Cover Page for Statistical Analysis Plan

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Statistical Analysis Plan

A Study to Evaluate the Efficacy and Safety of Once-weekly Insulin Icodec when Switching from Daily Basal Insulins Compared to Once-daily Insulin Glargine U100 in Adults with Type 2 Diabetes

Substance name: insulin icodec

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Version History

This Statistical Analysis Plan (SAP) for study NN1436-7724 is based on the protocol version 2.0 dated 02 April 2024.

SAP Version	Date	Change	Rationale
1.0	11Apr2024	Not Applicable	Original version

List of abbreviations

AE	adverse event
ANCOVA	analysis of covariance
ANOVA	analysis of variance
BG	blood glucose
CGM	continuous glucose monitoring
CI	confidence interval
DTSQs	Diabetes Treatment Satisfaction Questionnaire status version
FGM	flash glucose monitoring
LAOT	last available planned on-treatment
PGI-S	Patient Global Impression of Status
PRO	patient-reported outcome
SAP	statistical analysis plan
SMPG	self-measured plasma glucose
T2D	type 2 diabetes
TAR	time above range
TBR	time below range
TIR	time in range
TRIM-D	Treatment-Related Impact Measure for Diabetes

1 Introduction

This SAP is based on the protocol: A Study to Evaluate the Efficacy and Safety of Once-weekly Insulin Icodec when Switching from Daily Basal Insulins Compared to Once-daily Insulin Glargine U100 in Adults with Type 2 Diabetes. There are no changes to the analyses described in the protocol, however additional information has been included in case of insufficient data for meaningful imputation of missing data for the primary analysis as well as for the sensitivity analysis to the primary analysis. The SAP also contains specification of additional derivations and analyses.

1.1 Objectives, Endpoints, and Estimands

1.1.1 Objectives and Endpoints

Objectives	**Endpoints**		
Primary	**Title**	**Time frame**	**Unit**
To demonstrate the effect on glycaemic control of once-weekly insulin icodec, switched unit-to-unit from a daily basal insulin, with or without non-insulin anti-diabetic drugs, in participants with T2D treated with basal insulin. This includes comparing the difference in change from baseline in HbA_{1c} between insulin icodec and insulin glargine U100 after 26 weeks of treatment to a non-inferiority margin of 0.3%-point.	Primary endpoint:		
	Change in HbA_{1c}	From baseline week 0 (V6) to week 26 (V32)	%-point
Secondary	**Title**	**Time frame**	**Unit**
To compare parameters of glycaemic control, patient-reported outcomes and safety of once-weekly insulin icodec, switched unit-to-unit from a daily basal insulin, compared to once-daily insulin glargine U100, both treatment arms with or without non-insulin anti-diabetic drugs, in participants with T2D treated with basal insulin.	Supportive secondary endpoints:		
	Secondary efficacy endpoints:		
	Change in time in range 3.9–10.0 mmol/L (70–180 mg/dL)[a]	From baseline week -4–0 (V2–V6) to week 22–26 (V28–V32)	% of time
	Change in DTSQs (Diabetes Treatment Satisfaction Questionnaire status version) total treatment satisfaction	From baseline week 0 (V6) to week 26 (V32)	Score of 0–36. 6 items scored on a scale of 0 to 6. The higher the score the greater the satisfaction with treatment.
	Secondary safety endpoints:		
	Number of severe hypoglycaemic episodes (level 3)	From baseline week 0 (V6) to week 31 (V34)	Number of episodes

Objectives	**Endpoints**		
	Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter)	From baseline week 0 (V6) to week 31 (V34)	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 (V6) to week 31 (V34)	Number of episodes
	Time spent < 3.0 mmol/L (54 mg/dL)[a]	During week 22–26 (V28–V32)	% of time
	Change in time spent > 10.0 mmol/L (180 mg/dL)[a]	From baseline week -4–0 (V2–V6) to week 22–26 (V28–V32)	% of time
	Mean weekly insulin dose	From week 24 (V30) to week 26 (V32)	U
	Change in body weight	From baseline week 0 (V6) to week 26 (V32)	kg
	Exploratory endpoints:		
	Change in TRIM-D (Treatment-Related Impact Measure for Diabetes) total	From baseline week 0 (V6) to week 26 (V32)	Score of 28–140. 28 items scored on a scale of 1 to 5 across 5 different domains. Transformed to a 0–100 scale with higher scores indicating a better health state.

