Cover Page for Statistical Analysis Plan

Sponsor name:	Novo Nordisk A/S
NCT number	NCT03689374
Sponsor trial ID:	NN9535-4386
Official title of study:	Effect of semaglutide once-weekly versus insulin aspart three times daily, both as add on to metformin and optimised insulin glargine (U100) in subjects with type 2 diabetes A 52-week, multi-centre, multinational, open-label, active-controlled, two armed, parallel-group, randomised trial in subjects with type 2 diabetes
Document date*:	25 January 2021

*Document date refers to the date on which the document was most recently updated.
Note: The date in the header of Page 2 is the date of compilation of the documents and not of an update to content.

16.1.9 Documentation of statistical methods

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

NN9535-4386

Statistical Analysis Plan

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0 Version history

The Statistical Analysis Plan (SAP) for trial NN9535-4386 is based on the protocol version 3 dated 08JUL2020.

Table 0-1 SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1		Not Applicable	Original version

1 Introduction

1.1 Objectives and endpoints

1.1.1 Objectives

1.1.1.1 Primary objective

To compare the effect of semaglutide once-weekly on glycaemic control versus insulin aspart three times daily (TID), both as add on to metformin and optimised insulin glargine (U100) in subjects with T2D.

1.1.1.2 Secondary objectives

To demonstrate that semaglutide once-weekly has a lower risk of severe hypoglycaemic episodes compared to IAsp TID, both as add on to metformin and optimised insulin glargine (U100) in subjects with T2D.

To compare the effect of semaglutide OW versus IAsp TID, both as add on to metformin and optimised insulin glargine (U100) in subjects with T2D with regards to:

- body weight
- lipids
- blood pressure
- health-related quality of life
- safety

1.1.2 Estimand

For all objectives the primary estimand is the treatment difference between semaglutide OW and IAsp TID for all randomised subjects if all subjects initiated and remained on randomised treatment throughout the trial.

Patients who are lost to follow-up, who have withdrawn consent, or who discontinue trial drug are assumed, in the time following this event, to behave like patients that remain in the trial and are treated with trial drug.

Table 1-1 Overview of the planned estimand

Objective	Estimand category	Estimand				
		Treat-ment condition	Variable/ Endpoint	Popula-tion of interest	Intercur-rent event strategy	Population-Level Summary Measure
Primary objective To compare the effect of semaglutide once-weekly on glycaemic control versus insulin	Primary	Sema-glutide OW vs IAsp TID.	Change from baseline to week 52 in HbA_{1c} (%-point)	All randomi-sed	Subjects lost to follow-up, who have withdrawn consent, or who discontinue	Mean treatment difference.

aspart three times daily (TID), both as add on to metformin and optimised insulin glargine (U100) in subjects with T2D.					trial drug are assumed, in the time following this event, to behave like subjects that remain in the trial and are treated with trial drug (hypothetical strategy).	
Secondary objective To demonstrate that semaglutide once-weekly has a lower risk of severe hypoglycaemic episodes compared to IAsp TID, both as add on to metformin and optimised insulin glargine (U100) in subjects with T2D. To compare the effect of semaglutide OW versus IAsp TID, both as add on to metformin and optimised insulin glargine (U100) in subjects with T2D with regards to: • body weight • lipids • blood pressure • health-related quality of life • safety	Secondary		Time to first event adjudication committee (EAC) confirmed severe hypoglycaemic episode (ADA) from randomisation up to week 52 (days)			Hazard ratio.
	Secondary		Time to first EAC confirmed severe hypoglycaemic episode (ADA) requiring hospitalisation, documented medical help, or is life threatening from randomisation up to week 52 (days)			Hazard ratio.
	Secondary		Change from baseline to week 52 in body weight (kg)			Mean treatment difference.

1.1.3 Endpoints

Definition of baseline

For each assessment, the baseline assessment is defined as the measurement at the randomisation visit (V8). However, if a visit 8 assessment is missing then the assessment from visit 7, if available, will be used as the baseline assessment.

1.1.3.1 Primary endpoint

- Change from baseline to week 52 in HbA_{1c} (%-point)

1.1.3.2 Secondary endpoints

1.1.3.2.1 Confirmatory secondary endpoints

- Time to first event adjudication committee (EAC) confirmed severe hypoglycaemic episode (ADA) from randomisation up to week 52 (days)
- Time to first EAC confirmed severe hypoglycaemic episode (ADA) requiring hospitalisation, documented medical help, or is life threatening from randomisation up to week 52 (days)
- Change from baseline to week 52 in body weight (kg)

1.1.3.2.2 Supportive secondary endpoints

- Change from baseline to week 52 in:
    - Fasting plasma glucose (FPG) (mmol/L)
    - 7-point self-measured plasma glucose profile
        - Mean 7-point profile (mmol/L)
        - Mean post-prandial increment (over all meals) (mmol/L)
    - Systolic and diastolic blood pressure (mmHg)
    - Fasting blood lipids (total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides) (mmol/L)
    - Body mass index (BMI) (kg/m2)
    - Waist circumference (cm)
    - Body weight (%)
    - Pulse (bpm)

- Number of EAC confirmed severe hypoglycaemic episodes (ADA) from randomisation to week 52
- Number of EAC confirmed severe (ADA) or blood glucose confirmed, symptomatic hypoglycaemic episodes (PG < 3.1 mmol/L (56 mg/dL)) from randomisation to week 52
- Number of EAC confirmed severe (ADA) or blood glucose confirmed, symptomatic hypoglycaemic episodes (PG ≤ 3.9 mmol/L (70 mg/dL)) from randomisation to week 52
- Number of EAC confirmed severe hypoglycaemic episodes (ADA) requiring hospitalisation, documented medical help, or is life threatening from randomisation to week 52
- Number of EAC confirmed severe (ADA) or clinically significant hypoglycaemic episodes (PG < 3.0 mmol/L (54 mg/dL)) from randomisation to week 52

- Insulin dose
    - Daily basal insulin dose at week 52 (U)
    - Total daily insulin dose at week 52 (U)

