Cover Page for Statistical Analysis Plan

Sponsor name:	Novo Nordisk A/S
NCT number	NCT05514535
Sponsor trial ID:	NN9535-4801
Official title of study:	Efficacy and safety of once-weekly semaglutide s.c. 2.0 mg as add-on to dose-reduced insulin glargine vs titrated insulin glargine in participants with type 2 diabetes and overweight
Document date:	12-March-2025

Statistical Analysis Plan

Efficacy and safety of once-weekly semaglutide s.c. 2.0 mg as add-on to dose-reduced insulin glargine vs titrated insulin glargine in participants with type 2 diabetes and overweight

Substance: *Semaglutide*

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Version History

This Statistical Analysis Plan (SAP) for study NN9535-4801 is based on the protocol Efficacy and safety of once-weekly semaglutide s.c. 2.0 mg as add-on to dose-reduced insulin glargine vs titrated insulin glargine in participants with type 2 diabetes and overweight version 5.0 dated 22DEC2023.

SAP Version	Date	Change	Rationale
3.0	12MAR2025	Section 4.3 and 4.6	To provide further clarification on which data should be considered for the baseline, for end of treatment and for the analysis for the endpoints relative change in daily insulin dose, DTSQc, SF-36 and CGM.
2.0	24JAN2024	Section 4.6	To update the CGM endpoints in 'Other Analysis' section to align with updated CGM endpoint catalogue and align with latest version (version 5.0) of protocol
1.0	24AUG2022	Not Applicable	Original version

Overall rationale for preparing SAP, version 3.0

The overall rationale for the changes implemented in the amended SAP is to provide the detailed clarification on the data to be used for endpoint analysis in terms of baseline and end of treatment consideration.

Section # and name	Description of change	Brief rationale
Section 4.3 Secondary Endpoints Analysis	• Baseline consideration for Relative change in daily insulin dose and data to consider for insulin dose 0U are provided (Section 4.3.1.2, 4.3.1.3 and 4.3.2.1). • Maximum visit window days for DTSQc provided (Section 4.3.1.2 and 4.3.1.3). • Analysis requirement along with range of scores mentioned in detail for SF-36 endpoint (Section 4.3.2.3).	To clarify which data should be considered as the baseline and ensure that no data is lost.
Section 4.6 Other Analysis	• CGM baseline consideration updated (Section 4.6.1). • Detailed description on Subgroup analysis provided (Section 4.6.2).	To provide detailed description on requirement.

List of abbreviations

AE	*adverse event*
ANCOVA	*analysis of covariance*
BG	*blood glucose*
BMI	*body mass index*
CGM	*continuous glucose monitoring*
CI	*confidence interval*
CV	*cardiovascular/ coefficient of variation*
DBL	*database lock*
DMC	*data monitoring committee*
DTSQc	*Diabètes Treatment Satisfaction Questionnaire – change*
DTSQs	*Diabètes Treatment Satisfaction Questionnaire – status*
EMA	*European Medicines Agency*
FDA	*US Food and Drug Administration*
FPG	*fasting plasma glucose*
GFR	*Glomerular Filtration Rate*
HDL	*High Density Lipoprotein*
ICH	*International Council on Harmonization*
LDL	*Low Density Lipoprotein*
LPLT	*last participant last treatment*
MAGE	*mean amplitude of glycemic excursion*
MAR	*missing at random*
MedDRA	*medical dictionary for regulatory activities*
OW	*Once Weekly*
PRO	*Patient report outcome*

SAE	*serious adverse event*
SAP	*Statistical Analysis Plan*
SMQs	*standardized MedDRA queries*
TFL	*tables, figures and listings*

1 Introduction

This SAP covers specification of the statistical analyses for data on efficacy.

There are no changes to the analyses described in the protocol.

Specifications of tables, figures, and listings (TFL) and other specifications not included in this SAP will be described in the mock TFL.

1.1 Objectives, Endpoints, and Estimands

In this section 'dose-reduced insulin glargine U100' and 'titrated insulin glargine U100' refer to algorithms for dose modification as described in Section 6.5 of the protocol.

The objectives and endpoints are presented in Table 1-1.

