Cover Page for Statistical Analysis Plan

Sponsor name:	Novo Nordisk A/S
NCT number	NCT05259033
Sponsor trial ID:	NN1535-4592
Official title of study:	A 52-week study comparing the efficacy and safety of once weekly IcoSema and once weekly semaglutide, both treatment arms with or without oral anti-diabetic drugs, in participants with type 2 diabetes inadequately controlled with a GLP-1 receptor agonist. COMBINE 2
Document date:	23 June 2022

Statistical Analysis Plan

A 52-week study comparing the efficacy and safety of once weekly IcoSema and once weekly semaglutide, both treatment arms with or without oral anti-diabetic drugs, in participants with type 2 diabetes inadequately controlled with a GLP-1 receptor agonist. COMBINE 2

Substance: IcoSema (insulin icodec and semaglutide)

Table of contents

Page

Version History

This Statistical Analysis Plan (SAP) for study NN1535-4592 is based on the protocol version 7.0 dated 10May2022.

SAP Version	Date	Change	Rationale
1.0	23Jun2021	Not Applicable	Original version
2.0	02Jul2021	Reference to protocol version updated	The protocol was updated to version 2.0.
3.0	10Aug2021	Reference to protocol version updated	The protocol was updated to version 4.0.
4.0	16Mar2022	Clarification of analysis	The offset in a statistical analysis has been clarified.
5.0	23Jun2022	Reference to protocol version updated Addition of Hungary and removal of Ukraine in the definition of regions	To reflect the new country allocation for the study

1 Introduction

This SAP is based on the protocol: *A 52-week study comparing the efficacy and safety of once weekly IcoSema and once weekly semaglutide, both treatment arms with or without oral anti-diabetic drugs, in participants with type 2 diabetes inadequately controlled with a GLP-1 receptor agonist. COMBINE 2*. This SAP include details on analysis of secondary estimands related to supportive secondary endpoints. There are no changes to the analyses described in the protocol, however additional information has been included in case of insufficient data for meaningful imputation of missing data for the primary analysis. The SAP also contains specification of additional derivations and analyses.

1.1 Objectives, Endpoints, and Estimands

1.1.1 Objectives

1.1.1.1 Primary objective

To confirm superiority of once weekly IcoSema compared with once weekly semaglutide, both treatment arms with or without OADs, in terms of glycaemic control measured by change in HbA_{1c} from baseline after 52 weeks in participants with T2D inadequately controlled a GLP-1 receptor agonist.

1.1.1.2 Secondary objectives

To compare parameters of glycaemic control and safety of once weekly IcoSema with once weekly semaglutide, both treatment arms with or without OADs, in participants with T2D inadequately controlled with a GLP-1 receptor agonist.

1.1.2 Endpoints

1.1.2.1 Primary endpoint

Endpoint title	Time frame	Unit
Change in HbA_{1c}	From baseline week 0 (V2) to week 52 (V54)	%-point

1.1.2.2 Secondary endpoints

1.1.2.2.1 Supportive secondary endpoints

Secondary efficacy endpoints

Endpoint title	Time frame	Unit
Change in fasting plasma glucose (FPG)	From baseline week 0 (V2) to week 52 (V54)	mmol/L
Change in body weight	From baseline week 0 (V2) to week 52 (V54)	Kg

Secondary safety endpoints

Endpoint title	Time frame	Unit
Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) or severe hypoglycaemic episodes (level 3)	From baseline week 0 (V2) to week 57 (V56)	Number of episodes
Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter)	From baseline week 0 (V2) to week 57 (V56)	Number of episodes
Number of severe hypoglycaemic episodes (level 3)	From baseline week 0 (V2) to week 57 (V56)	Number of episodes

1.1.3 Estimands

1.1.3.1 Primary Estimand

The primary estimand is described by the following 5 attributes:

- Treatment condition: The effect of randomised treatment (titration of once weekly IcoSema versus fixed dose escalation of once weekly semaglutide 1 mg) with or without OAD(s), regardless of initiation of non-randomised insulin treatment or additional antidiabetic treatments for more than 2 weeks and adherence to randomised treatment
- Population: T2D inadequately controlled with a GLP-1 receptor agonist
- Endpoint: Change in HbA_{1c} from baseline to week 52
- Remaining ICEs: None. The two intercurrent events are captured under treatment condition and handled as follows:
    - Initiation of non-randomised insulin treatment or additional antidiabetic treatments for more than 2 weeks by the treatment policy strategy
    - Discontinuation of randomised treatment for any reason by the treatment policy strategy
- Population-level summary: Difference in mean changes from baseline

1.1.3.2 Supportive Secondary Estimands

Estimand related to change in body weight from baseline to week 52

The estimand is the same as for the primary estimand except with the endpoint attribute specified as: Change in body weight from baseline to week 52.