[a]Using continuous glucose monitoring (CGM) system, Dexcom G6.
Abbreviations: BG = blood glucose; DTSQs = Diabetes Treatment Satisfaction Questionnaire status version; HbA_{1c} = glycosylated haemoglobin; T2D = type 2 diabetes; TRIM-D = Treatment-Related Impact Measure for Diabetes; V = visit.

1.1.2 Primary Estimand

The primary clinical question of interest is:

What is the treatment difference between once-weekly insulin icodec, switched unit-to-unit from a daily basal insulin, and once-daily insulin glargine U100, both treatment arms with or without non-insulin anti-diabetic drugs, in terms of change in HbA_{1c} from baseline to week 26 in participants with T2D treated with basal insulin, regardless of initiation of bolus insulin treatment for more than 2 weeks and discontinuation of investigational intervention?

The primary estimand is described by the following five attributes:

- Treatment condition: The investigational interventions, both treatment arms with or without non-insulin anti-diabetic drugs, regardless of initiation of bolus insulin treatment for more than 2 weeks and discontinuation of investigational intervention
- Population: Participants with T2D treated with basal insulin
- Endpoint: Change in HbA_{1c} from baseline to week 26
- Remaining intercurrent events: None. The two intercurrent events are captured under treatment condition and handled as follows:
    - Initiation of bolus insulin treatment for more than 2 weeks by the treatment policy strategy
    - Discontinuation of investigational intervention by the treatment policy strategy
- Population-level summary: Difference in mean changes between treatment conditions

The rationale for the primary estimand is that this estimand captures both the efficacy and safety of the investigational interventions, both treatment arms with or without non-insulin anti-diabetic drugs, regardless of initiation of bolus insulin treatment for more than 2 weeks and discontinuation of investigational intervention and, thus, aims to reflect clinical practice.

1.1.3 Secondary Estimands

See Section 4.3.1 for details.

1.2 Study Design

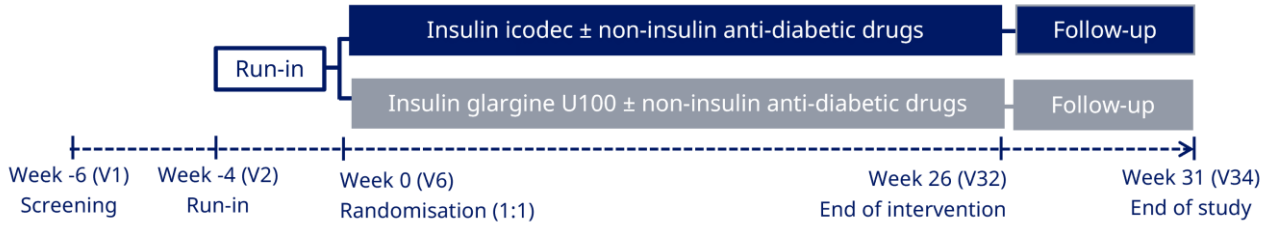
This is an interventional, multi-national, multi-centre, randomised, 26-week, parallel-group, treat-to-target, open-label, active-comparator study. The study is designed to investigate the effect on glycaemic control, safety and PROs of once-weekly insulin icodec, switched unit-to-unit from a daily basal insulin, versus once-daily insulin glargine U100, both treatment arms with or without non-insulin anti-diabetic drugs, in adults with T2D treated with basal insulin.

The study consists of:

- an up to 2-week screening period
- a 4-week run-in period with CGM
- a 26-week intervention period
- a 5-week safety follow-up period

The overall study design is outlined in Figure 1-1. For further details see the study protocol.

Figure 1-1 Study design



2 Statistical Hypothesis

The primary hypothesis to be tested is that insulin icodec is non-inferior to insulin glargine U100 in terms of change in HbA_{1c} from baseline week 0 to week 26.