Table 1-1 Objectives and endpoints

Objectives	**Endpoints**		
Primary	Title	Time frame	Unit
To confirm that efficacy as measured by change from baseline to week 40 in HbA1c (%-point) of OW semaglutide s.c. 2.0 mg as add-on to dose-reduced insulin glargine U100 is not unacceptably worse (i.e., non-inferior) to that of titrated insulin glargine U100 on change from baseline to week 40 in HbA_{1c} (%-point) in participants with T2D and overweight treated with 40 units or less of insulin glargine per day. Non-inferiority is assessed based on the clinically acceptable margin of 0.3%-point for the mean treatment difference in HbA_{1c}.	Primary		
	Change in HbA_{1c}	From baseline (week 0) to end of treatment (week 40)	%-point
Secondary	Title	Time frame	Unit
To confirm superiority of OW semaglutide s.c. 2.0 mg as add-on to dose-reduced insulin glargine U100 versus titrated insulin glargine U100 on change from baseline to week 40 in body weight (kg) in participants with T2D and overweight treated with 40 units or less of insulin glargine per day.	Confirmatory		
	Change in body weight	From baseline (week 0) to end of treatment (week 40)	Kg
To confirm superiority of OW semaglutide s.c. 2.0 mg as add-on to dose-reduced insulin glargine U100 versus titrated insulin glargine U100 on relative change from baseline to week 40 in daily insulin dose (%) in participants with T2D and overweight treated with 40 units or less of insulin glargine per day.	Confirmatory		
	Relative change in daily insulin dose	From baseline (week 0) to end of treatment (week 40)	%
	Confirmatory		

Objectives	**Endpoints**		
To confirm superiority of OW semaglutide s.c. 2.0 mg as add-on to dose-reduced insulin glargine U100 versus titrated insulin glargine U100 on change from baseline to week 40 in HbA_{1c} (%-point) in participants with T2D and overweight treated with 40 units or less of insulin glargine per day.	Change in HbA_{1c}	From baseline (week 0) to end of treatment (week 40)	%-point
To confirm superiority of OW semaglutide s.c. 2.0 mg as add-on to dose-reduced insulin glargine U100 versus titrated insulin glargine U100 on change from baseline to week 40 in DTSQc score in participants with T2D and overweight treated with 40 units or less of insulin glargine per day.	Confirmatory		
	Score of Diabetes Treatment Satisfaction Questionnaire – change version (DTSQc)	At end of treatment (week 40)	Score points (range -18 to +18)
To compare the effect of OW semaglutide s.c. 2.0 mg as add-on to dose-reduced insulin glargine U100 versus titrated insulin glargine U100 on insulin requirements, glycaemic control, hypoglycaemia, and patient reported outcome in participants with T2D and overweight treated with 40 units or less of insulin glargine per day.	Supportive		
	Participants achieving: Insulin dose = 0U	At end of treatment (week 40)	Y/N
	Participants achieving: Insulin dose reduced from baseline by at least 50%	At end of treatment (week 40)	Y/N
	Participants achieving: HbA_{1c} < 7%	At end of treatment (week 40)	Y/N
	Number of severe hypoglycaemic episodes (level 3)	From baseline (week 0) to end of treatment (week 40)	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) to end of treatment (week 40)	Number of episodes
	Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) or severe hypoglycaemic episodes (level 3)	From baseline (week 0) to end of treatment (week 40)	Number of episodes
	Participants achieving all of the following targets: HbA_{1c} reduced from baseline by at least 0.3%-points Insulin dose reduced from baseline No hypoglycaemic episodes (< 3.9 mmol/L (70 mg/dL) confirmed by BG meter) No weight gain	At end of treatment (week 40)	Y/N
	Change in score of Diabetes Treatment Satisfaction Questionnaire – status version (DTSQs)	From baseline (week 0) to end of treatment (week 40)	Score points (range: 0 to 36)

Objectives	Endpoints		
	Change in score of Short Form 36 version 2 (SF-36 v2)	From baseline (week 0) to end of treatment (week 40)	Score points

Notes: [a] Hypoglycaemia events collected in the eDiary.