Estimand related to change in fasting plasma glucose (FPG) from baseline to week 52

The estimand is described by the following 5 attributes:

- Treatment condition: The effect of randomised treatment (titration of once weekly IcoSema versus fixed dose escalation of once weekly semaglutide 1 mg) with or without OAD(s),

regardless of initiation of non-randomised insulin treatment or additional antidiabetic treatments for more than 2 weeks and had all participants adhered to randomised treatment

- Population: T2D inadequately controlled with a GLP-1 receptor agonist
- Endpoint: Change in fasting plasma glucose (FPG) from baseline to week 52
- Remaining ICEs: None. The two intercurrent events are captured under treatment condition and handled as follows:
    - Initiation of non-randomised insulin treatment or additional antidiabetic treatments for more than 2 weeks by the treatment policy strategy
    - Discontinuation of randomised treatment for any reason by the hypothetical strategy
- Population-level summary: Difference in mean

Estimands related to supportive secondary safety endpoints

Supportive secondary estimands related to supportive secondary safety endpoints are similar to the estimand specified for FPG except for the endpoints attributes being specified as the respective supportive secondary safety endpoint and the population-level summary attributed being specified as “Rate ratio”.

1.2 Study Design

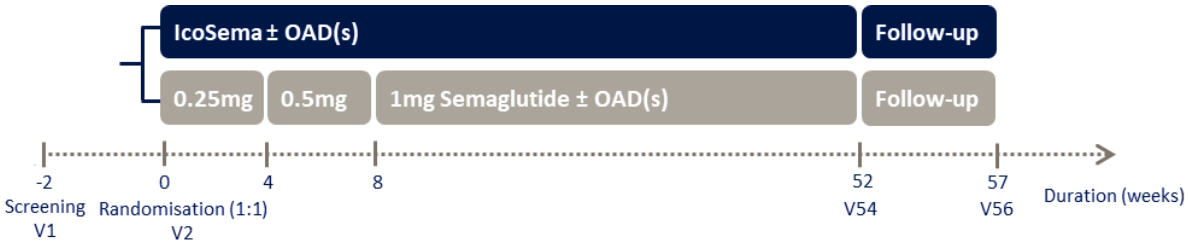
This is an interventional, multi-national, multi-centre, randomised, 52-week, open label, parallel group, treat-to-target/dose escalation, confirmatory study with two treatment arms. The study investigates the efficacy and safety of treatment with once weekly IcoSema compared to once weekly semaglutide, both treatment arms with or without OADs, in participants with T2D inadequately controlled with a GLP-1 receptor agonist.

The study duration is approximately 59 weeks and consists of:

- an up to 2 weeks screening period
- a 52-week treatment period
- a 5-week follow-up period

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

Figure 1-1 Study design



2 Statistical Hypotheses

The primary objective is to show that IcoSema is superior to semaglutide in terms of change in HbA_{1c} (%) from baseline week 0 (V2) to week 52 (V54).

Formally, let D be the mean treatment difference 'IcoSema' minus 'semaglutide' of the change in HbA_{1c} (%) from baseline week 0 (V2) to week 52 (V54). The null-hypothesis of IcoSema not being superior will be tested against the alternative hypothesis of superiority as given by

$$H_0: D \geq 0\% \text{ against } H_A: D < 0\%$$

Superiority will be considered confirmed if the upper bound of the two-sided 95% confidence interval for D is strictly below 0 %.

2.1 Multiplicity Adjustment

Not applicable for this study.

3 Analysis Sets

The following populations are defined:

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

The following data points sets are defined:

Data points sets	Description
In-study	All data from randomisation until the last date of any of the following: • The last direct participant-site contact • Withdrawal for participants who withdraw their informed consent • The last participant-investigator contact as defined by the investigator for participants who are lost to follow-up (i.e. possibly an unscheduled phone visit) • Death for participants who die before any of the above
On-treatment	All data from the date of first dose of randomised treatment as recorded on the eCRF until the first date of any of the following: • The last follow-up visit (V56) • The last date on randomised treatment +6 weeks (corresponding to 5 weeks after the end of the dosing interval for both treatment arms) • The end-date for the in-study data points sets

The on-treatment data points set represent data collected in the period in which a participant is considered exposed to randomised treatment.

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

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

Efficacy will be evaluated using the full analysis set and in-study data points set. Whereas safety will be evaluated using the on-treatment data points set with descriptive statistics being based on the safety analysis set and statistical analyses being based on full analysis set unless otherwise specified.

4 Statistical Analyses

4.1 General Considerations

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.

