Cover Page for SAP

Sponsor name:	Novo Nordisk A/S
NCT number	NCT04460885
Sponsor trial ID:	NN1436-4477
Official title of study:	A 78-week Trial Comparing the Effect and Safety of Once Weekly Insulin Icodec and Once Daily Insulin Glargine 100 units/mL, Both in Combination With Non-insulin Anti-diabetic Treatment, in Insulin Naïve Subjects With Type 2 Diabetes (ONWARDS 1)
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*Document date refers to the date on which the document was most recently updated.

Statistical Analysis Plan

NN1436-4477

A 78-week trial comparing the effect and safety of once weekly insulin icodec and once daily insulin glargine 100 units/mL, both in combination with non-insulin anti-diabetic treatment, in insulin naïve subjects with type 2 diabetes.

ONWARDS 1

Trial Phase: 3a

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Version history

This Statistical Analysis Plan (SAP) for trial NN1436-4477 is based on the protocol version 4.0 dated 30Nov2020 including local amendments in the United Kingdom dated 21Aug2020 and Italy dated 03Nov2020.

Table 1-1 SAP Version History Summary

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

1 Introduction

This Statistical Analysis Plan (SAP) is based on the protocol: *A 78-week trial comparing the effect and safety of once weekly insulin icodec and once daily insulin glargine 100 units/mL, both in combination with non-insulin anti-diabetic treatment, in insulin naïve subjects with type 2 diabetes. ONWARDS 1*, version 4.0 (dated 30Nov2020). Most of the statistical analyses and derivations of endpoints presented in this SAP are identical to those described in the protocol, but some have been updated or added for technical or clinical reasons. The SAP also contains specifications of additional derivations and analyses. The changes to the protocol-planned statistical analyses and the reasons for these changes are described in Appendix 2 section 6.2.

1.1 Objectives and endpoints

1.1.1 Primary, secondary and exploratory objective and estimand

1.1.1.1 Primary objective

To demonstrate the effect on glycaemic control of once weekly insulin icodec, in combination with non-insulin anti-diabetic drugs, in insulin naïve subjects with type 2 diabetes (T2D). This includes comparing the difference in change from baseline in HbA_{1c} between insulin icodec and insulin glargine after 52 weeks of treatment to a non-inferiority limit of 0.3%.

1.1.1.2 Secondary objective

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

1.1.1.3 Estimand

The estimand is the 'treatment policy estimand' defined as the treatment difference between insulin icodec and insulin glargine of the change in HbA_{1c} from baseline to week 52 for all randomised subjects, irrespective of adherence to randomised treatment and changes to anti-diabetic background medication. The following intercurrent events will be handled by the treatment policy strategy: Initiation of bolus insulin treatment for more than 2 weeks, discontinuation of randomised insulin treatment, and withdrawal from the trial (measurements collected after these intercurrent events are used in the primary analysis).

1.1.2 Primary, secondary and exploratory endpoints

1.1.2.1 Primary endpoint

Endpoint title	Time frame	Unit
Change in HbA_{1c}	From baseline week 0 (V2) to week 52 (V46)	%-point

1.1.2.2 Secondary endpoints

1.1.2.2.1 Confirmatory secondary endpoint

Endpoint title	Time frame	Unit
Time in target range 3.9-10.0 mmol/L (70-180 mg/dL)*	From week 48 (V42) to week 52 (V46)	% of readings

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

1.1.2.2.2 Supportive secondary endpoints

Secondary efficacy endpoint

Endpoint title	Time frame	Unit
Change in fasting plasma glucose (FPG)	From baseline week 0 (V2) to week 52 (V46)	mmol/L

Secondary safety endpoints

Endpoint title	Time frame	Unit
Number of severe hypoglycaemic episodes (level 3)	From baseline week 0 (V2) to week 52 (V46)	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 (V46)	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 (V46)	Number of episodes
Number of severe hypoglycaemic episodes (level 3)	From baseline week 0 (V2) to week 83 (V63)	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 83 (V63)	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 83 (V63)	Number of episodes
Mean weekly insulin dose	From week 50 (V44) to week 52 (V46)	U
Change in body weight	From baseline week 0 (V2) to week 52 (V46)	kg
Time spent < 3.0 mmol/L (54 mg/dL)*	From week 48 (V42) to week 52 (V46)	% of readings
Time spent > 10 mmol/L (180 mg/dL)*	From week 48 (V42) to week 52 (V46)	% of readings