Supportive secondary HRQoL endpoints

Change from baseline to week 52 in the following scores for the selected patient-reported outcomes (PRO):

- 36-item Short Form Health Survey version 2 (SF-36v2™)
  - Physical Component Summary (PCS) score (range:7.32-70.14)
  - Mental Component Summary (MCS) score (range: 5.79-69.91)
  - Physical Functioning (PF) domain score (range:19.26-57.54)
  - Role-Physical (RP) domain score (range: 21.23-57.16)
  - Bodily Pain (BP) domain score (range: 21.68-62.00)
  - General Health (GH) domain score (range: 18.95-66.50)
  - Vitality (VT) domain score (range: 22.89-70.42)
  - Social Functioning (SF) domain score (range: 17.23-57.34)
  - Role-Emotional (RE) domain score (range: 14.39-56.17)
  - Mental Health (MH) domain score (range: 11.63-63.95)

The ten scores related to SF-36v2™ are measured on a scale from 5.79-70.42, and calculated using the 2009 General U.S. Population.
Higher scores are indicative of a better health state.

- Diabetes Quality Of Life Clinical Trial Questionnaire (DQLCTQ-R)
  - Physical functioning domain score
  - Energy / fatigue domain score
  - Health distress domain score
  - Mental health domain score
  - Satisfaction domain score
  - Treatment satisfaction domain score
  - Treatment flexibility domain score
  - Frequency of symptoms domain score

The eight scores related to DQLCTQ-R are measured on a scale from 0-100.
Higher scores are indicative of better health state.

1.1.3.2.3 Exploratory endpoints

Exploratory responder endpoints

- HbA1c ≤ 7.5% (58 mmol/mol) at week 52 (Y/N)
- HbA1c < 7.0% (53 mmol/mol) at week 52 (Y/N) (ADA)
- HbA1c ≤ 6.5% (48 mmol/mol) at week 52 (Y/N) (AACE)
- HbA1c ≤ 7.5% (58 mmol/mol) at week 52 without an EAC confirmed severe hypoglycaemic episode (ADA) from randomisation to week 52 (Y/N)
- HbA1c ≤ 7.5% (58 mmol/mol) at week 52 without an EAC confirmed severe hypoglycaemic episode (ADA) requiring hospitalisation, documented medical help, or is life threatening from randomisation to week 52 (Y/N)
- HbA1c <7.0% (53 mmol/mol) at week 52 without an EAC confirmed severe (ADA) or clinically significant hypoglycaemic episode (PG < 3.0 mmol/L (54 mg/dL)) (Y/N)

- HbA1c <7.0% (53 mmol/mol) at week 52 without an EAC confirmed severe (ADA) or clinically significant hypoglycaemic episode (PG < 3.0 mmol/L (54 mg/dL)) and no weight gain from randomisation to week 52 (Y/N)
- Weight loss ≥ 5% at week 52 (Y/N)
- Weight loss ≥ 10% at week 52 (Y/N)
- Total daily insulin dose ≤ 10U at week 52 (Y/N)
- Total daily insulin dose ≤ 20U at week 52 (Y/N)

Exploratory PRO endpoints

Change from baseline to week 52 in the scores for the Treatment Related Impact Measure for Diabetes (TRIM-D):

- TRIM-D Total Score
- Treatment Burden Domain Score
- Daily Life Domain Score
- Diabetes Management Domain Score
- Compliance Domain Score
- Psychological Health Domain Score

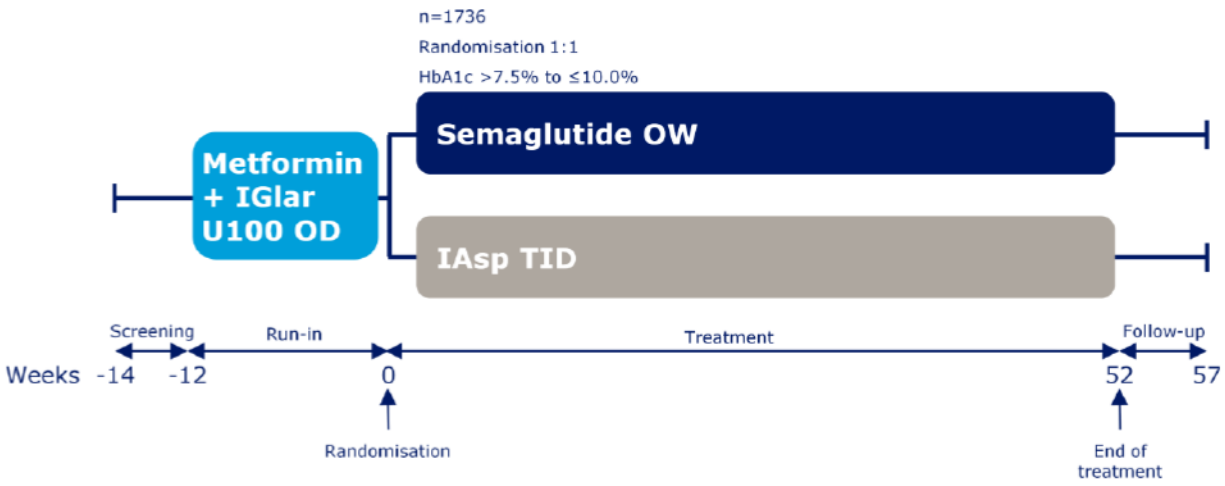
The six scores related to TRIM-D are measured on a scale from 0-100.
Higher scores are indicative of better health state (less negative impact).