Presentation of results from a statistical analysis will include the estimated mean treatment difference (or ratio) presented together with the two-sided 95% confidence interval and the corresponding two-sided p-value.

In the statistical models, explanatory factors will be coded as follows:

- Randomised treatment: Once weekly IcoSema, Once weekly semaglutide
- Region: Asia, Europe, North America, Other

The regions will be defined as follows:

- Asia: Japan, China, Taiwan
- Europe: France, Greece, Slovakia, Switzerland, Sweden, Hungary
- North America: United States, Canada
- Other: Russia, Israel, Brazil

4.2 Primary Estimand Analysis

4.2.1 Definition of Endpoint

The primary endpoint is change in HbA_{1c} from baseline week 0 (V2) to week 52 (V54).

4.2.2 Main Analytical Approach

The primary endpoint is change in HbA_{1c} from baseline week 0 (V2) to week 52 (V54).

The estimand (see Section 1.1.3.1), will be estimated based on the full analysis set using the in-study data points set which includes all HbA_{1c} measurements obtained at week 52 (V54) especially measurements from participants experiencing intercurrent events. The imputation approach for the primary estimand is a multiple imputation similar to the one described by McEvoy.[1]

- Missing HbA_{1c} measurements at week 52 (V54) for participants experiencing intercurrent events will be imputed from participants experiencing intercurrent events and have a measurement at week 52 (V54) in each treatment arm.

- Missing HbA_{1c} measurements at week 52 (V54) for participants not experiencing intercurrent events are imputed from available measurements at week 52 (V54) from participants not experiencing intercurrent events in each treatment arm.

The multiple imputation approach will be done the following way:

- Imputation: An ANCOVA model for change in HbA_{1c} from baseline week 0 (V2) to week 52 (V54) for participants experiencing intercurrent events and have a measurement at week 52 (V54) with randomised treatment as fixed factor, last available planned on-treatment HbA_{1c} observation without initiation of non-randomised insulin treatment or additional anti-diabetic treatments for more than 2 weeks, the time point (study day) of last available planned on-treatment HbA_{1c} observation without initiation of non-randomised insulin treatment or additional anti-diabetic treatments for more than 2 weeks and baseline HbA_{1c} as covariate. If participants not experiencing intercurrent events are missing measurements at week 52 (V54) an ANCOVA model will be defined in a similar way using available data from participants not experiencing intercurrent events. The estimated parameters, and their variances, from the imputation models will be used to impute missing HbA_{1c} measurements at week 52 (V54). This will be done 1000 times and results in 1000 complete datasets.
- 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 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.[2]
- From the pooled estimate and standard deviation the 95% confidence interval for the treatment difference will be calculated. The corresponding two-sided p-value will also be calculated.

This analysis has the underlying assumption that participants with missing data behave similarly as comparable participants within the same treatment arm i.e. that participants experiencing intercurrent events with missing data at week 52 (V54) behave like participants experiencing intercurrent events with data at week 52 (V54) within the same treatment arm and similar for participants not experiencing intercurrent events.

In case the amount of data for the described imputation model is insufficient for meaningful imputation, the first alternative will be the following:

1. Simplifying the imputation model by removing the following covariates from the imputation model: Last available planned on-treatment HbA_{1c} observation without initiation of non-randomised insulin treatment or additional anti-diabetic treatments for more than 2 weeks and the time point (study day) of last available planned on-treatment HbA_{1c} observation without initiation of non-randomised insulin treatment or additional anti-diabetic treatments for more than 2 weeks.

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 (V54) 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 discontinuation of randomised treatment as described for change in FPG (see section 4.3.1.1.2).

Missing HbA_{1c} at week 52 (V54) will be summarised by participant randomised treatment completion status.

4.2.3 Sensitivity Analysis

The following sensitivity analysis will evaluate the robustness of the results towards the missing data assumption.

For the primary endpoint, a two-dimensional tipping point analysis will be performed where participants having imputed HbA_{1c} measurement at week 52 (V54) are assumed to have a worse outcome in the IcoSema arm and a better outcome in the semaglutide arm compared to what was imputed in the primary analysis. This is done by adding or subtracting values Δ_i to the imputed HbA_{1c} values before analysing the data. The value of Δ_i will be varied independently in the two treatment arms. The plausibility of the values of Δ_i where the conclusion of the primary analysis change will be evaluated to assess the robustness of the primary analysis results.

4.2.4 Supplementary Analysis

The following supplementary analysis addressing a attributable estimand similar to the one described by Darken[3] will be prepared. This estimand aims at estimating the effect of randomised treatment had all participants stayed on the randomised treatment for the entire 52 weeks treatment period. Intercurrent events that are considered adversely related to randomised treatment are considered attributable and are handled with a composite estimand strategy and a hypothetical estimand strategy is used for the remainder intercurrent events and data missing e.g. due to participants being lost to follow-up.

