Cover Page for Statistical Analysis Plan

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NCT number	NCT05813912
Sponsor trial ID:	NN1436-4910
Official title of study:	A single arm study investigating the glycaemic control and safety of adding semaglutide to insulin icodec in participants with type 2 diabetes qualifying for treatment intensification.
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Statistical Analysis Plan

A single arm study investigating the glycaemic control and safety of adding semaglutide to insulin icodec in participants with type 2 diabetes qualifying for treatment intensification

Substance: Insulin icodec

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

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Author

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Insulin & Devices

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Version History

This Statistical Analysis Plan (SAP) for study NN1436-4910 is based on the protocol version 3.0 dated 07SEP2023.

SAP Version	Date	Change	Rationale
1.0	30-Aug-2023	Not Applicable	Original version
2.0	12-Sep-2023	Change in Fasting plasma glucose (exploratory endpoint) time frame corrected to "from baseline (defined as time of treatment initiation with insulin icodec and semaglutide (week 26, V28)) to week 34 (V36)" in Table 1-2 and Appendix A	For correctness

List of abbreviations

AE	Adverse event
BG	Blood glucose
CI	Confidence interval
FPG	Fasting plasma glucose
GI	Gastro intestinal
HbA1c	glycated haemoglobin
Kg	Kilograms
LLOQ	Lower limit of quantification
MMRM	Mixed models for repeated measures
SMPG	Self measured plasma glucose
T2D	Type 2 diabetes
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
V	Visit

1. Introduction

This SAP is based on the protocol: A single arm study investigating the glycaemic control and safety of adding semaglutide to insulin icodec in participants with type 2 diabetes qualifying for treatment intensification. Most of the statistical analyses and derivations of endpoints presented in this SAP are identical to those described in the protocol, but some additional details have been added. The changes to protocol-planned statistical analyses are described in section 4.8. The SAP also contains specifications of additional derivations and analyses in Appendix A, section 6 .

1.1 Objectives, endpoints, and estimands

1.1.1 Objectives and endpoints

Table 1-1 Objectives and endpoints

Objective	**Endpoints**		
Primary	**Title**	**Time frame**	**Unit**
To investigate the effect on glycaemic control of intensification of insulin icodec with semaglutide in patients with T2D	Primary		
	Change in HbA_{1c}	From baseline (defined as time of treatment initiation with insulin icodec and semaglutide (week 26, V28)) to week 52 (V54)	%-point
	Supportive secondary		
	Change in mean 7-point SMPG profiles	From baseline (defined as time of treatment initiation with insulin icodec and semaglutide (week 26, V28)) to week 52 (V54)	mmol/L
	Change in mean post-prandial glucose increment (over all meals)	From baseline (defined as time of treatment initiation with insulin icodec and semaglutide (week 26, V28)) to week 52 (V54)	mmol/L
	Change in FPG	From baseline (defined as time of treatment initiation with insulin icodec and semaglutide (week 26, V28)) to week 52 (V54)	mmol/L
Secondary	**Title**	**Time frame**	**Unit**
To investigate the safety of intensification of insulin icodec with semaglutide in patients with T2D	Supportive Secondary		
	Number of severe hypoglycaemic episodes (level 3)	From baseline (defined as time of treatment initiation with insulin icodec and semaglutide (week 26, V28)) to week 57 (V56)	Number of episodes

	Number of clinically significant hypoglycaemic episodes (level 2) (<3.0mmol/L (54 mg/dL), confirmed by BG meter)	From baseline (defined as time of treatment initiation with insulin icodec and semaglutide (week 26, V28)) to week 57 (V56)	Number of episodes
	Number of clinically significant hypoglycaemic episodes (level2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) or severe hypoglycaemic episodes (level 3)	From baseline (defined as time of treatment initiation with insulin icodec and semaglutide (week 26, V28)) to week 57 (V56)	Number of episodes
	Change in body weight	From baseline (defined as time of treatment initiation with insulin icodec and semaglutide (week 26, V28)) to week 52 (V54)	Kg
	Relative change in weekly insulin icodec dose	From the week prior to intensification, week 25 (V27) to week 52 (V54)	U

Abbreviations: BG=blood glucose; FPG=fasting plasma glucose; HbA_{1c}=glycated haemoglobin; kg=kilograms; SMPG=self-measured plasma glucose; T2D=type 2 diabetes mellitus; V=visit