Formally, let D be the mean treatment difference 'insulin icodec' minus 'insulin glargine U100' of the change in HbA_{1c} from baseline week 0 to week 26. The null hypothesis will be tested against the alternative hypothesis of non-inferiority as given by

$$H_0: D \geq 0.3\% \text{ against } H_A: D < 0.3\%$$

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] Also, this margin is considered to provide sufficient assay sensitivity based on the below considerations:

- The margin does not represent an unacceptable loss of efficacy with insulin icodec relative to treatment with a basal insulin.
- It represents less than 50% of a suitably conservative estimate of insulin glargine U100's treatment effect on HbA_{1c} in a placebo-controlled study; the treatment effect of glargine U100 versus placebo in a basal insulin treated population is unknown, but in a similar progressed T2D population of participants 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] and other basal insulin analogues have previously been shown to yield similar reduction in HbA_{1c} compared to insulin degludec.

2.1 Multiplicity Adjustment

Not applicable for this study.

3 Analysis Sets

The following participant analysis sets are defined:

Participant analysis set	Description
Full analysis set	All randomised participants. Participants will be included in the analyses according to the planned investigational intervention.
Safety analysis set	All randomised participants who are exposed to investigational intervention. Participants will be included in the analyses according to the investigational intervention they actually received.

The following data points sets are defined:

Data points set	Description
In-study	All data points obtained at or after randomisation until last participant contact
On-treatment	All data points obtained while the participant is considered exposed to investigational intervention, i.e., data points collected from first dose of investigational intervention until 5 weeks after end of last dosing interval

Baseline assessments are always included in the in-study and on-treatment data points sets.

In exceptional cases, participants or observations may be excluded from the analysis sets or the data points sets. In such case the reasons for their exclusion will be documented before unblinding. The participants and observations excluded from efficacy analyses, and the reason for this, will be described in the clinical study report.

The full analysis set and the in-study data points set will be used to estimate the primary estimand.

In general, all efficacy, all PROs and all CGM metrics will be evaluated using the full analysis set and the in-study data points set. Safety will be evaluated using the on-treatment data points set with descriptive statistics being based on the safety analysis set and statistical analyses being based on the full analysis set unless otherwise specified.

4 Statistical Analyses

4.1 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:

- Randomised treatment: Once-weekly insulin icodec, Once-daily insulin glargine U100
- Region: Asia, Europe, North America, Africa
- Personal CGM/FGM device: Yes, No

The regions will be defined as follows:

- Asia: India, Japan
- Europe: Bulgaria, Germany, Poland, Spain
- North America: United States
- Africa: South Africa

Baseline is defined as information collected at week 0 (V6). In case a measurement is not available at week 0 (V6) the most recent measurement prior to week 0 (V6) will be used as baseline.

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

4.2 Primary Estimand Analysis

4.2.1 Definition of Endpoint

The primary endpoint is change in HbA_{1c} from baseline week 0 to week 26.

4.2.2 Main Analytical Approach

The estimand (see Section 1.1.2) will be estimated based on the full analysis set using the in-study data points set which includes all HbA_{1c} measurements obtained at the week 26 visit, especially measurements from participants experiencing intercurrent events. Missing HbA_{1c} values at the week 26 visit (regardless of treatment completion status) will be imputed from participants who discontinue investigational intervention 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 participants who discontinue investigational intervention and have an HbA_{1c} 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 analysis of variance (ANOVA) model with randomised treatment as fixed factor. 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 derive the missing HbA_{1c} values at the week 26 visit.
- For each of the complete data sets, the primary endpoint will be analysed using an ANCOVA model with randomised treatment, region and personal CGM/FGM device

(yes/no) 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.[4]

This analysis has the underlying assumption that participants with missing data behave similarly as participants who discontinue investigational intervention.

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

- Missing values at the week 26 visit will be imputed with baseline value adding a random error term. The imputation step will also include measurements from participants who discontinue treatment while the analysis step will include all measurements regardless of occurrence of 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 time in range 3.9–10.0 mmol/L (see Section 4.3.1.1).

Non-inferiority is confirmed if the upper bound of the two-sided 95% confidence interval is strictly below 0.3%.

Missing HbA_{1c} at week 26 will be summarised by participant's randomised treatment completion status.