Abbreviations: BG = blood glucose; OW = once-weekly; s.c. = subcutaneous; T2D = type 2 diabetes.

1.1.1 Estimands

The estimands and their rationale are described in detail for each of the confirmatory objectives in Sections 1.1.1.1 and 1.1.1.2. The estimands account for the following intercurrent events:

- premature treatment discontinuation for any reason (adverse event (AE) or other)
- change in background medication.

1.1.1.1 Addressing the primary objective

1.1.1.1.1 Primary estimand

For participants with T2D and overweight who are treated with 40 units or less of basal insulin , the primary clinical question is concerned with evaluating efficacy as measured by change from baseline in HbA_{1c} between the two treatment regimens:

- Once-weekly semaglutide s.c. 2.0 mg as add-on to dose-reduced insulin glargine U100 as per treatment guideline (see Section 10.7 of the protocol).
- Titrated insulin glargine U100 as per the titration guideline (see Section 10.7 of the protocol).

The two treatment regimens are compared based on non-inferiority testing (margin 0.3%-points) irrespective of premature treatment discontinuation and/or change in background medication. Titration of insulin glargine U100 will be guided by the titration guidelines and adjusted as required per investigator discretion.

A non-inferiority margin of 0.3%-point for the HbA_{1c} treatment difference is judged as being a clinical acceptable loss of efficacy versus titrated insulin glargine U100 in context of expected benefits in terms of a greater weight loss. This is supported by the fact that insulin glargine is a well-established comparator that has extensively evaluated in superiority studies. Furthermore, titration of insulin been glargine U100 is expected to result in at least 0.5%-points improvement in HbA_{1c}, justifying the smaller margin of 0.3%-point specified as threshold for the primary objective in this study.[1-3]

The primary estimand is defined by the following five attributes as defined in ICH E9(R1)[4]:

- Population: Participants with T2D and overweight.
- Endpoint: Change from baseline to week 40 in HbA_{1c} (%-point).
- Treatment condition: OW semaglutide s.c. 2.0 mg as add-on to dose-reduced insulin glargine U100 or titrated insulin glargine U100 for up to 40 weeks with or without change in background medication.

- Remaining intercurrent events: No further intercurrent events are identified. The intercurrent events described as part of the treatment condition will all implicitly be handled by a treatment policy strategy.
- Population-level summary: Difference in mean changes between randomised treatment groups.

Rationale for estimand: This estimand quantifies the difference in treatment effects between the two different treatment regimens that can be expected in practice. It reflects the clinical practice, under which the treatment regimens are to be applied.

1.1.1.1.2 Additional estimand

An additional question of interest for the primary objective is concerned with evaluating the two treatment regimens as described under the primary estimand, had participants remained on treatment irrespective of change in background medication. The estimand attributes: population, endpoint, and population-level summary are the same as for the primary estimand. The remaining estimand attributes are:

- Treatment condition: OW semaglutide s.c. 2.0 mg as add-on to dose-reduced insulin glargine U100 or titrated insulin glargine U100 for the planned treatment duration of 40 weeks with or without change in background medication.
- Remaining intercurrent events: The intercurrent event of 'randomised treatment discontinuation for any reason' will be handled by a hypothetical strategy. The intercurrent event of 'change in background medication' will implicitly be handled by a treatment policy strategy.

Rationale for estimand: This estimand quantifies the achievable difference in treatment effects between the two different treatment regimens. It reflects the drug efficacy.

1.1.1.2 Addressing the secondary objectives

1.1.1.2.1 Change in body weight (kg)

The main clinical question of interest for this secondary confirmatory objective is to evaluate whether the treatment regimen described under the primary estimand with OW semaglutide s.c. 2.0 mg as add-on to dose-reduced insulin glargine U100 is superior to titrated insulin glargine U100 in terms of change from baseline in body weight (kg).

The estimand attributes: population, treatment condition, remaining intercurrent events, and population-level summary are the same as for the primary estimand. The remaining estimand attribute is:

- Endpoint: Change from baseline to week 40 in body weight (kg).

Rationale for estimand: The rationale is the same as for the primary estimand.