The supplementary analysis will be done the following way:

- Participants experiencing intercurrent events that are considered attributable are identified, see Appendix 3 (section 6.36.3) for split into attributable and none attributable intercurrent events.

- Outcome after intercurrent events which are deemed attributable to randomised treatment are assigned the same unfavourable value in the following way:

    - A mixed-effect model for repeated measurements (MMRM) for change from baseline in HbA_{1c} is fitted to data obtained before experiencing intercurrent events. The model include treatment, visit and interaction between treatment and visit as fixed effects, and subject as random effect.
    - The unfavourable value is assigned as the estimated change from baseline from the comparator arm at week 52 (V54) plus the standard deviation of the random intercept multiplied by the 90^{th} percentile of the standard normal distribution.

- The remaining missing data is imputed using a similar approach as for the primary analysis.

4.3 Secondary Estimands Analyses

4.3.1 Supportive Secondary Estimands

4.3.1.1 Supportive Secondary Efficacy Estimands

The following subsections describe how the supportive secondary estimands related to supportive secondary efficacy endpoints (see section 1.1.3.2) will be estimated. The subsections refer to the corresponding supportive secondary endpoint. For calculation of endpoints please see appendix 2, section 6.2.

4.3.1.1.1 Change in body weight from baseline week 0 (V2) to week 52 (V54)

The supportive secondary estimand regarding change in body weight from baseline week 0 (V2) to week 52 (V54) will be estimated using a model similar to the primary analysis above substituting body weight for HbA_{1c}.

4.3.1.1.2 Change in fasting plasma glucose (FPG) from baseline week 0 (V2) to week 52 (V54)

The supportive secondary estimand regarding change in FPG from baseline week 0 (V2) to week 52 (V54) will be estimated using a multiple imputation model as described below.

Missing FPG values at week 52 (V54) (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 last available observation before experiencing intercurrent events. 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 last available observation before experiencing intercurrent events.
- 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 zero and standard deviation *s*. This will be done 1000 times.
- For each of the complete data sets, the endpoint will be analysed using an ANCOVA model with region 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]
- From the pooled estimate and standard deviation the 95% confidence interval for the treatment difference will be calculated. The corresponding two-sided p-value will also be calculated.

4.3.1.2 Supportive Secondary Safety Estimands

4.3.1.2.1 Hypoglycaemic episodes

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

- Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L [54 mg/dL], confirmed by BG meter) or severe hypoglycaemic episodes (level 3) from baseline week 0 (V2) to week 57 (V56)
- Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L [54 mg/dL], confirmed by BG meter) from baseline week 0 (V2) to week 57 (V56)
- Number of severe hypoglycaemic episodes (level 3) from baseline week 0 (V2) to week 57 (V56)

For participants who discontinued randomised treatment, the number of episodes in the period where hypoglycaemic episodes are not collected (the period from time of follow-up 2 visit (V56) to planned end of the on-treatment data point set) will be imputed using a multiple imputation technique, assuming that the episode rate pre-follow-up 2 (V56) follows the respective treatment arms rate whilst post-follow-up 2 (V56) episode rate is the rate of the comparator arm. The imputation will be done as follows:

- First, a Bayes negative binomial model with log-link function is fitted to the number of episodes data for participants in the comparator arm to obtain the posterior distribution of model parameters. The model will include region as fixed factor and the logarithm of the time period in which a participant is considered exposed to randomised treatment as offset.

- Second, based on the estimated parameters for the comparator arm in this model, the number of episodes in the missing period will be imputed for participants having discontinued randomised treatment. One thousand (1000) complete dataset are generated by sampling from the estimated distribution.

- For each of the complete datasets, the number of episodes will be analysed using a negative binomial model with log-link function, treatment and region fixed factors and offset as described in step 1 plus the missing period for which the number of episodes have been imputed. The estimates and standard errors for the 1000 data sets will be pooled to one estimate and associated standard deviation using Rubin's rule.[4]

- From the pooled estimate and standard deviation the 95% confidence interval will be calculated and back-transformed to the original scale resulting in a treatment ratio and a 95% confidence interval for the treatment ratio. The corresponding two-sided p-value will also be calculated.

The endpoints are defined as described in Protocol Appendix 7.

4.4 Exploratory Estimands Analysis

Not applicable for this study.

4.5 Other Safety Analysis

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

4.5.1 Hypoglycaemic episodes

Number of nocturnal clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) or nocturnal severe hypoglycaemic episodes (level 3) from baseline week 0 (V2) to week 57 (V56) will be derived and analysed using the same model as specified for the supportive secondary estimands related to the supportive secondary safety endpoints.