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

1.1.2.3 Exploratory endpoints

Endpoint title	Time frame	Unit
Number of severe hypoglycaemic episodes (level 3)	From baseline week 0 (V2) to week 78 (V61)	Number of episodes

Endpoint title	Time frame	Unit
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 78 (V61)	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 78 (V61)	Number of episodes

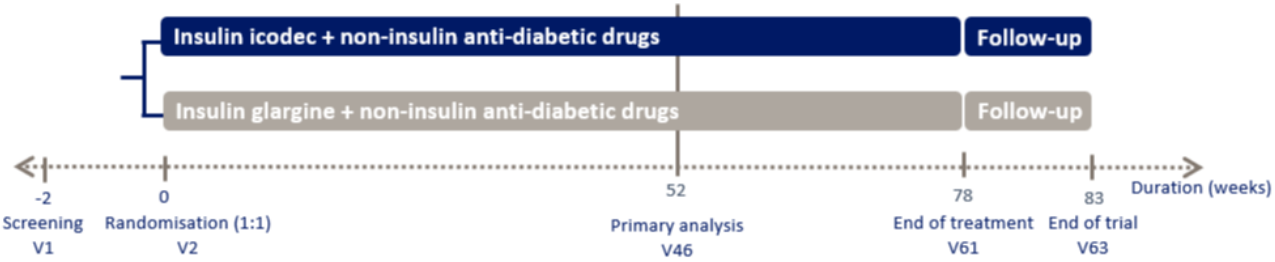
1.2 Trial design

This is a 78-week, randomised, open label, active-controlled, parallel-group, multicentre, multinational, treat-to-target trial with two treatment arms investigating the effect on glycaemic control and safety of treatment with once weekly insulin icodec compared to once daily insulin glargine, both in combination with non-insulin anti-diabetic drugs, in insulin naïve subjects with T2D inadequately controlled on non-insulin anti-diabetic drugs in need for insulin initiation.

The trial duration is approximately 85 weeks, consisting of a 2-week screening period, followed by a 78-week randomised treatment period and a 5-week follow-up period. The first 52 weeks of the trial constitute the main phase, after which the primary and confirmatory secondary endpoints are analysed. The focus of the 26 weeks extension phase is to evaluate long term safety.

The overall trial design is outlined in Figure 1-1.

Figure 1-1 Trial design



For further details see the trial protocol.

2 Statistical hypotheses

The primary hypothesis to be tested is that insulin icodec is non-inferior to insulin glargine in terms of change from baseline to week 52 in HbA_{1c}.

Formally, let D be the treatment difference 'insulin icodec' minus 'insulin glargine' 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 efficacy with insulin icodec relative to treatment with a basal insulin analogue.
- It represents less than 50% of a suitable 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]

The following sections detail the secondary confirmatory hypotheses. 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 down the following hierarchy as long as the confirmatory secondary hypothesis at a given stage is confirmed:

- Insulin icodec is superior to insulin glargine in terms of 'time in target range 3.9 – 10.0 mmol/L (70-180 mg/dL)' from week 48 to week 52.
- Insulin icodec is superior to insulin glargine in terms of change from baseline to week 52 in HbA_{1c}.

Formally, let D^T be the mean difference with respect to percent 'time in target range 3.9 – 10.0 mmol/L (70-180 mg/dL)' from week 48 to week 52 for 'insulin icodec' minus 'insulin glargine'. The null-hypothesis will be tested against the alternative hypothesis of superiority as given by:

$$H0: D^T \leq 0\% \text{ against } HA: D^T > 0\%$$

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

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

3 Sample size determination

Please see the 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 electronic case report form (eCRF), and ends at the first date of any of the following:

- The end of trial visit (V63)
- 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.

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 52 (V46).

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

All efficacy endpoints will be summarised and analysed using the full analysis set and the 'in-trial' period. Safety endpoints will be evaluated using 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. The main-on-treatment period will be used to report the main phase of the trial and the on-treatment period will be used to report the complete trial.