Table 1-2 Exploratory endpoints

Title	Timeframe	Unit
Exploratory		
Change in mean 7-point SMPG profiles	From baseline (defined as time of treatment initiation with insulin icodec and semaglutide (week 26, V28) to week 34 (V36)	mmol/L
Change in mean post-prandial increment (over all meals)	From baseline (defined as time of treatment initiation with insulin icodec and semaglutide (week 26, V28) to week 34 (V36)	mmol/L
Change in Fasting C-peptide	From baseline (defined as time of treatment initiation with insulin icodec and semaglutide (week 26, V28)) to week 52 (V54)	nmol/L
Change in Fasting plasma glucose	From baseline (defined as time of treatment initiation with insulin icodec and semaglutide (week 26, V28)) to week 34 (V36)	mmol/L

Abbreviations: SMPG = self-measured plasma glucose; V=visit

1.1.2 Estimands

Primary estimand : The primary clinical question of interest is : What is the glycaemic control in terms of change in HbA_{1c} 26 weeks after insulin icodec treatment intensification with semaglutide in T2D patients treated with insulin icodec in need for treatment intensification had patients been able to adhere to both treatments and tolerate semaglutide treatment?

The primary estimand is defined with the five attributes as defined in ICH E9(R1) addendum[2]:

- Treatment condition: The treatment regimen evaluated is the intensification of insulin icodec with semaglutide regardless of initiation of bolus insulin treatment for more than 2 weeks. This includes also subjects being treated with lower than planned semaglutide dose, either if never titrated to one of the maintenance doses (0.5 or 1 mg) or if the dose is temporarily or permanently decreased during the study.
- Population: Participants with T2D treated with insulin icodec and qualifying for treatment intensification.
- Endpoint: Change in HbA_{1c} from baseline (defined as time of treatment initiation with insulin icodec and semaglutide (week 26, V28)) to week 52 (V54)
- Remaining intercurrent events:
  The following intercurrent events will be handled by the treatment policy strategy and are captured under treatment condition:
  - Initiation of bolus insulin for more than two weeks
  - Participants take lower than planned semaglutide dose, either if never titrated to one of the maintenance doses (0.5 or 1 mg) or if the dose is temporarily or permanently decreased during the study.

  Apart from above two the following intercurrent events will be handled by the hypothetical strategy:
  - Discontinuation of insulin icodec treatment
  - Discontinuation of semaglutide treatment including discontinuation due to GI side effects.
- Population-level summary: Difference in mean changes between treatment conditions

Supportive secondary estimands :
Supportive secondary estimands related to supportive secondary endpoints have the following attributes. Population attributes are the same as specified for the primary estimand, and endpoint attributes are the corresponding supportive secondary endpoint. Treatment condition attribute and intercurrent events are the same as specified for the primary estimand. Population-level summary attributes would instead be treatment ratio for relative change in mean weekly insulin dose.

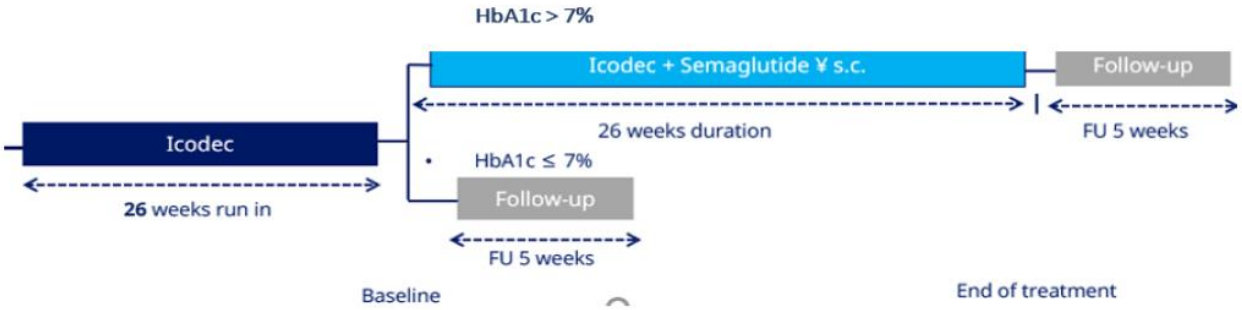
1.2 Study design

This is an interventional, multi-national, multi-centre, treat-to-target, single-arm and open-label study. The study is designed to investigate the glycaemic control of adding semaglutide (s.c.) to insulin icodec in participants with T2D qualifying for intensification. The study is planned to enroll 148 participants.