4.2.3 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 participants 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 glargine U100 arm compared to what was imputed in the primary analysis. This is done by adding or subtracting values Δ_i to the imputed HbA_{1c} values before analysing the data. The value of Δ_i will be varied independently in the two treatment arms. The non-inferiority margin of 0.3% will be among the Δ_i values investigated. The plausibility of the values of Δ_i where the conclusion of the primary analysis changes will be evaluated to assess the robustness of the primary analysis result.

This implies that the sensitivity analysis in the scenario in which participants having imputed HbA_{1c} measurement at the week 26 visit in the icodec arm will have 0.3% (non-inferiority margin) added (no penalty for imputed values in the insulin glargine U100 arm) will be performed.

4.3 Secondary Estimands Analysis

4.3.1 Supportive Secondary Estimands

Supportive secondary estimands related to supportive secondary endpoints have the following attributes. Population attributes are the same as specified for the primary estimand, and endpoint attributes are the corresponding supportive secondary endpoint. Treatment condition attribute and intercurrent events for change in body weight are the same as specified for the primary estimand. For all other supportive secondary endpoints, treatment condition attributes are the investigational

interventions regardless of initiation of bolus insulin treatment for more than 2 weeks and had participants not discontinued investigational intervention with the former intercurrent event handled by the treatment policy estimand and the latter intercurrent event handled by the hypothetical strategy, though, except for hypoglycaemic episodes, participants are assumed to return to baseline. Population-level summary attributes would instead be rate ratio for hypoglycaemic episodes, and treatment ratio for time spent < 3.0 mmol/L (54 mg/dL) and mean weekly insulin dose.

4.3.1.1 Supportive Secondary Efficacy Estimands

The following subsections describe how the supportive secondary estimands related to supportive secondary efficacy endpoints (see Section 1.1) will be estimated. The subsections refer to the corresponding supportive secondary endpoint. For calculation of endpoints see Appendix 1, Section 6.1.

Change in time in range 3.9–10.0 mmol/L (70–180 mg/dL) from baseline week -4–0 (V2–V6) to week 22–26 (V28–V32)

The supportive secondary estimand regarding change in time in range 3.9–10.0 mmol/L (70–180 mg/dL) (TIR) from baseline week -4–0 to week 22–26 will be estimated using a multiple imputation model as described below.

Missing TIR during week 22–26 (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 randomised treatment, region and personal CGM/FGM device (yes/no) 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 1000 times.
- For each of the completed data sets, the endpoint will be analysed using an ANCOVA model with randomised treatment, region and personal CGM/FGM device (yes/no) 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.[4]

Change in DTSQs total treatment satisfaction score from baseline week 0 (V6) to week 26 (V32)

The supportive secondary estimand regarding change in DTSQs total treatment satisfaction score from baseline week 0 to week 26 will be estimated using a model similar to the analysis for change in TIR substituting DTSQs total treatment satisfaction score for TIR.

4.3.1.2 Supportive Secondary Safety Estimands

The following subsections describe how the supportive secondary estimands related to supportive secondary safety endpoints (see Section 1.1) will be estimated. For calculation of endpoints see Appendix 1, Section 6.1.

Hypoglycaemic episodes

The supportive secondary estimands regarding the following supportive secondary safety endpoints will be analysed separately to the extent data allows using the method described below:

- Number of severe hypoglycaemic episodes (level 3) from baseline week 0 (V6) to week 31 (V34)
- Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) from baseline week 0 (V6) to week 31 (V34)
- 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 (V6) to week 31 (V34)

For participants who discontinued their randomised treatment, the number of episodes in the missing period (time of follow-up 2 visit (V34) to planned end of the on-treatment data points set) will be imputed using a multiple imputation technique, assuming that the event rate pre-follow-up 2 visit (V34) follows the respective treatment arms rate whilst post-follow-up 2 visit (V34) event rate is the rate of the comparator arm. 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 randomised treatment, region and personal CGM/FGM device (yes/no) as fixed factors, and the logarithm of the period for the on-treatment data points set as offset.
- Second, based on the estimated parameters for the comparator arm in this model, the number of episodes in the missing period will be imputed for participants 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 function, fixed factors and the logarithm of the period for the on-treatment data points set plus the missing period for which the number of episodes have been imputed as offset. 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]

The endpoints are defined as described in Protocol Appendix 7.