The following derivations will be analysed separately using the model as specified for the supportive secondary estimand related to number of hypoglycaemic episodes substituting the on-treatment data point set with data points from baseline week 0 (V2) to week 52 (V54), and substituting 'follow-up 2 visit (V56)' with 'discontinuation of randomised treatment':

- 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 (V54)
- 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 (V54)
- Number of severe hypoglycaemic episodes (level 3) from baseline week 0 (V2) to week 52 (V54)

The derivations is defined as described in Protocol Appendix 7.

4.5.2 Relative change in lipids from baseline week 0 (V2) to week 52 (V54)

Relative change in lipids from baseline week 0 (V2) to week 52 (V54) will be analysed separately for each of the lipid parameters (see Protocol Appendix 2) using a model similar to the analysis for change in FPG substituting the respective lipid parameter for FPG. A multiplicative model will be used, i.e. the parameter together with the corresponding baseline value will be log-transformed before analysis. The treatment difference and the 95% confidence interval will be back-transformed to the original scale resulting in a treatment ratio and a 95% confidence interval for the treatment ratio.

4.5.3 Change in vital signs from baseline week 0 (V2) to week 52 (V54)

Change in vital signs (pulse rate, systolic and diastolic blood pressure) from baseline week 0 (V2) to week 52 (V54) will be analysed separately for each of the parameters using a model similar to the analysis for change in FPG substituting the respective vital signs parameter for FPG.

4.5.4 Anti-insulin icodec antibodies

Antibodies will be evaluated using the in-study data points set. The following will be summarised by visit for participants randomised to IcoSema:

- Anti-insulin icodec binding antibodies (positive/negative)
- Anti-insulin icodec antibodies cross-reactivity to human insulin status (positive/negative)
- Anti-insulin icodec antibody titres and change from baseline in anti-insulin icodec antibody titres

The correlation between anti-insulin icodec antibodies titres and actual weekly basal insulin dose, HbA_{1c}, and change from baseline in HbA_{1c}, respectively, will be illustrated using mean plots by treatment week for quartiles of peak post baseline to week 52 (V54) titre values.

The Spearman's rank correlation coefficient between change in anti-insulin icodec antibodies titres at week 52 (V54) and each of the following assessments will be derived with the corresponding p-value for test of no correlation:

- actual weekly basal insulin dose from week 50 (V52) to week 52 (V54)
- HbA_{1c} at week 52 (V54)
- change from baseline in HbA_{1c} at week 52 (V54)
- level 2 and level 3 combined hypoglycaemic episodes for episodes in the on-treatment data points set

Number and percentage of participants with "treatment-induced" and "treatment-boosted" anti-insulin icodec antibodies will also be summarised. "Treatment-induced" anti-insulin icodec antibodies are defined as cases in which participants switch from negative anti-insulin icodec antibodies at baseline to positive anti-insulin icodec antibodies during the study. "Treatment-boosted" anti-insulin icodec antibodies are defined as cases in which participants, who have positive anti-insulin icodec antibodies at baseline, experience that anti-insulin icodec antibodies titres increase by at least two 2-fold dilution steps during the study.

4.5.5 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 participant 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.

4.6 Other Analyses

4.6.1 Other Variables and/or Parameters

For calculation of derivations please see appendix 2, section 6.2.

4.6.1.1 Change in waist circumference from baseline week 0 (V2) to week 52 (V54)

Change in waist circumference from baseline week 0 (V2) to week 52 (V54) will be analysed using a model similar to the analysis for change in FPG substituting waist circumference for FPG.

4.6.1.2 Achievement of targets

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

- Achievement of HbA_{1c}<7.0% at week 52 (V54) (yes/no)
- Achievement of HbA_{1c}<7.0% at week 52 (V54) without severe (level 3) or clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) during the prior 12 weeks (yes/no)

- Achievement of HbA_{1c}<7.0% at week 52 (V54) without severe hypoglycaemic episodes (level 3) during the prior 12 weeks (yes/no)
- Achievement of HbA_{1c}≤6.5% at week 52 (V54) (yes/no)
- Achievement of HbA_{1c}≤6.5% at week 52 (V54) without severe (level 3) or clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) during the prior 12 weeks (yes/no)
- Achievement of HbA_{1c}≤6.5% at week 52 (V54) without severe hypoglycaemic episodes (level 3) during the prior 12 weeks (yes/no)
- Achievement of HbA_{1c}<7.0% at week 52 (V54) without body weight gain (yes/no)
- Achievement of HbA_{1c}<7.0% at week 52 (V54) without body weight gain and severe (level 3) or clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) during the prior 12 weeks (yes/no)
- Achievement of HbA_{1c}<7.0% at week 52 (V54) without body weight gain and severe hypoglycaemic episodes (level 3) during the prior 12 weeks (yes/no)
- Achievement of HbA_{1c}≤6.5% at week 52 (V54) without body weight gain (yes/no)
- Achievement of HbA_{1c}≤6.5% at week 52 (V54) without body weight gain and severe (level 3) or clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) during the prior 12 weeks (yes/no)
- Achievement of HbA_{1c}≤6.5% at week 52 (V54) without body weight gain and severe hypoglycaemic episodes (level 3) during the prior 12 weeks (yes/no)

See Appendix 2, section 6.2, for further details.