1.2 Trial design

- This is a 52-week, multi-centre, multinational, open-label, active controlled, two armed, parallel, randomised phase 3b trial with a 12-week run-in period in subjects with T2D.
- The total duration of the trial will be approximately 71 weeks: 2 weeks for screening, a 12-week run-in period, a 52-week treatment period and a follow-up period of 5 weeks.
- At run-in, eligible subjects will discontinue pre-trial basal insulin and the additional OAD (if applicable, including conversion from fixed drug combination medications with metformin and DPP-4i (Dipeptidyl peptidase-4 inhibitor) to metformin only) and start treatment with IGlar U100.
- During run-in, subjects will be treated with metformin and IGlar U100. During run-in metformin can be optimised within the dose range of ≥ 1500 mg to ≤ 3000 mg. The IGlar U100 dose will be optimised as described in protocol appendix 8.
- Subjects treated with metformin and IGlar U100 who are not in glycaemic control (defined as HbA1c of > 7.5% to ≤ 10% [> 58 mmol/mol to ≤ 86 mmol/mol]) after run-in, will be randomised 1:1 to receive add-on treatment with semaglutide OW or IAsp TID. For details of the dosing of IGlar, IAsp and semaglutide, refer protocol appendix 8.

A schematic overview of the trial design is shown in Figure 1-1.

Figure 1-1 Trial design



The trial includes a screening visit to assess the subject's eligibility, additional visits and phone contacts during run-in and treatment period, and a follow-up phone contact at week 57 to ensure the capture of adverse events (AEs) during wash-out of semaglutide OW. The visit schedule described in protocol section 2 is chosen to secure an optimal insulin titration and semaglutide OW dose adjustment according to a predefined treatment algorithm.

2 Statistical hypotheses

Multiplicity control and criteria for confirming hypotheses

In order to preserve the overall type-I error the conclusion of non-inferiority and superiority of semaglutide versus IAsp will be evaluated hierarchically according to the sequence below, and starting with the first hypothesis. In this testing sequence it is necessary to fulfil the test criteria, which is to reject the corresponding null hypothesis in order to go to the next step. If the corresponding null hypothesis is not rejected, the testing will stop and no further conclusions will be drawn. The treatment difference is defined as μ = (semaglutide minus IAsp). The hazard ratio (HR) is for the comparison of semaglutide vs. IAsp.

1. HbA1c non-inferiority of semaglutide vs. IAsp
   - H_0: $\mu \geq 0.3$%-point against H_a: $\mu < 0.3$%-point
2. Superiority of semaglutide vs. IAsp on EAC confirmed severe hypoglycaemic episodes (ADA)
   - H_0: HR ≥ 1.0 against H_a: HR < 1.0
3. Superiority of semaglutide vs. IAsp on EAC confirmed severe hypoglycaemic episodes (ADA) requiring hospitalisation, documented medical help, or is life threatening
   - H_0: HR ≥ 1.0 against H_a: HR < 1.0
4. Superiority of semaglutide vs. IAsp on body weight
   - H_0: $\mu \geq 0.0$ kg against H_a: $\mu < 0.0$ kg
5. Superiority of semaglutide vs. IAsp on HbA1c
   - H_0: $\mu \geq 0.0$%-point against H_a: $\mu < 0.0$%-point

Non-inferiority and superiority of semaglutide versus IAsp will be considered confirmed if the associated H_0 is rejected.

The non-inferiority margin of 0.3%-point is chosen based on the EMA guideline[1] and the effect of faster-acting insulin aspart (FIAsp) on glycaemic effect seen in a similar trial (NN1218-4049) where FIAsp was used in a basal-bolus regimen versus basal insulin therapy, both in combination with metformin[2]. In this trial FIAsp showed an HbA_{1c} treatment difference to placebo of -0.94%-point. FIAsp is non-inferior to IAsp in terms of lowering HbA_{1c} levels[3]. Hence, based on this trial, the chosen margin of 0.3%-point provides assurance that semaglutide has an effect compared to placebo greater than 0 with a clinically relevant size. With regards to the constancy assumption, controlled clinical trials have consistently established that IAsp is an effective anti-diabetic drug. Therefore, lack of trial sensitivity with IAsp as comparator is not anticipated to be an issue in this trial.

3 Sample size determination

Please refer to the protocol section 10.1.

4 Analysis sets

For the purposes of analysis, the following analysis sets are defined.

Table 4-1 Subject analysis sets

Subject Analysis Set	Description
Full Analysis Set (FAS)	All randomised subjects. Subjects will be analysed according to the treatment to which they were assigned at randomisation.
Safety Analysis Set (SAS)	All subjects exposed to at least one dose of trial product. Subjects will be analysed according to the trial product received for the majority of the period they were on treatment.
Per protocol (PP) analysis set	Includes all subjects in the FAS who fulfil the following criteria: • Have not violated any inclusion criteria • Have not fulfilled any exclusion criteria • Have not fulfilled any run-in exclusion criteria • Have not violated any randomisation criteria • Have a valid HbA_{1c} measurement at the randomisation visit (V8) and/or the last run-in visit (V7) • Is on trial product at visit 21 and have at least one valid HbA_{1c} measurement at or after visit 21

Subjects will be analysed according to the trial product received for the majority of the period they were on treatment.

Table 4-2 Analysis data sets

Defined Analysis Data Sets	Description
In-trial	This observation period is defined as the period from date of randomisation to the first date of any of the following, both inclusive: • date of end-of-trial follow-up visit • date of death • date when subject withdrew consent • date of last contact for subjects lost to follow-up
On-treatment	This observation period is a sub-set of the 'in-trial' observation period and represents the time period where subjects are considered exposed to trial product. The observation period starts at the date of first dose of trial product and ends at an endpoint-specific end-date according to the

	flow chart. For adverse events, (excluding hypoglycaemic events), the observation period ends at the first date of any of the following: • The follow-up visit (P37) • The premature discontinuation follow-up visit (P37A) • Date of last dose of trial product + 42 days • The end-date for the 'in-trial' observation period

The follow-up visit is scheduled to take place 5 weeks after the last date on trial product corresponding to approximately five half-lives of semaglutide OW. The visit window for the follow-up visit is +7 days, a total of 42 days.

For efficacy and other safety assessments (hypoglycaemic episodes, laboratory assessments, body measurements, SMPG, PRO questionnaires, and vital signs) the 'on-treatment' observation period ends at the last date on trial product with a visit window of +7 days in accordance to the trial flow chart. Hence, for these assessments, the 'on-treatment' observation period reflects the period in which subjects are treated.