1.1.1.2.2 Change in body weight (kg) – Additional

An additional clinical question of interest for this secondary confirmatory objective is concerned with evaluating whether the treatment regimen described under the additional estimand for primary

objective with OW semaglutide s.c. 2.0 mg as add-on to dose-reduced insulin glargine U100 is superior to titrated insulin glargine in terms of change from baseline in body weight (kg).

The estimand attributes: population, treatment condition, remaining intercurrent events, and population-level summary are the same as for the additional estimand for the primary objective. The remaining estimand attribute is:

- Endpoint: Change from baseline to week 40 in body weight (kg).

Rationale for estimand: The rationale is the same as for the additional estimand for the primary objective.

1.1.1.2.3 Relative change in daily insulin dose (%)

The main clinical question of interest for this secondary confirmatory objective is to evaluate whether the treatment regimen described under the primary estimand with OW semaglutide s.c. 2.0 mg as add-on to dose-reduced insulin glargine U100 is superior to titrated insulin glargine U100 in terms of relative change from baseline in daily insulin dose.

The estimand attributes: population, treatment condition, and remaining intercurrent events are the same as for the primary estimand. The remaining estimand attributes are:

- Endpoint: Relative change from baseline to week 40 in daily insulin dose (%).
- Population level summary: Difference in mean relative changes between randomised treatment groups.

Rationale for estimand: The rationale is the same as for the primary estimand.

1.1.1.2.4 Relative change in daily insulin dose (%) – Additional

An additional clinical question of interest for this secondary confirmatory objective is concerned with evaluating whether the treatment regimen described under the additional estimand for the primary objective with OW semaglutide s.c. 2.0 mg as add-on to dose-reduced insulin glargine U100 is superior to titrated insulin glargine U100 in terms of relative change from baseline in daily insulin dose.

The estimand attributes: population, treatment condition, and remaining intercurrent events are the same as for the additional estimand for the primary objective. The remaining estimand attributes are:

- Endpoint: Relative change from baseline to week 40 in daily insulin dose (%).
- Population level summary: Difference in mean relative changes between randomised treatment groups.

Rationale for estimand: The rationale is the same as for the additional estimand for the primary objective.

1.1.1.2.5 Change in HbA_{1c} (%-point)

The main clinical question of interest for this secondary confirmatory objective is to evaluate whether the treatment regimen described under the primary estimand with OW semaglutide s.c. 2.0 mg as add-on to dose-reduced insulin glargine U100 is superior to titrated insulin glargine U100 in terms of change from baseline in HbA_{1c}.

The estimand attributes are the same as for the primary estimand.

Rationale for estimand: The rationale is the same as for the primary estimand.

1.1.1.2.6 Change in HbA_{1c} (%-point) – Additional

An additional clinical question of interest for this secondary confirmatory objective is concerned with evaluating whether the treatment regimen described under the additional estimand for the primary objective with OW semaglutide s.c. 2.0 mg as add-on to dose-reduced insulin glargine U100 is superior to titrated insulin glargine U100 in terms of change from baseline in HbA_{1c}.

The estimand attributes are the same as for the additional estimand for the primary objective.

Rationale for estimand: The rationale is the same as for the additional estimand for the primary objective.

1.1.1.2.7 DTSQc (score)

The main clinical question of interest for this secondary confirmatory objective is to evaluate whether the treatment regimen described under the primary estimand with OW semaglutide s.c. 2.0 mg as add-on to dose-reduced insulin glargine U100 is superior to titrated insulin glargine U100 in terms of participant satisfaction.

The estimand attributes: population, treatment condition, and remaining intercurrent events are the same as for the primary estimand. The remaining estimand attributes are:

- Endpoint: Diabetes Treatment Satisfaction Questionnaire - change version (DTSQc) score at week 40.
- Population level summary: Difference in mean score between randomised treatment groups.

Rationale for estimand: The rationale is the same as for the primary estimand.

1.1.1.2.8 DTSQc (score) – Additional

An additional clinical question of interest for this secondary confirmatory objective is concerned with evaluating whether the treatment regimen described under the additional estimand for primary objective with OW semaglutide s.c. 2.0 mg as add-on to dose-reduced insulin glargine U100 is superior to titrated insulin glargine U100 in terms participant satisfaction.