Missing change in HbA_{1c} at week 52 (V54) and missing change in body weight at week 52 (V54) will be imputed in the same way as for the primary analysis (step 1 in section 4.2.2), substituting body weight for HbA_{1c} when imputing missing body weight assessments, before deriving the dichotomous outcome. Participants who discontinue randomised treatment will have the dichotomous outcome also evaluating hypoglycaemia set to 'no'. For each of the 1000 complete data sets, the derivation will be analysed using a logistic regression model with 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.[4]

4.6.1.3 Self-measured plasma glucose (SMPG)

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

4.6.1.4 Antidiabetic background medication

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

4.6.2 Pharmacokinetic modelling

Insulin icodec serum concentration data and semaglutide plasma concentration data will be used for population PK analysis. The objective of the population PK analysis is to evaluate the effects of relevant covariates on insulin icodec and semaglutide exposure.

The population PK analysis will be performed by Quantitative Clinical Pharmacology, Novo Nordisk. A more technical and detailed elaboration of the population PK analysis will be given in a modelling analysis plan, which will be prepared before database lock. In brief, previously developed PK models for insulin icodec and semaglutide will be applied. The absorption rate constants in the models will be fixed, and the apparent clearance and volume of distribution parameters will be re-estimated. The covariates of interest will be incorporated into the PK models using criteria which will be specified in the modelling analysis plan.

The population PK analysis will be reported in a separate modelling report, which will not be part of the clinical study report. The individual insulin icodec serum concentration data and the individual semaglutide plasma concentration data will be tabulated in the bioanalytical report.

4.7 Interim Analysis

Not applicable for this study.

4.8 Changes to Protocol-planned Analysis

There are no changes to the protocol-planned analysis.

4.9 Partial database lock

A partial database lock may be performed at the end of the treatment period for all participants, i.e. after the date of the last participant last treatment visit. The database will be updated after the partial database lock to include remaining safety information. The full database lock will be performed after the date of the last participant last visit.

The analysis of the primary endpoint and all other efficacy endpoints will be performed based on the data from the partial database lock. Analysis of safety data will be performed after the full database lock. This approach is implemented to allow earlier availability of IcoSema to a T2D patient population in need of treatment intensification expected to benefit from an insulin and GLP-1 combination product. A detailed plan for data handling and operational aspects of the partial database lock and the database update will be finalised before the partial database lock.

5 Sample size determination

Please see the protocol section 9.5.

6 Supporting Documentation

6.1 Appendix 1: List of abbreviations

AE	Adverse event
ANCOVA	Analysis of covariance
BG	Blood glucose
CGM	Continuous glucose monitoring
FPG	Fasting plasma glucose
ICE	Intercurrent event
MMRM	Mixed-effect model for repeated measurements
OAD	Oral anti-diabetic drug
PK	Pharmacokinetic
SAP	Statistical analysis plan
SMPG	Self-measured plasma glucose
T2D	Type 2 diabetes mellitus

6.2 Appendix 2: Definition and calculation of endpoints, assessments and derivations

Type	Title	Time frame	Unit	Details
Primary endpoint	Change in HbA_{1c}	From baseline week 0 (V2) to week 52	%-point	The HbA_{1c} value at baseline week 0 subtracted from the HbA_{1c} value at week 52.
Supportive secondary efficacy endpoint	Change in body weight	From baseline week 0 (V2) to week 52 (V54)	Kg	The body weight value at baseline week 0 subtracted from the body weight value at week 52.
Supportive secondary efficacy endpoint	Change in fasting plasma glucose (FPG)	From baseline week 0 (V2) to week 52 (V54)	mmol/L	The FPG value at baseline week 0 subtracted from the FPG value at week 52.
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 57 (V56)	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 clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter)	From baseline week 0 (V2) to week 57 (V56)	Number of 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 severe hypoglycaemic episodes (level 3)	From baseline week 0 (V2) to week 57 (V56)	Number of episodes	The count of all severe hypoglycaemic episodes (level 3) within the time frame.