Time spent < 3.0 mmol/L (54 mg/dL) during week 22–26 (V28–V32)

The supportive secondary estimand regarding time spent < 3.0 mmol/L (54 mg/dL) (time below range [TBR]) during week 22–26 will be estimated using a negative binomial model on the number of recorded measurements below range with a log-link function and the logarithm of the total number of recorded measurements as an offset. The model will include randomised treatment,

region and personal CGM/FGM device (yes/no) as factors and baseline number of recorded measurements below range as a covariate.

Change in time spent > 10.0 mmol/L (180 mg/dL) from baseline week -4–0 (V2–V6) to week 22–26 (V28–V32)

The supportive secondary estimand regarding change in time spent > 10.0 mmol/L (180 mg/dL) (time above range [TAR]) from baseline week -4–0 to week 22–26 will be estimated using a model similar to the analysis for change in TIR substituting TAR for TIR.

Mean weekly insulin dose (U) from week 24 (V30) to week 26 (V32)

The supportive secondary estimand regarding mean weekly insulin dose (U) from week 24 to week 26 will be estimated using a model similar to the analysis for change in TIR substituting change in TIR with log-transformed mean weekly insulin dose from week 24 to week 26 and using the log-transformed pre-randomisation (baseline) weekly insulin dose as a covariate. The imputation will also be done on log-transformed values, i.e., missing values will be imputed by the log-transformed baseline value adding a random error term. The random error term will be normally distributed with a standard deviation set equal to the estimated residual standard deviation of an ANCOVA analysis on the log-transformed LAOT values.

Change in body weight from baseline week 0 (V6) to week 26 (V32)

The supportive secondary estimand regarding change in body weight from baseline week 0 to week 26 will be estimated based on the in-study data points set using a model similar to the primary analysis above substituting body weight for HbA_{1c}.

4.4 Exploratory Endpoint Analysis

Change in TRIM-D total score from baseline week 0 (V6) to week 26 (V32)

Change in TRIM-D total score from baseline week 0 to week 26 will be analysed using a model similar to the analysis for change in TIR substituting TRIM-D total score for TIR.

4.5 Other Safety Analyses

The standard safety assessments (AEs, safety laboratory parameters, vital signs, etc.) will be reported descriptively, including any notable changes of clinical interest in laboratory parameters.

4.5.1 Nocturnal hypoglycaemic episodes

The following derivations of nocturnal hypoglycaemia are defined as described in Protocol Appendix 7 and will be analysed separately, to the extent data allows, using the same model as specified for the supportive secondary estimand related to number of hypoglycaemic episodes (see Section 4.3.1.2):

- Number of nocturnal severe hypoglycaemic episodes (level 3) from baseline week 0 (V6) to week 31 (V34)
- Number of nocturnal clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) from baseline week 0 (V6) to week 31 (V34)

- 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 (V6) to week 31 (V34)

4.5.2 Mean weekly insulin dose (U/kg) from week 24 (V30) to week 26 (V32)

Mean weekly insulin dose (U/kg) from week 24 to week 26 will be analysed using a model similar to the analysis for mean weekly insulin dose (U) substituting mean weekly insulin dose (U/kg) for mean weekly insulin dose (U).

4.6 Other Analyses

4.6.1 Other Variables and/or Parameters

For calculation of derivations see Appendix 1, Section 6.1.

4.6.1.1 Achievement of HbA_{1c} targets

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

- Achievement of HbA_{1c} < 7.0% at week 26 (V32) (yes/no)
- Achievement of HbA_{1c} < 7.0% at week 26 (V32) 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% at week 26 (V32) without severe hypoglycaemic episodes (level 3) during the prior 12 weeks (yes/no)
- Achievement of HbA_{1c} ≤ 6.5% at week 26 (V32) (yes/no)
- Achievement of HbA_{1c} ≤ 6.5% at week 26 (V32) 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% at week 26 (V32) without severe hypoglycaemic episodes (level 3) during the prior 12 weeks (yes/no)

See Appendix 1, Section 6.1, for further details.