The study duration is approximately 59 weeks and consists of:
- an up to 2-week screening period
- a 26-week run-in period with insulin icodec
- a 26-week treatment period with insulin icodec and semaglutide
- 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

For the primary estimand with primary endpoint, change from baseline (defined as time of treatment initiation with insulin icodec and semaglutide (week 26, V28)) to week 52 (V54) in HbA_{1c}, the following 1-sided hypothesis will be tested.

Formally, let D be the change from baseline (week 26) to week 52 in HbA_{1c}. The null-hypothesis of no decrease in HbA_{1c} will be tested against the alternative hypothesis of a decrease in HbA_{1c} as given by

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

Operationally the hypothesis will be evaluated by a 2-sided test.

2.1 Multiplicity adjustment

Not applicable for this study.

3. Analysis sets

The following participant analysis sets are defined:

Participant Analysis Set	Description
Full analysis set	• All participants allocated to the intensification phase
Safety analysis set	• All participants who are exposed to investigational intervention (s)

The following data point sets are defined:

Defined data points sets	Description
Run-in-in-study	All observed data during the run-in period: • From the run-in visit (V2) until the day before the intensification visit (V28) for participants continuing for the intensification period. • From the run-in visit (V2) until last participant contact for participants not being assigned to semaglutide treatment at the end of the run-in period or discontinuing insulin icodec treatment during the run-in period.
Run-in-on-treatment	All observed data during the run-in period while on insulin icodec treatment: • From the first dose of insulin icodec until the day before the intensification visit (V28) for participants continuing for the intensification period. • All data from the first dose until 6 weeks after last dose of insulin icodec for participants not being assigned to semaglutide treatment at the end of the run in period or discontinuing insulin icodec treatment during the run-in period.
Treatment-phase-in-study	All observed data from time of the intensification visit (V28) until last participant contact.
Treatment-phase-on-treatment	All observed data from time of the intensification visit (V28) until 6 weeks after last date of either insulin icodec or semaglutide treatment (whichever comes last).
On-intensification	Observed data at planned visits from time of the intensification visit (V28) until the end of treatment visit (V54), i.e., for participants who permanently discontinue either insulin icodec or semaglutide treatment, post-discontinuation observations will not be included.

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

The on-treatment data points sets represent data collected in the period in which a participant is considered exposed to assigned treatment(s).

V2 is always included in the run-in-in-study and run-in-on-treatment data point sets.

Information on V28 will be included while presenting descriptive statistics for run-in-in-study and run-in-on-treatment data point sets.

Baseline (V28) is included in the treatment-phase-in-study, treatment-phase-on-treatment, on-intensification data point sets who have treatment initiation of both insulin icodec and semaglutide.

Full analysis set and on-intensification data points set are used for efficacy evaluations and specifically to estimate the primary estimand.

Safety data will be presented separately for run-in-on-treatment and treatment-phase-on-treatment data points sets based on the safety analysis set. SAEs will also be presented based on the safety analysis set and on run-in-in-study and treatment-phase-in-study data points sets, respectively.

4. Statistical Analyses

4.1 General Considerations

Presentation of results from a statistical analysis will include the estimated mean treatment difference (or ratio) presented together with the two-sided 95% confidence interval and the corresponding two-sided p-value. Baseline is defined as the time of treatment intensification with semaglutide (week 26, V28).

The number 14364910 will be used as the seed for all imputations.

4.2 Primary endpoint analysis

4.2.1 Definition of endpoint

The primary endpoint is change in HbA_{1c} from baseline (week 26, V28) to week 52 (V54).

4.2.2 Main analytical approach

The primary endpoint will be analysed by a mixed model for repeated measurements (MMRM) with an unstructured covariance matrix. The model will include visit as fixed factor and baseline HbA_{1c} as a covariate. Interactions between visit and baseline HbA_{1c} will also be included in the model. All post-intensification values obtained at planned visits that are in the on-intensification data points set will be included in the analysis.