Derivation	Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) or severe hypoglycaemic episodes (level 3)	From baseline week 0 (V2) to week 52 (V54)	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 clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter)	From baseline week 0 (V2) to week 52 (V54)	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.
Derivation	Number of severe hypoglycaemic episodes (level 3)	From baseline week 0 (V2) to week 52 (V54)	Number of episodes	The count of all severe hypoglycaemic episodes (level 3) within the time frame.
Derivation	Number of nocturnal clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) or nocturnal severe hypoglycaemic episodes (level 3)	From baseline week 0 (V2) to week 57 (V56)	Number of episodes	Nocturnal hypoglycaemic episodes: episodes occurring between 00:01 and 05:59 both inclusive.
Derivation	Number of nocturnal clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter)	From baseline week 0 (V2) to week 57 (V56)	Number of episodes	Nocturnal hypoglycaemic episodes: episodes occurring between 00:01 and 05:59 both inclusive.
Derivation	Number of nocturnal severe hypoglycaemic episodes (level 3)	From baseline week 0 (V2) to week 57 (V56)	Number of episodes	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 (V54)	Count of subject	Dichotomous outcome variable: *Yes*: Participant achieved HbA_{1c} <7.0% *No*: Participant 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 (V54)	Count of subject	Dichotomous outcome variable: *Yes*: Participant achieved HbA_{1c} <7.0% without severe or clinically significant hypoglycaemic episodes during the prior 12 weeks

				No: Participant did not achieve HbA1c <7.0% **or** participant had a severe or clinically significant hypoglycaemic episode during the prior 12 weeks **or** participant had discontinued randomised treatment 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 (V54)	Count of subject	Dichotomous outcome variable: *Yes*: Participant achieved HbA_{1c} <7.0% without severe hypoglycaemic episodes during the prior 12 weeks *No*: Participant did not achieve HbA_{1c} <7.0% **or** participant had a severe hypoglycaemic episode during the prior 12 weeks **or** participant had discontinued randomised treatment 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% (yes/no)	At week 52 (V54)	Count of subject	Dichotomous outcome variable: *Yes*: Participant achieved HbA_{1c} ≤6.5% *No*: Participant 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 (V54)	Count of subject	Dichotomous outcome variable: *Yes*: Participant achieved HbA_{1c} ≤6.5% without severe or clinically significant hypoglycaemic episodes during the prior 12 weeks *No*: Participant did not achieve HbA1c ≤6.5% **or** participant had a severe or clinically significant hypoglycaemic episode during the prior 12 weeks **or** participant had discontinued randomised treatment 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 (V54)	Count of subject	Dichotomous outcome variable: *Yes*: Participant achieved HbA_{1c} ≤6.5% without severe hypoglycaemic episodes during the prior 12 weeks *No*: Participant did not achieve HbA_{1c} ≤6.5% **or** participant had a severe hypoglycaemic episode during the prior 12 weeks **or** participant had discontinued randomised treatment 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 body weight gain (yes/no)	At week 52 (V54)	Count of subject	Dichotomous outcome variable: *Yes*: Participant achieved HbA_{1c} <7.0% and change in body weight from baseline week 0 to week 52 ≤ 0 kg *No*: Participant did not achieve HbA_{1c} <7.0% **or** participant had a change in body weight from baseline week 0 to week 52 > 0 kg Missing HbA_{1c} data at 52 weeks will be imputed in the same way as in the primary analysis and missing body weight data will be imputed in the same way as in analysis of body weight before deriving the dichotomous outcome.
Derivation	Achievement of HbA_{1c}<7.0% without body weight gain and 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 (V54)	Count of subject	Dichotomous outcome variable: *Yes*: Participant achieved HbA_{1c} <7.0% without severe or clinically significant hypoglycaemic episodes during the prior 12 weeks and change in body weight from baseline week 0 to week 52 ≤ 0 kg *No*: Participant did not achieve HbA1c <7.0% **or** participant had a severe or clinically significant hypoglycaemic episode during the prior 12 weeks **or** participant had discontinued randomised treatment **or** participant had a change in body weight from baseline week 0 to week 52 > 0 kg