The estimand attributes: population, treatment condition, and remaining intercurrent events are the same as for the additional estimand for the primary objective. The remaining estimand attributes are:

- Endpoint: DTSQc score at week 40.
- Population level summary: Difference in mean score between randomised treatment groups.

Rationale for estimand: The rationale is the same as for the additional estimand for the primary objective.

1.1.1.2.9 Supportive Secondary endpoints

All supportive secondary endpoints will employ primary estimand as described for the primary endpoints. The clinical question of interest for these supportive secondary objectives is to compare the effect of OW semaglutide s.c. 2.0 mg as add-on to dose-reduced insulin glargine U100 versus titrated insulin glargine U100 on insulin requirements, glycaemic control, hypoglycaemia, and patient reported outcome in participants with T2D and overweight treated with 40 units or less of insulin glargine per day (Table 1-1).

The estimand attributes: population, treatment condition, and remaining intercurrent events are the same as for the primary estimand for the primary objective. The remaining estimand attributes - endpoints and the population level summary are as given in Table 1-2.

Table 1-2 Endpoints and population-level summary- Supportive endpoints

Endpoints	Unit	Population level summary measures
Participants achieving: • Insulin dose = 0 U	Y/N	Odds ratio between randomised treatment groups
Participants achieving: • Insulin dose reduced from baseline by at least 50%	Y/N	Odds ratio between randomised treatment groups
Participants achieving: • HbA1c < 7%	Y/N	Odds ratio between randomised treatment groups
Number of severe hypoglycaemic episodes (level 3)	Number of episodes	Rate ratio between randomised treatment groups
Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL) confirmed by BG meter)	Number of episodes	Rate ratio between randomised treatment groups
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)	Number of episodes	Rate ratio between randomised treatment groups
Participants achieving all of the following targets: • HbA_{1c} reduced from baseline by at least 0.3%-points • Insulin dose reduced from baseline • No hypoglycaemic episodes (< 3.9 mmol/L (70 mg/dL) confirmed	Y/N	Odds ratio between randomised treatment groups

Endpoints	Unit	Population level summary measures
by BG meter) • No weight gain		
Change in score of Diabetes Treatment Satisfaction Questionnaire – status version (DTSQs)	Score points (range: 0 to 36)	Difference in mean changes in score between randomised treatment groups
Change in score of Short Form 36 version 2 (SF-36 v2)	Score points	Difference in mean changes in score between randomised treatment groups

Rationale for estimand: The rationale is the same as for the primary estimand for the primary objective.

1.2 Study Design

This is an interventional, 40-week, randomised, open-label, two-armed, multi-national, parallel group, multi-centre, active comparator study comparing insulin glargine (IGlar) (reduced) + semaglutide (sema): OW semaglutide s.c. 2.0 mg as an add-on to dose-reduced insulin glargine U100 (see Section 10.7 of the protocol) with IGlar (titrated): titrated insulin glargine U100 (see Section 10.7 of the protocol) in participants with T2D and overweight using insulin glargine U100 up to 40 U/day and metformin with or without SGLT-2 inhibitors, with a baseline HbA1c of 7-10% (both inclusive).

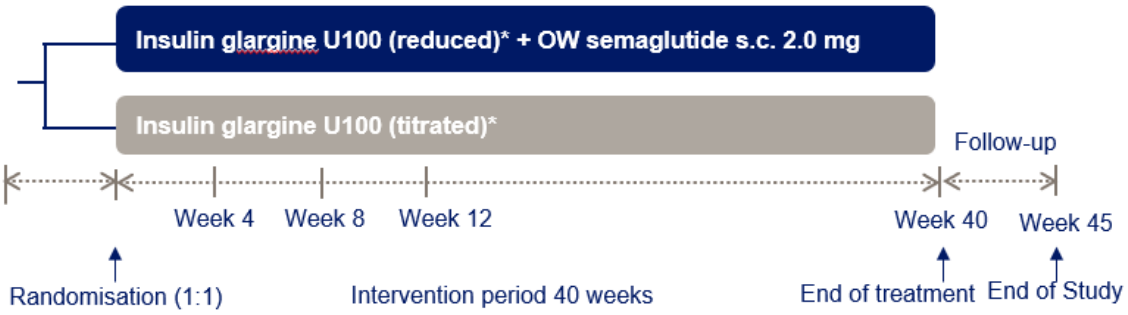
A total of 568 participants will be randomised in a 1:1 manner to receive either OW semaglutide s.c. 2.0 mg and insulin glargine U100 which will be reduced or insulin glargine U100 which will be titrated as per the titration algorithm.