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 glargine
- Region: Asia, Europe, North America, South America
- The regions will be defined as follows:
- Asia: India, Japan
- Europe: Croatia, Italy, Israel, Poland, Russia, Slovakia, Spain, United Kingdom
- North America: United States
- South America: Mexico

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

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

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]

5.2 Subject disposition

Subject disposition will summarised descriptively.

5.3 Primary endpoint analysis

5.3.1 Definition of endpoint

The primary endpoint is change in HbA_{1c} from baseline week 0 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 or initiating treatment with bolus insulin for more than 2 weeks. Missing HbA_{1c} values at the week 52 visit (regardless of treatment completion status) will be imputed from trial participants, who have discontinued their randomised treatment or initiated bolus insulin treatment for more than 2 weeks prior to the week 52 visit and have a measurement at the week 52 visit in the following way:

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

2. Second, for subjects who discontinued their randomised treatment or initiated treatment with bolus insulin for more than 2 weeks at any time prior to the week 52 visit and have an HbA_{1c} measurement at the week 52 visit, the change in HbA_{1c} from last available planned on-treatment without initiation of more than 2 weeks bolus treatment (LAOT-WOB) 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-WOB value and the time point (study day) of this assessment as covariates. The estimated parameters, and their variances, from the model will be used to impute missing HbA_{1c} values for the change from LAOT-WOB to the week 52 visit and subsequently the missing HbA_{1c} value at the week 52 visit.

3. 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 SDs for the 1000 data sets will be pooled to one estimate and associated standard deviation (SD) using Rubin's rule.[4]

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

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

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

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

2. 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 FPG (see section 5.4.2.1.1).

Provided that the hierarchical testing described in section 2 was not stopped the evaluation of superiority for the primary endpoint will be based on the same model as above.

Missing HbA_{1c} at week 52 will be summarised by subject 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 arm and a better outcome in the insulin glargine 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 non-inferiority or superiority change will be evaluated to assess the robustness of the primary analysis result.

5.4 Secondary endpoints analysis

5.4.1 Confirmatory secondary endpoint

5.4.1.1 Definition of endpoint

The confirmatory secondary endpoint ‘time in range 3.9-10.0 mmol/L (70-180 mg/dL)’ from week 48 to week 52 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]

5.4.1.2 Main analytical approach

The confirmatory secondary endpoint ‘time in target range 3.9 – 10.0 mmol/L (70-180 mg/dL)’ from week 48 to week 52 will be analysed similarly to the primary endpoint specified above without inclusion of a baseline covariate.

In case the amount of data for the described imputation model is insufficient for meaningful imputation, the first alternative approach will be similar to that for the primary endpoint. However for the second alternative approach missing values will be imputed from trial participants in the insulin glargine arm who have completed their randomised insulin treatment. 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 and no baseline value is available as described for mean weekly insulin dose (see section 5.4.2.2.2).

5.4.1.3 Sensitivity analysis

The robustness of the assumptions about the missing data will be evaluated by performing a two-dimensional tipping point analysis following the same principle as for the primary endpoint.

5.4.2 Supportive secondary endpoints

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

5.4.2.1 Efficacy endpoint

5.4.2.1.1 Change in fasting plasma glucose (FPG) from baseline week 0 (V2) to week 52 (V46)

Missing FPG values 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-WOB values. Specifically, the imputations and analyses will be carried out 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-WOB 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 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 SDs for the 1000 data sets will be pooled to one estimate and associated SD using Rubin's rule[4].

5.4.2.2 Safety endpoints

5.4.2.2.1 Hypoglycaemic episodes endpoints

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 52 (V46).
- 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 (V46).
- 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 (V46).

The following hypoglycaemic endpoints will be analysed separately using the method described below, 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 83 (V63).
- 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 83 (V63).
- 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 83 (V63).

For subjects who discontinued their randomised treatment, the number of episodes in the missing period (time of follow-up 2 visit (V63) 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 (V63) follows the respective treatment groups rate whilst post-follow-up 2 visit (V63) event rate is the rate of the comparator group. The imputation will be done as follows:

1. 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 main-on-treatment period as offset.
2. 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.
3. 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[4].

For the definition and classification of hypoglycaemic episodes refer to Appendix 7 in the protocol.