				Missing HbA_{1c} data at 52 weeks will be imputed in the same way as in the primary analysis and missing body weight data will be imputed in the same way as in analysis of body weight before deriving the dichotomous outcome.
Derivation	Achievement of HbA_{1c}<7.0% without body weight gain and severe hypoglycaemic episodes (level 3) during the prior 12 weeks (yes/no)	At week 52 (V54)	Count of subject	Dichotomous outcome variable: *Yes*: Participant achieved HbA_{1c} <7.0% without severe hypoglycaemic episodes during the prior 12 weeks and change in body weight from baseline week 0 to week 52 ≤ 0 kg *No*: Participant did not achieve HbA_{1c} <7.0% **or** participant had a severe hypoglycaemic episode during the prior 12 weeks **or** participant had discontinued randomised treatment **or** participant had a change in body weight from baseline week 0 to week 52 > 0 kg Missing HbA_{1c} data at 52 weeks will be imputed in the same way as in the primary analysis and missing body weight data will be imputed in the same way as in analysis of body weight before deriving the dichotomous outcome.
Derivation	Achievement of HbA_{1c}≤6.5% without body weight gain (yes/no)	At week 52 (V54)	Count of subject	Dichotomous outcome variable: *Yes*: Participant achieved HbA_{1c} ≤6.5% and change in body weight from baseline week 0 to week 52 ≤ 0 kg *No*: Participant did not achieve HbA_{1c} ≤6.5% **or** participant had a change in body weight from baseline week 0 to week 52 > 0 kg Missing HbA_{1c} data at 52 weeks will be imputed in the same way as in the primary analysis and missing body weight data will be imputed in the same way as in analysis of body weight before deriving the dichotomous outcome.

Derivation	Achievement of HbA_{1c}≤6.5% without body weight gain and 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 (V54)	Count of subject	Dichotomous outcome variable: *Yes*: Participant achieved HbA_{1c} ≤6.5% without severe or clinically significant hypoglycaemic episodes during the prior 12 weeks and change in body weight from baseline week 0 to week 52 ≤ 0 kg *No*: Participant did not achieve HbA1c ≤6.5% **or** participant had a severe or clinically significant hypoglycaemic episode during the prior 12 weeks **or** participant had discontinued randomised treatment **or** participant had a change in body weight from baseline week 0 to week 52 > 0 kg Missing HbA_{1c} data at 52 weeks will be imputed in the same way as in the primary analysis and missing body weight data will be imputed in the same way as in analysis of body weight before deriving the dichotomous outcome.
Derivation	Achievement of HbA_{1c}≤6.5% without body weight gain and severe hypoglycaemic episodes (level 3) during the prior 12 weeks (yes/no)	At week 52 (V54)	Count of subject	Dichotomous outcome variable: *Yes*: Participant achieved HbA_{1c} ≤6.5% without severe hypoglycaemic episodes during the prior 12 weeks and change in body weight from baseline week 0 to week 52 ≤ 0 kg *No*: Participant did not achieve HbA_{1c} ≤6.5% **or** participant had a severe hypoglycaemic episode during the prior 12 weeks **or** participant had discontinued randomised treatment **or** participant had a change in body weight from baseline week 0 to week 52 > 0 kg Missing HbA_{1c} data at 52 weeks will be imputed in the same way as in the primary analysis and missing body weight data will be imputed in the same way as in analysis of body weight before deriving the dichotomous outcome.
Derivation	Change in waist circumference	From baseline week 0 (V2) to week 52 (V54)	cm	The waist circumference value at baseline week 0 subtracted from the waist circumference value at week 52.

Derivation	Change in systolic blood pressure	From baseline week 0 (V2) to week 52 (V54)	mmHg	The systolic blood pressure value at baseline week 0 subtracted from the systolic blood pressure value at week 52.
Derivation	Change in diastolic blood pressure	From baseline week 0 (V2) to week 52 (V54)	mmHg	The diastolic blood pressure value at baseline week 0 subtracted from the diastolic blood pressure value at week 52.
Derivation	Change in pulse	From baseline week 0 (V2) to week 52 (V54)	bpm	The pulse value at baseline week 0 subtracted from the pulse value at week 52.
Parameter	Cholesterol	At week 52 (V54)	mmol/L	
Parameter	High density lipoprotein (HDL) cholesterol	At week 52 (V54)	mmol/L	
Parameter	Low density lipoprotein (LDL) cholesterol	At week 52 (V54)	mmol/L	
Parameter	Very low density lipoprotein (VLDL) cholesterol	At week 52 (V54)	mmol/L	
Parameter	Triglycerides	At week 52 (V54)	mmol/L	
Parameter	Free fatty acids	At week 52 (V54)	mmol/L	

6.3 Appendix 3: Attributable intercurrent events

Intercurrent event		**Attributable**
Initiation of non-randomised insulin treatment or additional antidiabetic treatments for more than 2 weeks		Yes
Discontinuation of randomised treatment for any reason	Adverse events possible or probable related to randomised treatment	Yes
	Adverse events not possible or probable related to randomised treatment	No
	Hypoglycaemic episodes	Yes
	Included in the study in violation of the inclusion and/or exclusion criteria	Yes
	Simultaneous use of an approved or non-approved investigational medicinal product in another clinical study	Yes
	Lack of efficacy	Yes
	Withdrawal of consent	Yes
	Pregnancy or intention of becoming pregnant	No
	Other	No

7 References

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