Due to inherently similar pharmacological characteristics of different bolus insulins, subjects randomised to IAsp who have changed to a different bolus insulin will be considered as being on randomised treatment. In this case the last date on randomised trial regimen will be the last date on any bolus insulin.

Data points collected outside an observation period will be treated as missing in the analysis. Baseline data will always be included in an observation period.

Before data are locked for statistical analysis, a review of all data will take place. Neither subjects nor observations should be excluded from data. If subjects or observations are excluded, the reasons for their exclusion must be documented before database lock and described in the clinical trial report. Any decision to exclude either a subject or single observations from the statistical analysis is the joint responsibility of the members of the Novo Nordisk study group.

Definition of treatment discontinuation

A "treatment discontinuer" is defined as a subject who discontinues randomised treatment. If a subject discontinues treatment during the run-in period, the subject will not fulfil the randomisation criteria and therefore be defined as a run-in failure.

Definition of study discontinuation

A "study discontinuer" is defined as a subject who discontinues the study at any time after signing informed consent.

5 Statistical analyses

5.1 General considerations

No interim analyses or other analyses of un-blinded data will be performed before the database is locked.

The comparison presented from a statistical analysis will be semaglutide versus IAsp.

If no statistical analysis is specified, data will be presented using relevant summary statistics. Accordingly, adverse events will be summarised descriptively. Data collected before randomisation (V8) will only be summarised descriptively.

Data transformations

Some of the continuous parameters will be log-transformed prior to statistical analysis. The output tables and figures will show the results of the analysis back-transformed to the original scale, implying that log-treatment-differences are reported as treatment ratios.

Laboratory values below the lower limit of quantification (LLOQ) will be set to ½LLOQ. Laboratory values above the upper limit of quantification (ULOQ) will be set to ULOQ.

5.2 Subject disposition

See mock TFLs.

5.3 Primary endpoint analysis

5.3.1 Definition of endpoint

The primary endpoint is change from baseline to week 52 in HbA_{1c} (%-point).

5.3.2 Main analytical approach

According to the primary estimand, the primary analysis will be estimated based on the FAS using post-baseline measurements up to and including week 52 from the 'on-treatment' observation period. Imputation of missing data will be handled using multiple imputation assuming that missing data is missing at random (MAR). Missing data will be imputed using observed data within each of the two groups defined by the randomised treatment (semaglutide/IAsp). It is hereby assumed that the likely values of what the missing data would have been, if available, are best described by information from subjects who receive the same treatment.

Technically, missing values will be imputed as follows:

- Intermittent missing values are imputed using a Markov Chain Monte Carlo (MCMC) method, in order to obtain a monotone missing data pattern. This imputation is done for each of the treatment groups separately and 500 copies of the dataset will be generated.
- A sequential conditional linear regression approach for imputing monotone missing values at planned visits will be implemented starting with the first visit after baseline and

sequentially continuing to the last planned visit at week 52. A model used to impute missing values at each planned visit will be fitted for each of the randomised treatment groups using observed data. The model will include the baseline and post-baseline HbA_{1c} values observed prior to the visit in question as covariates. The resulting 500 complete datasets will furthermore be used for the subsequent tipping analysis to evaluate the robustness of the primary analysis.

- An analysis of covariance (ANCOVA) with treatment as categorical effect and baseline HbA_{1c} as a covariate will be used to analyse HbA_{1c} values at week 52 for each of the 500 complete data sets. Rubin's rule[4] will be used to combine the analysis results in order to draw inference.

From this analysis, the estimated treatment difference between semaglutide and IAsp at week 52 will be presented together with the associated two-sided 95% confidence interval (CI) and two-sided p-value.

5.3.3 Sensitivity analyses

The aim of the below pre-specified sensitivity analysis is to investigate the robustness of the conclusions from the primary analysis and to stress test the missing at random assumption.

Tipping point analysis

The tipping point analysis is based on the FAS using the 'on-treatment' observation period. In this analysis, subjects from the semaglutide group with missing observations will be given a penalty, i.e., it is assumed that subjects with missing observations who are randomised to semaglutide will receive a treatment that is less beneficial than subjects with observed values who are randomised to semaglutide. The 500 complete datasets created for the primary analysis will be re-used for the tipping-point analysis. For each of these datasets, penalty values are added stepwise to the imputed change from baseline at week 52 for subjects randomised to semaglutide, followed by performing an ANCOVA. The addition of the penalty values and subsequent analysis steps should be repeated with increasing penalty values until a significant result in the corresponding superiority and non-inferiority analyses are no longer significant.
Tipping point non-inferiority or superiority sensitivity analysis is only done if the corresponding primary non-inferiority or superiority analysis indicates statistical significance.

Retrieved dropout analysis

The retrieved dropout analysis will be based on the FAS using the 'in-trial' observation period. Missing data will be imputed using the same approach as described for the primary analysis of the primary estimand. However, the imputation will be done within the same group defined not only by the randomised treatment (semaglutide/ IAsp) but also by the treatment status (still on randomised treatment at week 52 yes/no) (4 groups in total). It is hereby assumed that the likely values of what the missing data would have been if available are best described by information from subjects who at week 52 are similar in terms of randomised treatment and treatment status. This analysis will be performed for both non-inferiority and superiority testing.

Per protocol analysis

The per protocol analysis is based on the PP analysis set using the 'on-treatment' observation period. This analysis will be carried out for non-inferiority testing only. The statistical analysis will be the same as the primary analysis for the primary estimand.

5.4 Secondary endpoints analyses

5.4.1 Confirmatory secondary endpoints

5.4.1.1 Definition of endpoints

The confirmatory secondary endpoints are time to first EAC confirmed severe hypoglycaemic episode (ADA), time to first EAC confirmed severe hypoglycaemic episode (ADA) requiring hospitalization, documented medical help, or is life threatening and change from baseline to week 52 in body weight.