Randomisation will be stratified based on background treatment with SGLT-2 inhibitors (Yes/No).

The study consists of a 2-week screening period followed by a randomisation visit and a 40-week intervention period. The intervention period of the semaglutide treatment arm will include a 12-week dose escalation period where OW semaglutide s.c. will be dose escalated at weeks 4, 8 and 12. Throughout the study, participants will be in contact with the site on a weekly basis (either at site visits or phone contacts) for adverse event (AE) assessment, electronic diary (e-Diary) review of self-measured plasma glucose (SMPG) values, doses taken of trial products and reported hypoglycaemic episodes, if any. Participants will use an e-Diary to report SMPG values, dose of trial products taken and hypoglycaemic episodes, if any. At week 16, the visit can be conducted at the participant's home or other alternative off site location for participants who have consented to have V18 conducted as a home visit.

Continuous glucose monitoring (CGM) will be applied at screening for a 10-day period and at week 38 for a 14-day period with a change of sensor after 7 days. After the end of treatment visit (V42) at week 40, all participants will enter a follow-up period of 5 weeks, ended by a follow-up remote contact, which corresponds to the end of study at week 45 (P43). The planned study duration for the individual participant will be approximately 47 weeks (including screening). The study design is illustrated in Figure 1-1.

Figure 1-1 Study design



*See Section 10.22 of the protocol.

Please refer to the protocol for further details.

2 Statistical Hypotheses

For the primary and secondary estimands with primary endpoint, change from baseline to week 40 in HbA_{1c} (%-point), the following confirmatory 1-sided hypotheses are planned to be tested. Let the mean treatment difference be defined as μ = ([mean change for IGlar (reduced) + sema] minus [mean change for IGlar (titrated)]).

Non-inferiority with a non-inferiority margin of 0.3 (primary estimand):

H_0: μ ≥ 0.3%-points against H_A: μ < 0.3%-points

Superiority (secondary confirmatory estimand):

H_0: μ ≥ 0.0%-points against H_A: μ < 0.0%-points

For the secondary estimand with secondary endpoint, change from baseline to week 40 in body weight (kg), the following confirmatory 1-sided hypothesis is planned to be tested. Let the mean treatment difference be defined as above.

Superiority (secondary confirmatory estimand):

H_0: μ ≥ 0.0kg against H_A: μ < 0.0kg

For the secondary estimand with secondary endpoint, relative change from baseline to week 40 in daily insulin dose (%), the following confirmatory 1-sided hypothesis is planned to be tested. Let the mean treatment difference be defined as μ = ([mean relative change for IGlar (reduced) + sema] minus [mean relative change for IGlar (titrated)]).

Superiority (secondary confirmatory estimand):

H0: μ ≥ 0.0%-points against HA: μ < 0.0%-points

For the secondary estimand with secondary endpoint, DTSQc score at week 40, the following confirmatory 1-sided hypothesis is planned to be tested. Let the mean treatment difference be defined as μ = ([mean score for IGlar (reduced) + sema] minus [mean score for IGlar (titrated)]).

Superiority (secondary confirmatory estimand):

H_0: μ ≤ 0 score points against H_A: μ > 0 score points

Operationally the hypotheses will be evaluated by two-sided tests.

2.1 Multiplicity Adjustment

The type I error will be controlled in the strong sense using a hierarchical (fixed sequence) testing procedure. This is based on priority ordering of the null hypotheses and testing them in this order using the two-sided 95% confidence interval approach until an insignificant result appears. Consequently, a null hypothesis will only be tested if the previous null hypothesis of the test hierarchy has been rejected in favour of IGlar (reduced) + sema.