Missing HbA_{1c} data at the week 26 visit will be imputed in the same way as for the primary analysis (step 1 and 2 in Section 4.2.2) before deriving the dichotomous outcome. Participants who discontinue randomised treatment will have the dichotomous outcome also evaluating hypoglycaemia set to 'no'. For each of the 1000 complete data sets, the derivation will be analysed using a logistic regression model with randomised treatment, region and personal CGM/FGM device (yes/no) 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.[4]

4.6.1.2 TIR, TAR and TBR during week 0–4 (V6–V10)

TIR, TAR and TBR during week 0–4 will be summarized descriptively.

4.6.1.3 Change in TRIM-D domain scores from baseline week 0 (V6) to week 26 (V32)

Change in each of the individual TRIM-D domain scores from baseline week 0 to week 26 will be analysed separately using a model similar to the analysis for change in TRIM-D total score substituting the respective domain score for total score.

4.6.1.4 Achievement of clinically relevant improvement in DTSQs total treatment satisfaction score

Threshold for patient-perceived relevant improvement in DTSQs total treatment satisfaction score is calculated as the mean change in DTSQs total treatment satisfaction score from baseline week 0 to week 26 in participants with a one category improvement in anchor measure (PGI-S Diabetes Treatment Satisfaction). No imputation of missing scores for DTSQs total treatment satisfaction or PGI-S diabetes treatment satisfaction is performed prior to derivation of the threshold.

Achievement of change in DTSQs total treatment satisfaction score from baseline week 0 to week 26 ≥ threshold for patient-perceived relevant improvement (yes/no) will be analysed using a model similar to the analysis for achievement of HbA_{1c} targets substituting baseline DTSQs total treatment satisfaction score for baseline HbA_{1c}. Missing DTSQs total treatment satisfaction scores at the week 26 visit will be imputed in the same way as for change in DTSQs total treatment satisfaction score from baseline week 0 to week 26 before deriving the dichotomous outcome.

4.6.1.5 Self-measured plasma glucose (SMPG)

Mean pre-breakfast SMPG used for dose adjustment will be summarised by visit and randomised treatment. Furthermore, number and percentage of participants achieving mean pre-breakfast SMPG used for dose adjustment within range (4.4–7.2 mmol/L) will be presented by visit and randomised treatment.

4.6.1.6 Antidiabetic background medication

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

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

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

4.7 Interim Analysis

Not applicable for this study.

4.8 Changes to Protocol-planned Analysis

In Section 4.2.2 a description of an alternative imputation strategy in case of insufficient amount of data for imputation has been added.

In Section 4.2.3 it has been elaborated that the sensitivity analysis in the specific scenario of the non-inferiority margin will be investigated.

In Sections 4.4, 4.5 and 4.6 descriptions of exploratory endpoint analysis, other safety analyses and other analyses, respectively, have been added.

5 Sample size determination

See Protocol Section 9.5.

6 Supporting Documentation

6.1 Appendix 1: Definition and calculation of endpoints, assessments and derivations

Type	Title	Time frame	Unit	Details
Primary endpoint	Change in HbA_{1c}	From baseline week 0 (V6) to week 26 (V32)	%-point	The HbA_{1c} value at baseline week 0 subtracted from the HbA_{1c} value at week 26.
Supportive secondary efficacy endpoint	Change in time in range 3.9–10.0 mmol/L (70-180 mg/dL)	From baseline week -4–0 (V2–V6) to week 22–26 (V28–V32)	% of time	The time in range value at baseline week -4–0 subtracted from the time in range value at week 22–26. For each CGM period, the CGM metric is calculated as 100 times the number of recorded measurements in the given glycaemic range, divided by the total number of recorded measurements. Sufficient coverage is required of CGM periods to contribute to the analysis. Sufficient coverage is defined as at least the number of recorded measurements corresponding to 48 hours of non-consecutive CGM within a CGM period.
Supportive secondary efficacy endpoint	Change in DTSQs (Diabetes Treatment Satisfaction Questionnaire status version) total treatment satisfaction	From baseline week 0 (V6) to week 26 (V32)	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 safety endpoint	Number of severe hypoglycaemic episodes (level 3)	From baseline week 0 (V6) to week 31 (V34)	Number of episodes	The count of all severe hypoglycaemic episodes (level 3) within the time frame.
Supportive secondary safety endpoint	Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter)	From baseline week 0 (V6) to week 31 (V34)	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 safety endpoint	Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed	From baseline week 0 (V6) to week 31 (V34)	Number of episodes	The count of all clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) or severe hypoglycaemic episodes (level 3) within the time frame.