5.4.1.2 Main analytical approach

The statistical analysis of time to first EAC confirmed severe hypoglycaemic episode (ADA) will be based on the FAS using the 'on-treatment' observation period. The hazard ratio comparing semaglutide versus IAsp will be estimated from a Cox proportional hazards model with treatment group (semaglutide, IAsp) as fixed factor together with the two-sided 95% CI and the two-sided p-value. Subjects who have not experienced an EAC confirmed severe hypoglycaemic episode (ADA) within the 'on-treatment' observation period will be considered censored with the censoring date given by the end-date of the 'on-treatment' observation period. Superiority will be tested according to the statistical analysis approach to multiplicity described in Section 2.

The statistical analysis of time to first EAC confirmed severe hypoglycaemic episode (ADA) requiring hospitalization, documented medical help, or is life threatening will be analysed in the same manner as the confirmatory endpoint time to first EAC confirmed severe hypoglycaemic episode (ADA) as described above. This analysis will be based on the FAS and the 'on-treatment' observation period.

For each time-to-event endpoint, a Kaplan-Meier plot with numbers of subjects at risk at specific time points for each treatment group will be presented.

Body weight will be analysed using a similar approach as described in Section 5.3.2. Body weight will be tested for superiority according to the statistical analysis approach to multiplicity described in Section 2. Baseline and post-baseline body weight will be used as covariates instead of HbA_{1c}.

5.4.1.3 Sensitivity analyses

An in-trial sensitivity analysis will be performed to evaluate the robustness of the conclusions from the statistical analysis of time to first EAC confirmed severe hypoglycaemic episode (ADA). This in-trial analysis is based on the FAS using the 'in-trial' observation period. Subjects who have not experienced an EAC confirmed severe hypoglycaemic episode (ADA) within the 'in-trial'

observation period will be considered censored with the censoring date given by the in-trial end-date. The statistical analysis will be the same as the statistical analysis for the primary estimand.

Moreover, the time to first EAC confirmed severe hypoglycaemic episode (ADA) requiring hospitalization, documented medical help, or is life threatening will be analysed using the same model as described above but using all data collected in the 'in-trial' observation period instead.

The tipping point sensitivity analysis pre-specified to evaluate the robustness of the conclusions from the primary analysis of HbA_{1c} will also be performed to evaluate the robustness of the conclusions from the body weight superiority test. The tipping point sensitivity analysis is only done if the corresponding confirmatory superiority analysis of body weight indicates statistical significance. In addition, the retrieved dropout sensitivity analysis will also be performed for body weight.

5.4.2 Supportive secondary endpoints

The following continuous supportive secondary endpoints are considered. Change from baseline to week 52 in:

- Fasting plasma glucose (mmol/L)
- Mean 7-point self-measured plasma glucose profile (mmol/L)
- Mean post-prandial increment (over all meals) (mmol/L)
- Systolic and diastolic blood pressure (mmHg)
- Fasting blood lipids (total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides) (mmol/L)
- Body mass index (BMI) (kg/m^2)
- Waist circumference (cm)
- Body weight (%)

The above continuous endpoints will be analysed separately using a similar model approach as for the primary endpoint with the associated baseline value as covariate instead of HbA_{1c} for their respective analyses. These analyses will be based on the FAS and the 'on-treatment' observation period.

Fasting blood lipid endpoints will be log-transformed prior to analysis with the associated log-transformed baseline value as a covariate.

Pulse rate

Change from baseline to week 52 in pulse rate (bpm) will be analysed using an analysis similar to the primary analysis of the primary endpoint but with the baseline pulse rate value as covariate instead of HbA_{1c}. This analysis will be based on the SAS using the 'on-treatment' observation period.

Hypoglycaemic episodes

The supportive secondary safety endpoints related to hypoglycaemic episodes are:

- Number of EAC confirmed severe hypoglycaemic episodes (ADA) from randomisation to week 52
- Number of EAC confirmed severe (ADA) or blood glucose confirmed, symptomatic hypoglycaemic episodes (PG < 3.1 mmol/L (56 mg/dL)) from randomisation to week 52
- Number of EAC confirmed severe (ADA) or blood glucose confirmed, symptomatic hypoglycaemic episodes (PG ≤ 3.9 mmol/L (70 mg/dL)) from randomisation to week 52
- Number of EAC confirmed severe hypoglycaemic episodes (ADA) requiring hospitalisation, documented medical help, or is life threatening from randomisation to week 52
- Number of EAC confirmed severe (ADA) or clinically significant hypoglycaemic episodes (PG < 3.0 mmol/L (54 mg/dL)) from randomisation to week 52

The number of hypoglycaemic episodes of the above types will be analysed using a negative binomial regression model with a log-link function and the logarithm of the time period covered by the subject's 'on-treatment' observation period as offset. The model will include treatment as a fixed factor and baseline HbA_{1c} as a covariate. This analysis will be based on the FAS using the 'on-treatment' observation period. The results will be described by the rate ratio between treatments and the associated 95% CI and p-value for no treatment difference.

Moreover, the above types of number of hypoglycaemic episodes will also be analysed based on the 'in-trial' observation period, still using the above mentioned model, however using all data collected in the 'in-trial' observation period.

If a negative binomial regression analysis fails to converge, a Poisson regression analysis will be used across all the supportive secondary safety endpoints related to hypoglycaemic episodes instead.

Insulin dose

Daily basal insulin dose (U) at week 52 and total daily insulin dose (U) at week 52 will be log-transformed and analysed using an analysis similar to the primary analysis of the primary endpoint described in Section 5.3.2, with the associated log-transformed baseline value as a covariate instead. The analyses will be based on multiple imputed datasets of insulin doses leading up to site visits only. The treatment differences and associated 95% CIs will be back-transformed to the original scale, implying that log-treatment-differences are reported as treatment ratios. The analyses will be based on the SAS using the 'on-treatment' observation period.