4.3 Secondary endpoints analysis

4.3.1 Supportive secondary endpoints

4.3.1.1 Supportive secondary efficacy endpoints

The following endpoints are defined to investigate the efficacy of intensification of insulin icodec with semaglutide in patients with T2D.

- Mean of the 7-point profile, defined as the area under the profile (calculated using the trapezoidal method) divided by the measurement time.
- Mean post-prandial PG increment over all meals will be derived as the mean of all available meal increments (from before meal to 90 min after for breakfast, lunch and dinner/main evening meal).
- Change in FPG from baseline to week 52 (V54)

For derivation of endpoints please see Appendix A, section 6

The secondary efficacy endpoints other than FPG will be analysed by using a model similar to primary analysis except with the corresponding baseline value as covariate. Change in FPG will be presented descriptively.

4.3.1.2 Supportive secondary safety endpoints

The following endpoints are defined to investigate the safety of intensification of insulin icodec with semaglutide in patients with T2D.

- Number of severe hypoglycaemic episodes (level 3) from baseline to week 57 (V56)
- Number of clinically significant hypoglycaemic episodes (level 2) (<3.0mmol/L (54 mg/dL), confirmed by BG meter) from baseline to week 57 (V56)
- 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 to week 57 (V56)
- Change in body weight from baseline to week 52 (V54)
- Relative change in weekly insulin icodec dose from week prior to intensification week 25 (V27) to week 52 (V54)

Supportive secondary safety endpoints related to hypoglycaemic episodes will be summarised descriptively.

Change in body weight from baseline to week 52 (V54) will be analysed using a model similar to primary analysis except with the corresponding baseline value as covariate.

Ratio to baseline of weekly insulin dose at week 52 (V54) will be log-transformed and analysed using the same statistical model as specified for primary analysis except with the corresponding log-transformed baseline value as covariate. The estimated means, estimated difference and the 95% confidence interval will be back-transformed to the original scale resulting in estimated geometric means, ratio and a 95% confidence interval for the ratio to baseline.

4.4 Exploratory endpoints analysis

Ratio to baseline of Fasting C-peptide at week 52 (V54) will be log-transformed and analysed using the same statistical model as specified for the primary analysis but including relevant log-transformed baseline as the covariate. The estimated means, estimated difference and the 95% confidence interval will be back-transformed to the original scale resulting in estimated geometric means, ratio to baseline and a 95% confidence interval for the ratio to baseline.

Other exploratory endpoints will be presented descriptively.

For derivation of endpoints please see Appendix A, section 6

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 Nocturnal hypoglycaemic episodes

Nocturnal hypoglycaemic episodes are hypoglycaemic episodes occurring between 00:01 and 05:59 both inclusive. The following nocturnal hypoglycaemic episodes derivations will be summarised descriptively:

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

- 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 to week 57 (V56)

4.6 Other analyses

4.6.1 Other derivations and assessments

4.6.1.1 Achievement of HbA1c target

The following derivations will be summarised descriptively based on the full analysis set and the on-intensification data points set.

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

See Appendix A, Section 6, for further details.

4.6.1.2 Self-measured plasma glucose (SMPG)

Mean fasting SMPG used for dose adjustment will be summarised by visit for all participants in safety analysis set and the run-in-in-study, treatment-phase-in-study data points sets.

4.7 Interim Analysis

Not applicable for this study.

4.8 Changes to protocol-planned Analysis

In section 3 the statement ‘Baseline (V28) is always included in the treatment-phase-in-study, treatment-phase-on-treatment, on-intensification data point sets’ is updated to ‘Baseline (V28) is always included in the treatment-phase-in-study, treatment-phase-on-treatment, on-intensification data point sets who have treatment initiation of both insulin icodec and semaglutide’.

Fasting C-peptide at week 52 (V54) has been updated to be evaluated as a ratio to baseline. Analysis description of insulin icodec dose and fasting C-peptide has been included and wording of endpoints as well as units is updated to reflect that these analyses are to be analysed on log-scale.

5. Sample size determination

Please see the protocol section 9.5.