5.4.2.2.2 Mean weekly insulin dose from week 50 (V44) to week 52 (V46)

Mean weekly insulin dose during the last 2 weeks of treatment (from week 50 to 52) will be analysed log-transformed. Missing mean weekly insulin doses during the last 2 weeks of treatment (from week 50 to 52) (regardless of treatment completion status) will be imputed from trial participants who are from the insulin glargine group, and who have completed and adhered to their randomised insulin treatment without initiation of bolus insulin treatment for more than 2 weeks at any time prior to the week 52 visit - i.e., data will be imputed based on the assumption that, subjects with missing endpoint data will behave like subjects completing insulin glargine treatment without initiation of bolus insulin treatment for more than 2 weeks at any time prior to the week 52 visit. Specifically, the imputations and analyses will be carried out as follows:

- First, one thousand (1000) copies of the dataset will be generated for mean week insulin dose.
- Second, for each dataset copy, an ANCOVA model will be fitted to mean weekly insulin dose values for subjects who completed their randomised treatment without initiation of bolus insulin for more than 2 weeks at any time prior to the week 52 visit in the insulin glargine 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 SDs for the 1000 data sets will be pooled to one estimate and associated SD using Rubin's rule[4].

5.4.2.2.3 Time spent < 3.0 mmol/L (54 mg/dL) and time spent > 10 mmol/L (180 mg/dL) from week 48 (V42) to week 52 (V46)

Time spent < 3.0 mmol/L (54 mg/dL) (below range) and time spent > 10 mmol/L (180 mg/dL) (above range) from week 48 to week 52 will be analysed separately in a similar manner as 'time in target range 3.9 – 10.0 mmol/L (70-180 mg/dL)' if deemed appropriate, i.e. if data can be considered normally distributed. However, if a large number of subjects have 0% time spent below range or above range, then an alternative analysis will be performed, where time spent below or above range will be analysed separately using a negative binomial model on the number of recorded measurements below and above range respectively with a log-link function and the logarithm of the total number of recorded measurements as offset. The model will include randomised treatment and region as factors.

5.4.2.2.4 Change in body weight from baseline week 0 (V2) to week 52 (V46)

Change in body weight from week 0 to week 52 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

The following hypoglycaemic exploratory endpoints will be analysed separately using the method described in section 5.4.2.2.1, substituting the main-on-treatment period with the period from week 0 to week 78, and substituting 'follow-up 2 visit (V63)' with 'discontinuation of treatment':

- Number of severe hypoglycaemic episodes (level 3), from baseline week 0 (V2) to week 78 (V61).
- 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 78 (V61).
- 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 78 (V61).

5.6 Other safety analyses

All safety analyses will be made on the safety analysis set. The standard safety assessments (serious adverse events (SAEs), adverse events (AEs), safety laboratory parameters, vital signs, etc.) will be reported descriptively based on both 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 5.4.2.2.1) or exploratory endpoint (see section 5.5).

- Number of nocturnal severe hypoglycaemic episodes (level 3) from baseline week 0 (V2) to week 52 (V46)
- 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 (V46)
- 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 (V46)

- Number of nocturnal severe hypoglycaemic episodes (level 3) from baseline week 0 (V2) to week 83 (V63)
- 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 83 (V63)
- 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 83 (V63).

- Number of nocturnal severe hypoglycaemic episodes (level 3) from baseline week 0 (V2) to week 78 (V61)
- 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 78 (V61)
- 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 78 (V61).

5.6.2 Record selection

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

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

5.7 Other analyses

5.7.1 Other derivations and assessments

5.7.1.1 Achievement of HbA_{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.

5.7.1.2 Self-measured plasma glucose (SMPG)

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

5.7.1.3 Antidiabetic background medication

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

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

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

5.7.1.4 Insulin dose

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

5.7.1.5 Assessments collected at week 78

Assessments collected at week 78 will be summarised and analysed in the similar way as at week 52, however the hierarchical testing procedure will not be applied.

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 before last subject last visit. 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 initially be limited to communication internally and with regulatory authorities.

5.9 Reporting of the main phase of the trial

A database lock is planned shortly after last subject last visit of the main phase of the trial. The results from this main phase will thereafter be reported. The complete trial will be reported after database lock of the extension phase.

