0 (V2) to week 57 (V8)	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) based on SMPG measurements or nocturnal severe hypoglycaemic episodes (level 3)	From baseline week 0 (V2) to week 57 (V8)	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) based on SMPG measurements	From baseline week 0 (V2) to week 52 (V6)	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) based on SMPG measurements or nocturnal severe hypoglycaemic episodes (level 3)	From baseline week 0 (V2) to week 52 (V6)	Number of episodes	Nocturnal hypoglycaemic episodes: episodes occurring between 00:01 and 05:59 both inclusive.

7 References

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