6. Supporting documentation

Appendix A : Definition and calculation of endpoints, assessments and derivations

Type	Title	Time frame	Unit	Details
Primary endpoint	Change in HbA_{1c}	From baseline (defined as time of treatment initiation with insulin icodec and semaglutide (week 26, V28)) to week 52 (V54)	%-point	The HbA_{1c} value at baseline week 26 subtracted from the HbA_{1c} value at week 52
Supportive secondary efficacy endpoint	Change in mean 7-point SMPG profiles	From baseline (defined as time of treatment initiation with insulin icodec and semaglutide (week 26, V28)) to week 52 (V54)	mmol/L	The mean of the 7-point SMPG profile is defined as the area under the curve profile divided by the measurement time, and is calculated using the linear trapezoidal technique. The difference of mean value at baseline and week 52 will give the change in mean 7-point SMPG profiles
Supportive secondary efficacy endpoint	Change in mean post-prandial glucose increment (over all meals)	From baseline (defined as time of treatment initiation with insulin icodec and semaglutide (week 26, V28)) to week 52 (V54)	mmol/L	Post-prandial PG increment for each meal (breakfast, lunch, main evening meal) will be derived from the 7-point SMPG profile as the difference between PPG values and the PG value before meal in each separate profile. The mean of the derived increments will then be calculated separately for each meal. Then the mean over all meals will be derived as mean of all corresponding mean meal increments. The difference of mean value at baseline and week 52 will give the change in mean post-prandial glucose increment (over all meals)
Supportive secondary efficacy endpoint	Change in FPG	From baseline (defined as time of treatment initiation with insulin icodec and semaglutide (week 26, V28)) to week 52 (V54)	mmol/L	The FPG value at baseline week 26 subtracted from the FPG value at week 52
Supportive secondary safety endpoint	Number of severe hypoglycaemic episodes (level 3)	From baseline (defined as time of treatment initiation with insulin icodec and semaglutide (week 26, V28)) to week 57 (V56)	Number of episodes	The count of all severe hypoglycaemic episodes (level 3) within the time frame.

Type	Title	Time frame	Unit	Details
Supportive secondary safety endpoint	Number of clinically significant hypoglycaemic episodes (level 2) (<3.0mmol/L (54 mg/dL), confirmed by BG meter)	From baseline (defined as time of treatment initiation with insulin icodec and semaglutide (week 26, V28)) 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 clinically significant hypoglycaemic episodes (level2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) or severe hypoglycaemic episodes (level 3)	From baseline (defined as time of treatment initiation with insulin icodec and semaglutide (week 26, V28)) 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	Change in body weight	From baseline (defined as time of treatment initiation with insulin icodec and semaglutide (week 26, V28)) to week 52 (V54)	Kg	The body weight value at baseline week 26 subtracted from the body weight value at week 52
Supportive secondary safety endpoint	Relative change in weekly insulin icodec dose	From the week prior to intensification, week 25 (V27) to week 52 (V54)	Ratio to baseline	Weekly insulin icodec dose value at initiation week 26 and at week 52 will be log-transformed and then the treatment difference would be calculated which will then again be back-transformed to get ratio to baseline measure.
Exploratory endpoint	Change in mean 7-point SMPG profiles	From baseline (defined as time of treatment initiation with insulin icodec and semaglutide (week 26, V28) to week 34 (V36)	mmol/L	The mean of the 7-point SMPG profile is defined as the area under the curve profile divided by the measurement time, and is calculated using the linear trapezoidal technique. The difference of mean value at baseline and week 34 will give the change in mean 7-point SMPG profiles.

Type	Title	Time frame	Unit	Details
Exploratory endpoint	Change in mean post-prandial increment (over all meals)	From baseline (defined as time of treatment initiation with insulin icodec and semaglutide (week 26, V28) to week 34 (V36)	mmol/L	Post-prandial PG increment for each meal (breakfast, lunch, main evening meal) will be derived from the 7-point SMPG profile as the difference between PPG values and the PG value before meal in each separate profile. The mean of the derived increments will then be calculated separately for each meal. Then the mean over all meals will be derived as mean of all corresponding mean meal increments. The difference of mean value at baseline and week 34 will give the change in mean post-prandial glucose increment (over all meals)
Exploratory endpoint	Relative change in Fasting C-peptide	From baseline (defined as time of treatment initiation with insulin icodec and semaglutide (week 26, V28)) to week 52 (V54)	Ratio to baseline	The fasting C-peptide value at initiation week 26 as well as fasting C-peptide value at week 52 will be log-transformed and then the treatment difference would be calculated which will then again be back-transformed to get ratio to baseline measure.
Exploratory endpoint	Change in Fasting plasma glucose	From baseline (defined as time of treatment initiation with insulin icodec and semaglutide (week 26, V28)) to week 34 (V36)	mmol/L	The FPG value at initiation week 26 subtracted from the FPG value at week 34
Derivation	Number of nocturnal severe hypoglycaemic episodes (level 3)	From baseline (defined as time of treatment initiation with insulin icodec and semaglutide (week 26, V28)) 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 (defined as time of treatment initiation with insulin icodec and semaglutide (week 26, V28)) 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) or nocturnal severe hypoglycaemic episodes (level 3)	From baseline (defined as time of treatment initiation with insulin icodec and semaglutide (week 26, V28)) to week 57 (V56)	Number of episodes	Nocturnal hypoglycaemic episodes: episodes occurring between 00:01 and 05:59 both inclusive.