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
eCRF	Electronic case report form
FDA	Food and Drug Administration
FPG	Fasting plasma glucose
LAOT-WOB	Last available planned on-treatment without initiation of more than 2 weeks bolus treatment
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SMPG	Self-measured plasma glucose
T2D	Type 2 diabetes

6.2 Appendix 2: Changes to protocol-planned analyses

6.2.1 Changes prior to first patient first visit

In section 1.1.1.3 presenting the estimand the time frame for the endpoint has been changed from "from baseline to week 78" to "from baseline to week 52" to align with the primary endpoint and the primary analysis.

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. It has also been clarified how the main-on-treatment and on-treatment periods will be used to report the main phase of the trial and the complete trial.

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

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

In section 5.3.3 it has been clarified that the sensitivity analysis will be performed to evaluate the conclusion of non-inferiority or superiority.

Besides that, additional derivations and assessments has 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 database lock for the main phase

Based on recommendations from FDA the method for imputing missing data for the second alternative approach for endpoints with data collection after premature treatment discontinuation (HbA_{1c} and BW) and change in FPG has been changed from imputing missing data using completing comparator subjects to imputing from baseline values within own arm.

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

Type	Title	Time frame	Unit	Details
Primary endpoint	Change in HbA_{1c}	From baseline week 0 (V2) to week 52 (V46)	%-point	The HbA_{1c} value at baseline week 0 week 52 subtracted from the HbA_{1c} value week 52.
Confirmatory secondary endpoint	Time in target range 3.9-10.0 mmol/L (70-180 mg/dL)*	From week 48 (V42) to week 52 (V46)	% 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 efficacy endpoint	Change in fasting plasma glucose (FPG)	From baseline week 0 (V2) to week 52 (V46)	mmol/L	The FPG value at baseline week 0 subtracted from the FPG value at week 52.
Supportive secondary safety endpoint	Number of severe hypoglycaemic episodes (level 3)	From baseline week 0 (V2) to week 52 (V46)	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 (V2) to week 52 (V46)	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 by BG meter) or severe hypoglycaemic episodes (level 3)	From baseline week 0 (V2) to week 52 (V46)	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 safety endpoint	Number of severe hypoglycaemic episodes (level 3)	From baseline week 0 (V2) to week 83 (V63)	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 (V2) to week 83 (V63)	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.

Type	Title	Time frame	Unit	Details
Supportive secondary safety 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 83 (V63)	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 safety endpoint	Mean weekly insulin dose	From week 50 (V44) to week 52 (V46)	U	The mean of weekly insulin doses during the two weeks.
Supportive secondary safety endpoint	Change in body weight	From baseline week 0 (V2) to week 52 (V46)	kg	The body weight value at baseline week 0 subtracted from the body weight value at week 52.
Supportive secondary safety endpoint	Time spent < 3.0 mmol/L (54 mg/dL)*	From week 48 (V42) to week 52 (V46)	% of readings	Calculated as 100 times the number of recorded measurements below 3.0 mmol/L (54 mg/dL) divided by the total number of recorded measurements. Following international consensus criteria, it will be required that at least 70% of the planned CGM measurements during the last four weeks of treatment are available for endpoint data to be included in the analysis.
Supportive secondary safety endpoint	Time spent > 10 mmol/L (180 mg/dL)*	From week 48 (V42) to week 52 (V46)	% 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.
Exploratory endpoint	Number of severe hypoglycaemic episodes (level 3)	From baseline week 0 (V2) to week 78 (V61)	Number of episodes	The count of all severe hypoglycaemic episodes (level 3) within the time frame.
Exploratory endpoint	Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter)	From baseline week 0 (V2) to week 78 (V61)	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 78 (V61)	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 52 (V46)	Number of episodes	The count of all nocturnal severe hypoglycaemic episodes (level 3) within the time frame. Nocturnal hypoglycaemic episodes:

Type	Title	Time frame	Unit	Details
				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 (V46)	Number of episodes	The count of all nocturnal clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL) confirmed by BG meter) within the time frame. 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 (V46)	Number of episodes	The count of all 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) within the time frame. 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 83 (V63)	Number of episodes	The count of all nocturnal severe hypoglycaemic episodes (level 3) within the time frame. 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 83 (V63)	Number of episodes	The count of all nocturnal clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL) confirmed by BG meter) within the time frame. 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 83 (V63)	Number of episodes	The count of all 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) within the time frame. 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 78 (V61)	Number of episodes	The count of all nocturnal severe hypoglycaemic episodes (level 3) within the time frame. Nocturnal hypoglycaemic episodes: episodes occurring between 00:01 and 05:59 both inclusive.