Supportive secondary HRQoL endpoints

Change from baseline to week 52 in the following scores for the selected PROs:

- 36-item Short Form Health Survey version 2 (SF-36v2™)
  - Physical Component Summary (PCS) score (range:7.32-70.14)
  - Mental Component Summary (MCS) score (range: 5.79-69.91)
  - Physical Functioning (PF) domain score (range:19.26-57.54)
  - Role-Physical (RP) domain score (range: 21.23-57.16)

- Bodily Pain (BP) domain score (range: 21.68-62.00)
- General Health (GH) domain score (range: 18.95-66.50)
- Vitality (VT) domain score (range: 22.89-70.42)
- Social Functioning (SF) domain score (range: 17.23-57.34)
- Role-Emotional (RE) domain score (range: 14.39-56.17)
- Mental Health (MH) domain score (range: 11.63-63.95)

The ten scores related to SF-36v2™ are measured on a scale from 5.79-70.42, and calculated using the 2009 General U.S. Population. Higher scores are indicative of a better health state.

- Diabetes Quality Of Life Clinical Trial Questionnaire (DQLCTQ-R)
  - Physical functioning domain score
  - Energy / fatigue domain score
  - Health distress domain score
  - Mental health domain score
  - Satisfaction domain score
  - Treatment satisfaction domain score
  - Treatment flexibility domain score
  - Frequency of symptoms domain score

The eight scores related to DQLCTQ-R are measured on a scale from 0-100. Higher scores are indicative of a better health state.

The PRO questionnaires, SF-36v2™ and DQLCTQ-R, will be used to evaluate the objective regarding Quality of Life. Each of the PRO endpoints will be analysed separately as the other continuous supportive secondary endpoints using a similar model approach as for the primary endpoint with the associated baseline value as covariates. These analyses will be based on the FAS and the 'on-treatment' observation period.

Scoring of DQLCTQ-R

By using reverse scoring for some questions in the DQLCTQ-R, all questions are scored such that higher scores are indicative of a better health state. The eight domain scores related to DQLCTQ-R are represented on a scale from 0-100 using the conversion-method described in Kotsanos et al[5].

5.5 Exploratory endpoints analyses

Exploratory responder endpoints

- $HbA_{1c} \leq 7.5\%$ at week 52 (Y/N)
- $HbA_{1c} < 7.0\%$ (53 mmol/mol) at week 52 (Y/N) (ADA)
- $HbA_{1c} \leq 6.5\%$ (48 mmol/mol) at week 52 (Y/N) (AACE)
- $HbA_{1c} \leq 7.5\%$ at week 52 without an EAC confirmed severe hypoglycaemic episode (ADA) from randomisation to week 52 (Y/N)

- $HbA_{1c} \leq 7.5\%$ at week 52 without an EAC confirmed severe hypoglycaemic episode (ADA) requiring hospitalisation, documented medical help, or is life threatening from randomisation to week 52 (Y/N)
- HbA1c <7.0% (53 mmol/mol) at week 52 without an EAC confirmed severe (ADA) or clinically significant hypoglycaemic episode (PG < 3.0 mmol/L (54 mg/dL)) (Y/N)
- HbA1c <7.0% (53 mmol/mol) at week 52 without an EAC confirmed severe (ADA) or clinically significant hypoglycaemic episode (PG < 3.0 mmol/L (54 mg/dL)) and no weight gain from randomisation to week 52 (Y/N)
- Weight loss ≥ 5% at week 52 (Y/N)
- Weight loss ≥ 10% at week 52 (Y/N)
- Total daily insulin dose ≤ 10U at week 52 (Y/N)
- Total daily insulin dose ≤ 20U at week 52 (Y/N)

The above binary endpoints will be analysed using a logistic regression model with treatment as fixed effect and baseline response as covariate (i.e. baseline HbA_{1c} for binary HbA_{1c} endpoints, baseline weight for weight endpoints). These analyses will be based on the FAS and the 'on-treatment' observation period, except the analyses regarding total daily insulin dose which will be based on the SAS and the 'on-treatment' observation period. To account for missing data, the analysis will be made using a sequential multiple imputation approach as described below:

- The binary endpoints will be derived based on the 500 imputed datasets from the primary analysis of HbA_{1c} and confirmatory analysis of body weight as well as the supportive analyses of insulin doses. For the responder endpoints related to hypoglycaemic episodes, the number of hypoglycaemic episodes for the remaining unobserved part of the observation period will be imputed and subsequently the total number of hypoglycaemic episodes will be dichotomised. This will be done using a Bayes Poisson log-link model with treatment as a fixed factor and baseline HbA_{1c} as a covariate, and the logarithm of the time period covered by the subject's 'on-treatment' observation period as offset.
- Each of the complete data sets will be analysed with the described logistic regression model. Estimated odds ratios will be log transformed and inference will be drawn using Rubin's rule[4].

The results will be back-transformed and described by the odds ratio between treatments and the associated 95% CI and p-value for no treatment difference.

Exploratory PRO endpoints

Change from baseline to week 52 in the following scores for the following PRO:

- Treatment Related Impact Measure For Diabetes (TRIM-D)
  - TRIM-D Total Score
  - Treatment Burden Domain Score
  - Daily Life Domain Score
  - Diabetes Management Domain Score
  - Compliance Domain Score
  - Psychological Health Domain Score

The six scores related to TRIM-D are measured on a scale from 0-100.
Higher scores are indicative of better health state (less negative impact).

The PRO questionnaire, TRIM-D, will be analysed as the other PRO questionnaires described in Section 5.4.2.

5.6 Other safety analyses

Not applicable.

5.7 Other analyses

5.7.1 Other derivations and assessments

A total of four additional analyses regarding hypoglycaemic episodes will be performed. These consider:

- Time to first EAC confirmed severe (ADA) or blood glucose confirmed, symptomatic hypoglycaemic episode (PG < 3.1 mmol/L (56 mg/dL)) from randomisation up to week 52 (days)
- Time to first EAC confirmed severe (ADA) or blood glucose confirmed, symptomatic hypoglycaemic episode (PG ≤ 3.9 mmol/L (70 mg/dL)) from randomisation up to week 52 (days)

These analyses will be performed in the same manner as the confirmatory analysis of the endpoint time to first EAC confirmed severe hypoglycaemic episode (ADA) as described in Section 5.4.1. These analyses will be based on FAS and the 'on-treatment' observation period. Moreover, these analyses will also be performed using FAS and all data collected in the 'in-trial' observation period.