Type	Title	Time frame	Unit	Details
Derivation	Number of nocturnal severe hypoglycaemic episodes (level 3)	From baseline (defined as time of treatment initiation with insulin icodec and semaglutide (week 26, V28)) 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 (defined as time of treatment initiation with insulin icodec and semaglutide (week 26, V28)) 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) or nocturnal severe hypoglycaemic episodes (level 3)	From baseline (defined as time of treatment initiation with insulin icodec and semaglutide (week 26, V28)) 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% (yes/no)	Week 52 (V54)	Count of participant	Dichotomous outcome variable: Yes: participant achieved HbA_{1c} <7% after 52 weeks No: participant did not achieve HbA_{1c} <7% after 52 weeks
Derivation	Achievement of HbA1c<7% without severe (level 3) or clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) during the prior 12 weeks (yes/no)	Week 52 (V54)	Count of participant	Dichotomous outcome variable: Yes: participant achieved HbA_{1c} <7% after 52 weeks without severe or clinically significant hypoglycaemic episodes during the prior 12 weeks No: participant did not achieve HbA_{1c} <7% after 52 weeks **or** participant had a severe or clinically significant hypoglycaemic episode during the prior 12 weeks **or** participant discontinued randomised treatment prematurely
Derivation	Achievement of HbA1c<7% without severe hypoglycaemic episodes (level 3) during the prior 12 weeks (yes/no)	Week 52 (V54)	Count of participant	Dichotomous outcome variable: Yes: participant achieved HbA_{1c} < 7% after 52 weeks without severe hypoglycaemic episodes during the prior 12 weeks No: participant did not achieve HbA_{1c} <7% after 52 weeks **or**

Type	Title	Time frame	Unit	Details
				participant had a severe hypoglycaemic episode during the prior 12 weeks **or** participant discontinued randomised treatment prematurely
Derivation	Achievement of HbA1c≤6.5% (yes/no)	Week 52 (V54)	Count of participant	Dichotomous outcome variable: Yes: participant achieved HbA_{1c} ≤6.5% after 52 weeks No: participant did not achieve HbA_{1c} ≤6.5% after 52 weeks
Derivation	Achievement of HbA1c≤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)	Week 52 (V54)	Count of participant	Dichotomous outcome variable: Yes: participant achieved HbA_{1c} ≤6.5% after 52 weeks without severe or clinically significant hypoglycaemic episodes during the prior 12 weeks No: participant did not achieve HbA_{1c} ≤6.5% after 52 weeks **or** participant had a severe or clinically significant hypoglycaemic episode during the prior 12 weeks **or** participant discontinued randomised treatment prematurely
Derivation	Achievement of HbA1c≤6.5% without severe hypoglycaemic episodes (level 3) during the prior 12 weeks (yes/no)	Week 52 (V54)	Count of participant	Dichotomous outcome variable: Yes: participant achieved HbA_{1c} ≤6.5% after 52 weeks without severe hypoglycaemic episodes during the prior 12 weeks No: participant did not achieve HbA_{1c} ≤6.5% after 52 weeks **or** participant had a severe hypoglycaemic episode during the prior 12 weeks **or** participant discontinued randomised treatment prematurely

7. References

1. Food and Drug Administration, CDER. Guidance for Industry. Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention, Draft Guidance. February 2008.
2. European Medicines Agency. ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials. Step 5 (EMA/CHMP/ICH/436221/2017). 17 Feb 2020.