Type	Title	Time frame	Unit	Details
	by BG meter) or severe hypoglycaemic episodes (level 3)			
Supportive secondary safety endpoint	Time spent < 3.0 mmol/L (54 mg/dL)	During week 22–26 (V28–V32)	% of time	For each CGM period, the CGM metric is 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. Sufficient coverage is required of CGM periods to contribute to the analysis. Sufficient coverage is defined as at least the number of recorded measurements corresponding to 48 hours of non-consecutive CGM within a CGM period.
Supportive secondary safety endpoint	Change in time spent > 10.0 mmol/L (180 mg/dL)	From baseline week -4–0 (V2–V6) to week 22–26 (V28–V32)	% of time	Time spent above 10.0 mmol/L (180 mg/dL) at baseline week -4–0 subtracted from time spent above 10.0 mmol/L (180 mg/dL) at week 22–26. For each CGM period, the CGM metric is calculated as 100 times the number of recorded measurements above 10.0 mmol/L (180 mg/dL) divided by the total number of recorded measurements. Sufficient coverage is required of CGM periods to contribute to the analysis. Sufficient coverage is defined as at least the number of recorded measurement corresponding to 48 hours of non-consecutive CGM within a CGM period.
Supportive secondary safety endpoint	Mean weekly insulin dose	From week 24 (V30) to week 26 (V32)	U	The mean of weekly insulin doses during the two weeks.
Supportive secondary safety endpoint	Change in body weight	From baseline week 0 (V6) to week 26 (V32)	kg	The body weight value at baseline week 0 subtracted from the body weight value at week 26.
Exploratory endpoint	Change in TRIM-D (Treatment-Related Impact Measure for Diabetes) total	From baseline week 0 (V6) to week 26 (V32)	Score of 28–140. 28 items scored on a scale of 1 to 5 across 5 different domains. Transformed to a 0–100 scale with higher scores indicating a better health state.	The TRIM-D total score at baseline week 0 subtracted from the TRIM-D total score at week 26.

Type	Title	Time frame	Unit	Details
Derivation	Number of nocturnal severe hypoglycaemic episodes (level 3)	From baseline week 0 (V6) to week 31 (V34)	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 (V6) to week 31 (V34)	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 (V6) to week 31 (V34)	Number of episodes	Nocturnal hypoglycaemic episodes: episodes occurring between 00:01 and 05:59 both inclusive.
Derivation	Mean weekly insulin dose	From week 24 (V30) to week 26 (V32)	U/kg	The mean of weekly insulin doses during the two weeks.
Derivation	Achievement of HbA_{1c}<7.0% (yes/no)	At week 26 (V32)	Count of participant	Dichotomous outcome variable: *Yes*: participant achieved HbA_{1c} < 7.0% at week 26 *No*: participant did not achieve HbA_{1c} < 7.0% at week 26
Derivation	Achievement of HbA_{1c}<7.0% 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)	At week 26 (V32)	Count of participant	Dichotomous outcome variable: *Yes*: participant achieved HbA_{1c} < 7.0% at week 26 without severe or clinically significant hypoglycaemic episodes during the prior 12 weeks *No*: participant did not achieve HbA_{1c} < 7.0% at week 26 <u>or</u> participant had a severe or clinically significant hypoglycaemic episode during the prior 12 weeks <u>or</u> participant discontinued randomised treatment prematurely
Derivation	Achievement of HbA_{1c}<7.0% without severe hypoglycaemic episodes (level 3) during the prior 12 weeks (yes/no)	At week 26 (V32)	Count of participant	Dichotomous outcome variable: *Yes*: participant achieved HbA_{1c} < 7.0% at week 26 without severe hypoglycaemic episodes during the prior 12 weeks *No*: participant did not achieve HbA_{1c} < 7.0% at week 26 <u>or</u> participant had a severe hypoglycaemic episode during the prior 12 weeks <u>or</u> participant discontinued randomised treatment prematurely