Type	Title	Time frame	Unit	Details
Derivation	Number of nocturnal clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter)	From baseline week 0 (V2) to week 78 (V61)	Number of episodes	The count of all nocturnal clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL) confirmed by BG meter) within the time frame. 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 78 (V61)	Number of episodes	The count of all 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) within the time frame. Nocturnal hypoglycaemic episodes: episodes occurring between 00:01 and 05:59 both inclusive.
Derivation	Achievement of HbA_{1c}<7.0% (yes/no)	At week 52 (V46)	Count of subject	Dichotomous outcome variable: *Yes*: subject achieved HbA_{1c} < 7.0% *No*: subject did not achieve HbA_{1c} < 7.0% Missing HbA_{1c} data at 52 weeks will be imputed in the same way as in the primary analysis before deriving the dichotomous outcome.
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 52 (V46)	Count of subject	Dichotomous outcome variable: *Yes*: subject achieved HbA_{1c} <7.0% without severe or clinically significant hypoglycaemic episodes during the prior 12 weeks *No*: subject did not achieve HbA1c <7.0% **or** subject had a severe or clinically significant hypoglycaemic episode during the prior 12 weeks **or** subject discontinued randomised treatment prematurely Missing HbA_{1c} data at 52 weeks will be imputed in the same way as in the primary analysis before deriving the dichotomous outcome.
Derivation	Achievement of HbA_{1c}<7.0% without severe hypoglycaemic episodes (level 3) during the prior 12 weeks (yes/no)	At week 52 (V46)	Count of subject	Dichotomous outcome variable: *Yes*: subject achieved HbA_{1c} <7.0% without severe hypoglycaemic episodes during the prior 12 weeks *No*: subject did not achieve HbA1c <7.0% **or** subject had a severe hypoglycaemic episode during the prior 12 weeks **or** subject discontinued randomised treatment prematurely Missing HbA_{1c} data at 52 weeks will be imputed in the same way as in the primary analysis before deriving the dichotomous outcome.

Type	Title	Time frame	Unit	Details
Derivation	Achievement of HbA_{1c}≤6.5% (yes/no)	At week 52 (V46)	Count of subject	Dichotomous outcome variable: *Yes*: subject achieved HbA_{1c} ≤6.5% *No*: subject did not achieve HbA_{1c} ≤6.5% Missing HbA_{1c} data at 52 weeks will be imputed in the same way as in the primary analysis before deriving the dichotomous outcome.
Derivation	Achievement of HbA_{1c}≤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 52 (V46)	Count of subject	Dichotomous outcome variable: *Yes*: subject achieved HbA_{1c} ≤6.5 without severe or clinically significant hypoglycaemic episodes during the prior 12 weeks *No*: subject did not achieve HbA_{1c} ≤6.5% **or** subject had a severe or clinically significant hypoglycaemic episode during the prior 12 weeks **or** subject discontinued randomised treatment prematurely Missing HbA_{1c} data at 52 weeks will be imputed in the same way as in the primary analysis before deriving the dichotomous outcome.
Derivation	Achievement of HbA_{1c}≤6.5% without severe hypoglycaemic episodes (level 3) during the prior 12 weeks (yes/no)	At week 52 (V46)	Count of subject	Dichotomous outcome variable: *Yes*: subject achieved HbA_{1c} ≤6.5% without severe hypoglycaemic episodes during the prior 12 weeks *No*: subject did not achieve HbA_{1c} ≤6.5% **or** subject had a severe hypoglycaemic episode during the prior 12 weeks **or** subject discontinued randomised treatment prematurely Missing HbA_{1c} data at 52 weeks will be imputed in the same way as in the primary analysis before deriving the dichotomous outcome.
Derivation	Change in HbA_{1c}	From baseline week 0 (V2) to week 78 (V61)	%-point	The HbA_{1c} value at baseline week 0 subtracted from the HbA_{1c} value at week 78.
Derivation	Time in target range 3.9-10.0 mmol/L (70-180 mg/dL)*	From week 74 (V57) to week 78 (V61)	% 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.
Derivation	Change in fasting plasma glucose (FPG)	From baseline week 0 (V2) to week 78 (V61)	mmol/L	The FPG value at baseline week 0 subtracted from the FPG value at week 78.