5.8 Interim analyses

No interim analyses or other analyses of un-blinded data will be performed before the database is locked.

6 Supporting documentation

6.1 Appendix 1: List of abbreviations

AACE	American Association of Clinical Endocrinologists
ADA	American Diabetes Association
AE	adverse event
ANCOVA	analysis of covariance
BMI	body mass index
CI	confidence interval
DPP-4i	dipeptidyl peptidase-4 inhibitor
DQLCTQ-R	Diabetes Quality Of Life Clinical Trial Questionnaire – Revised
EAC	event adjudication committee
FAS	full analysis set
FPG	fasting plasma glucose
HDL	high density lipoprotein
HR	hazard ratio
HRQoL	health-related quality of life
ICH	International Council on Harmonization
LDL	low density lipoprotein
LLOQ	lower limit of quantification
MAR	missing at random
MCMC	Markov Chain Monte Carlo
OAD	oral anti-diabetic drug
OW	once-weekly
PG	plasma glucose
PP	per protocol analysis set
PRO	patient reported outcomes

SAP	statistical analysis plan
SAS	safety analysis set
SMPG	self measured plasma glucose
TID	three times daily
TFL	tables, figures and listings
TRIM-D	Treatment Related Impact Measure For Diabetes
T2D	type 2 diabetes
ULOQ	upper limit of quantification

6.2 Appendix 2: Changes to protocol-planned analyses

The Bayes negative binomial log-link model used for imputation of hypoglycaemic episodes in connection with the composite endpoints has been changed to Bayes Poisson log-link model in order to mitigate computational issues due to few EAC confirmed severe hypoglycaemic episodes reported in this trial, see Section 5.5.
For the same reason, a Poisson regression analysis will be used to analyse all the supportive secondary safety endpoints related to hypoglycaemic episodes if one of the negative binomial regression analysis fails to converge, see Section 5.4.2.

Supplementary statistical analyses of insulin doses have been included to further compare the clinical profiles of the treatment arms, see Sections 1.1.3.2.2 and 1.1.3.2.3:

- Supportive secondary endpoints
  - Insulin dose
    - Daily basal insulin dose at week 52 (U)
    - Total daily insulin dose at week 52 (U)
- Exploratory responder endpoints
  - Total daily insulin dose ≤ 10U at week 52 (Y/N)
  - Total daily insulin dose ≤ 20U at week 52 (Y/N)

Furthermore, the following endpoints are added to further elaborate on the primary and secondary confirmatory endpoints, see Sections 1.1.3.2.2 and 1.1.3.2.3:

- Supportive secondary endpoints
  - Number of EAC confirmed severe (ADA) or clinically significant hypoglycaemic episodes (PG < 3.0 mmol/L (54 mg/dL)) from randomisation to week 52
- Exploratory responder endpoints
  - HbA1c <7.0% (53 mmol/mol) at week 52 without an EAC confirmed severe (ADA) or clinically significant hypoglycaemic episode (PG < 3.0 mmol/L (54 mg/dL)) (Y/N)

- HbA1c <7.0% (53 mmol/mol) at week 52 without an EAC confirmed severe (ADA) or clinically significant hypoglycaemic episode (PG < 3.0 mmol/L (54 mg/dL)) and no weight gain from randomisation to week 52 (Y/N)

A schematic overview of the estimand has been provided, see Table 1-1.

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

Type	Title	Time frame	Unit	Details
Primary endpoint	Change from baseline (week 0) to week 52 in HbA1c (%-point)	From week 0 to week 52 in HbA1c (%-point)	%-point	
Confirmatory secondary endpoint	Time to first event adjudication committee (EAC) confirmed severe hypoglycaemic episode (ADA) from randomisation (week 0) up to week 52 (days)	From randomisation (week 0) to week 52 (days)	Days	
Confirmatory secondary endpoint	Time to first EAC confirmed severe hypoglycaemic episode (ADA) requiring hospitalisation, documented medical help, or is life threatening from randomisation up to week 52 (days)	From randomisation (week 0) to week 52 (days)	Days	
Confirmatory secondary endpoint	Change from baseline (week 0) to week 52 in body weight (kg)	From week 0 to week 52 in body weight (kg)	Kg	
Supportive secondary endpoint	Change from baseline (week 0) to week 52 in fasting plasma glucose (mmol/L)	From week 0 to week 52 in fasting plasma glucose (mmol/L)	mmol/L	
Supportive secondary endpoint	Change from baseline (week 0) to week 52 in mean 7-point profile (mmol/L)	From week 0 to week 52 in mean 7-point profile (mmol/L)	mmol/L	
Supportive secondary endpoint	Change from baseline (week 0) to week 52 in mean post-prandial increment (over all meals) (mmol/L)	From week 0 to week 52 in mean post-prandial increment (mmol/L)	mmol/L	
Supportive secondary endpoint	Change from baseline (week 0) to week 52 in systolic blood pressure (mmHg)	From week 0 to week 52 in systolic blood pressure (mmHg)	mmHg	
Supportive secondary endpoint	Change from baseline (week 0) to week 52 in diastolic blood pressure (mmHg)	From week 0 to week 52 in diastolic blood pressure (mmHg)	mmHg	
Supportive secondary endpoint	Change from baseline (week 0) to week 52 in total cholesterol (mmol/L)	From week 0 to week 52 in total cholesterol (mmol/L)	mmol/L	
Supportive secondary endpoint	Change from baseline (week 0) to week 52 in low-density lipoprotein (mmol/L)	From week 0 to week 52 in low-density lipoprotein (mmol/L)	mmol/L	
Supportive secondary endpoint	Change from baseline (week 0) to week 52 in high-density lipoprotein (mmol/L)	From week 0 to week 52 in high-density lipoprotein (mmol/L)	mmol/L	
Supportive secondary endpoint	Change from baseline (week 0) to week 52 in triglycerides (mmol/L)	From week 0 to week 52 in triglycerides (mmol/L)	mmol/L	
Supportive secondary endpoint	Change from baseline (week 0) to week 52 in body mass index (kg/m2)	From week 0 to week 52 in body mass index (kg/m2)	kg/m2	