Type	Title	Time frame	Unit	Details
Derivation	Achievement of $HbA_{1c} \leq 6.5\%$ (yes/no)	At week 26 (V32)	Count of participant	Dichotomous outcome variable: *Yes*: participant achieved $HbA_{1c} \leq 6.5\%$ at week 26 *No*: participant did not achieve $HbA_{1c} \leq 6.5\%$ at week 26
Derivation	Achievement of $HbA_{1c} \leq 6.5\%$ 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)	At week 26 (V32)	Count of participant	Dichotomous outcome variable: *Yes*: participant achieved $HbA_{1c} \leq 6.5\%$ at week 26 without severe or clinically significant hypoglycaemic episodes during the prior 12 weeks *No*: participant did not achieve $HbA_{1c} \leq 6.5\%$ at week 26 or participant had a severe or clinically significant hypoglycaemic episode during the prior 12 weeks or participant discontinued randomised treatment prematurely
Derivation	Achievement of $HbA_{1c} \leq 6.5\%$ without severe hypoglycaemic episodes (level 3) during the prior 12 weeks (yes/no)	At week 26 (V32)	Count of participant	Dichotomous outcome variable: *Yes*: participant achieved $HbA_{1c} \leq 6.5\%$ at week 26 without severe hypoglycaemic episodes during the prior 12 weeks *No*: participant did not achieve $HbA_{1c} \leq 6.5\%$ at week 26 or participant had a severe hypoglycaemic episode during the prior 12 weeks or participant discontinued randomised treatment prematurely
Derivation	Change in TRIM-D (Treatment-Related Impact Measure for Diabetes) treatment burden domain	From baseline week 0 (V6) to week 26 (V32)	Score of 6–30. 6 items scored on a scale of 1 to 5. Transformed to a 0–100 scale with higher scores indicating a better health state.	The TRIM-D treatment burden domain score at baseline week 0 subtracted from the TRIM-D treatment burden domain score at week 26.
Derivation	Change in TRIM-D (Treatment-Related Impact Measure for Diabetes) daily life domain	From baseline week 0 (V6) to week 26 (V32)	Score of 5–25. 5 items scored on a scale of 1 to 5. Transformed to a 0–100 scale with higher scores indicating a better health state.	The TRIM-D daily life domain score at baseline week 0 subtracted from the TRIM-D daily life domain score at week 26.

Type	Title	Time frame	Unit	Details
Derivation	Change in TRIM-D (Treatment-Related Impact Measure for Diabetes) diabetes management domain	From baseline week 0 (V6) to week 26 (V32)	Score of 5–25. 5 items scored on a scale of 1 to 5. Transformed to a 0–100 scale with higher scores indicating a better health state.	The TRIM-D diabetes management domain score at baseline week 0 subtracted from the TRIM-D diabetes management domain score at week 26.
Derivation	Change in TRIM-D (Treatment-Related Impact Measure for Diabetes) compliance domain	From baseline week 0 (V6) to week 26 (V32)	Score of 4–20. 4 items scored on a scale of 1 to 5. Transformed to a 0–100 scale with higher scores indicating a better health state.	The TRIM-D compliance domain score at baseline week 0 subtracted from the TRIM-D compliance domain score at week 26.
Derivation	Achievement of clinically relevant improvement in DTSQs total treatment satisfaction (yes/no)	From baseline week 0 (V6) to week 26 (V32)	Count of participant	Dichotomous outcome variable: *Yes*: participant achieved change from baseline to week 26 in DTSQs total treatment satisfaction score ≥ threshold for patient-perceived relevant improvement (calculated as the mean change in DTSQs total treatment satisfaction score from baseline week 0 to week 26 in participants with a one category improvement in PGI-S diabetes treatment satisfaction) *No*: participant did not achieve change from baseline to week 26 in DTSQs total treatment satisfaction score ≥ threshold for patient-perceived relevant improvement

7 References

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