Type	Title	Time frame	Unit	Details
Derivation	Mean weekly insulin dose	From week 76 (V59) to week 78 (V61)	U	The sum of all actual insulin doses within the time frame divided by the actual number of days between the two visits multiplied by 7.
Derivation	Change in body weight	From baseline week 0 (V2) to week 78 (V61)	kg	The body weight value at baseline week 0 subtracted from the body weight value at week 78.
Derivation	Time spent < 3.0 mmol/L (54 mg/dL)*	From week 74 (V57) to week 78 (V61)	% 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.
Derivation	Time spent > 10 mmol/L (180 mg/dL)*	From week 74 (V57) to week 78 (V61)	% 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.
Derivation	Achievement of HbA_{1c}<7.0% (yes/no)	At week 78 (V61)	Count of subject	Dichotomous outcome variable: *Yes*: subject achieved HbA_{1c} < 7.0% *No*: subject did not achieve HbA_{1c} < 7.0% Missing HbA_{1c} data at 78 weeks will be imputed in the same way as in the primary analysis before deriving the dichotomous outcome.
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 78 (V61)	Count of subject	Dichotomous outcome variable: *Yes*: subject achieved HbA_{1c} <7.0% without severe or clinically significant hypoglycaemic episodes during the prior 12 weeks *No*: subject did not achieve HbA_{1c} <7.0% **or** subject had a severe or clinically significant hypoglycaemic episode during the prior 12 weeks **or** subject discontinued randomised treatment prematurely Missing HbA_{1c} data at 78 weeks will be imputed in the same way as in the primary analysis before deriving the dichotomous outcome.

Type	Title	Time frame	Unit	Details
Derivation	Achievement of HbA_{1c}<7.0% without severe hypoglycaemic episodes (level 3) during the prior 12 weeks (yes/no)	At week 78 (V61)	Count of subject	Dichotomous outcome variable: *Yes*: subject achieved HbA_{1c} <7.0% without severe hypoglycaemic episodes during the prior 12 weeks *No*: subject did not achieve HbA_{1c} <7.0% **or** subject had a severe hypoglycaemic episode during the prior 12 weeks **or** subject discontinued randomised treatment prematurely Missing HbA_{1c} data at 78 weeks will be imputed in the same way as in the primary analysis before deriving the dichotomous outcome.
Derivation	Achievement of HbA_{1c}≤6.5% (yes/no)	At week 78 (V61)	Count of subject	Dichotomous outcome variable: *Yes*: subject achieved HbA_{1c} ≤6.5% *No*: subject did not achieve HbA_{1c} ≤6.5% Missing HbA_{1c} data at 78 weeks will be imputed in the same way as in the primary analysis before deriving the dichotomous outcome.
Derivation	Achievement of HbA_{1c}≤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 78 (V61)	Count of subject	Dichotomous outcome variable: *Yes*: subject achieved HbA_{1c} ≤6.5 without severe or clinically significant hypoglycaemic episodes during the prior 12 weeks *No*: subject did not achieve HbA_{1c} ≤6.5% **or** subject had a severe or clinically significant hypoglycaemic episode during the prior 12 weeks **or** subject discontinued randomised treatment prematurely Missing HbA_{1c} data at 78 weeks will be imputed in the same way as in the primary analysis before deriving the dichotomous outcome.
Derivation	Achievement of HbA_{1c}≤6.5% without severe hypoglycaemic episodes (level 3) during the prior 12 weeks (yes/no)	At week 78 (V61)	Count of subject	Dichotomous outcome variable: *Yes*: subject achieved HbA_{1c} ≤6.5% without severe hypoglycaemic episodes during the prior 12 weeks *No*: subject did not achieve HbA_{1c} ≤6.5% **or** subject had a severe hypoglycaemic episode during the prior 12 weeks **or** subject discontinued randomised treatment prematurely Missing HbA_{1c} data at 78 weeks will be imputed in the same way as in the primary analysis before deriving the dichotomous outcome.

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

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