Supportive secondary endpoint	Change from baseline (week 0) to week 52 in waist circumference (cm)	From week 0 to week 52 in waist circumference (cm)	cm	
Supportive secondary endpoint	Change from baseline (week 0) to week 52 in body weight (%)	From week 0 to week 52 in body weight (%)	%	
Supportive secondary endpoint	Change from baseline (week 0) to week 52 in pulse (bpm)	From week 0 to week 52 in pulse (bpm)	bpm	
Supportive secondary endpoint	Number of EAC confirmed severe hypoglycaemic episodes (ADA) from randomisation to week 52	From randomisation (week 0) to week 52	Count	
Supportive secondary endpoint	Number of EAC confirmed severe (ADA) or blood glucose confirmed, symptomatic hypoglycaemic episodes (PG < 3.1 mmol/L (56 mg/dL)) from randomisation to week 52	From randomisation (week 0) to week 52	Count	
Supportive secondary endpoint	Number of EAC confirmed severe (ADA) or blood glucose confirmed, symptomatic hypoglycaemic episodes (PG ≤ 3.9 mmol/L (70 mg/dL)) from randomisation to week 52	From randomisation (week 0) to week 52	Count	
Supportive secondary endpoint	Number of EAC confirmed severe hypoglycaemic episodes (ADA) requiring hospitalisation, documented medical help, or is life threatening from randomisation to week 52	From randomisation (week 0) to week 52	Count	
Supportive secondary endpoint	Number of EAC confirmed severe (ADA) or clinically significant hypoglycaemic episodes (PG < 3.0 mmol/L (54 mg/dL)) from randomisation to week 52	From randomisation (week 0) to week 52	Count	
Supportive secondary endpoint	Daily basal insulin dose at week 52 (U)	At week 52 (U)	U	
Supportive secondary endpoint	Total daily insulin dose at week 52 (U)	At week 52 (U)	U	
Supportive secondary endpoint	Change from baseline (week 0) to week 52 in SF-36 domain scores	From week 0 to week 52 in SF-36 domain scores	Score (5.79-70.42)	
Supportive secondary endpoint	Change from baseline (week 0) to week 52 in DQLCTQ-R domain scores	From week 0 to week 52 in DQLCTQ-R domain scores	Score (0-100)	
Exploratory endpoint	HbA1c ≤ 7.5% (58 mmol/mol) at week 52 (Y/N)	At week 52 (Y/N)	Y/N	
Exploratory endpoint	HbA1c < 7.0% (53 mmol/mol) at week 52 (Y/N) (ADA)	At week 52 (Y/N)	Y/N	
Exploratory endpoint	HbA1c ≤ 6.5% (48 mmol/mol) at week 52 (Y/N) (AACE)	At week 52 (Y/N)	Y/N	
Exploratory endpoint	HbA1c ≤ 7.5% (58 mmol/mol) at week 52 without an EAC confirmed severe hypoglycaemic episode (ADA) from randomisation to week 52 (Y/N)	From randomisation (week 0) to week 52 (Y/N)	Y/N	

Exploratory endpoint	HbA1c ≤ 7.5% (58 mmol/mol) at week 52 without an EAC confirmed severe hypoglycaemic episode (ADA) requiring hospitalisation, documented medical help, or is life threatening from randomisation to week 52 (Y/N)	From randomisation (week 0) to week 52 (Y/N)	Y/N	
Exploratory endpoint	HbA1c <7.0% (53 mmol/mol) at week 52 without an EAC confirmed severe (ADA) or clinically significant hypoglycaemic episode (PG < 3.0 mmol/L (54 mg/dL)) (Y/N)	From randomisation (week 0) to week 52 (Y/N)	Y/N	
Exploratory endpoint	HbA1c <7.0% (53 mmol/mol) at week 52 without an EAC confirmed severe (ADA) or clinically significant hypoglycaemic episode (PG < 3.0 mmol/L (54 mg/dL)) and no weight gain from randomisation to week 52 (Y/N)	From randomisation (week 0) to week 52 (Y/N)	Y/N	
Exploratory endpoint	Weight loss ≥ 5% at week 52 (Y/N)	At week 52 (Y/N)	Y/N	
Exploratory endpoint	Weight loss ≥ 10% at week 52 (Y/N)	At week 52 (Y/N)	Y/N	
Exploratory endpoint	Total daily insulin dose ≤ 10U at week 52 (Y/N)	At week 52 (Y/N)	Y/N	
Exploratory endpoint	Total daily insulin dose ≤ 20U at week 52 (Y/N)	At week 52 (Y/N)	Y/N	
Exploratory endpoint	Change from baseline (week 0) to week 52 in TRIM-D domain scores	From week 0 to week 52 in TRIM-D domain scores	Score (0-100)	
Assessment	Change from baseline (week 0) to week 52 in physical examination	From week 0 to week 52 in physical examination	Categorical	Shift from baseline level (Normal, Abnormal not clinically significant, Abnormal clinically significant) to level at week 52
Assessment	Change from baseline (week 0) to week 52 in eye examination	From week 0 to week 52 in eye examination	Categorical	Shift from baseline level (Normal, Abnormal not clinically significant, Abnormal clinically significant) to level at week 52
Assessment	Change from baseline (week 0) to week 52 in biochemistry	From week 0 to week 52 in biochemistry	Multiple units	
Assessment	Change from baseline (week 0) to week 52 in urine albumin to creatinine ratio	From week 0 to week 52 in urine albumin to creatinine ratio	mg/mmol	

7 References

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