The steps in the hierarchical testing procedure are as follows:

Step 1: Change from baseline to week 40 in **HbA_{1c} (%-point) non-inferiority** of IGlar (reduced) + sema versus IGlar (titrated).

Step 2: Change from baseline to week 40 in **body weight (kg) superiority** of IGlar (reduced) + sema versus IGlar (titrated).

Step 3: Relative change from baseline to week 40 in **daily insulin dose (%) superiority** of IGlar (reduced) + sema versus IGlar (titrated).

Step 4: Change from baseline to week 40 in **HbA1c (%-point) superiority** of IGlar (reduced) + sema versus IGlar (titrated).

Step 5: **DTSQc score** at week 40 **superiority** of IGlar (reduced) + sema versus IGlar (titrated).

3 Analysis Sets

The following participant analysis sets are defined:

Participant Analysis Set (PAS)	Description
Full analysis set (FAS)	All randomised participants. Participants will be included in the analyses according to the planned intervention.
Safety analysis set	All participants who are exposed to study intervention. Participants will be included in the analyses according to the intervention they actually received.

The following data points sets are defined:

Data points set (DPS)	Description
DPS1 – in-study	All observed data points from randomisation until the first date of: end of study visit (P43) death withdrawal of informed consent last contact as defined by the investigator for participants that are lost to follow up
DPS2 – on-treatment	All observed data points from first drug date until the first date of: end of DPS1 – in-study last trial product administration +42 days

Full analysis set (FAS) and DPS1 are used to estimate the primary estimand for the primary and five confirmatory objectives.

FAS and DPS2 are used to estimate the additional estimands for the primary and five confirmatory objectives.

Safety analysis set and DPS2 are used to present safety data with a long lag-time (AEs, eye examination and hypoglycaemic episodes).

Safety analysis set and a modified DPS2 are used to present safety data with an acute onset (vital signs, laboratory assessments, physical examination). The DPS2 is modified by having an end date as date of last trial product administration +7 days (due to the dosing interval of semaglutide s.c.) or date of end of DPS1, whichever occurs first.

4 Statistical Analyses

4.1 General Considerations

The resulting comparisons of the statistical analyses will, unless otherwise specified, be presented as point estimates, two-sided 95% confidence intervals, and the associated two-sided p-values for IGlar (reduced) + sema versus IGlar (titrated) derived under the assumption of no difference.

A baseline assessment is defined as the most recent measurement available at the randomisation visit (V2). Participants with missing baseline values will not contribute to any analysis that adjust for the given baseline.

The randomisation is stratified based on background treatment with SGLT-2 inhibitors (Y/N).

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 (V2) will only be summarised descriptively.

4.2 Primary Endpoint Analysis

4.2.1 Definition of Endpoint

Type	Title	Time frame	Unit	Details
Primary endpoint	Change in HbA_{1c}	From baseline (week 0) to end of treatment (week 40)	%-points	Related to the primary objective (see Table 1-1).

4.2.2 Main Analytical Approach

The primary estimand, presented in Section 1.1.1.1, will be estimated based on the FAS and DPS1. Missing end of treatment data will be imputed using multiple imputation (MI) assuming that missing data are missing at random (MAR). The imputation will be performed by imputing missing end of treatment data separately within groups defined by randomised treatment and treatment status at end of treatment, in total, four groups as follows:

I. IGlar (reduced) + sema and on-treatment at end of treatment.
II. IGlar (reduced) + sema and off-treatment at end of treatment.
III. IGlar (titrated) and on-treatment at end of treatment.
IV. IGlar (titrated) and off-treatment at end of treatment

For each group an analysis of covariance (ANCOVA) with SGLT-2 inhibitor use (Y/N) and region as factors and baseline HbA_{1c} as a covariate will be fitted to the observed end of treatment values. The estimated location and dispersion parameters will then be used to impute 500 values for each participant with missing end of treatment data. The seed for imputation will be set to 22071430.

The 500 complete datasets will be analysed using an ANCOVA with randomised treatment, SGLT-2 inhibitor use (Y/N) and region as factors and baseline HbA_{1c} as a covariate. Rubin's rule[5] will then be applied to combine these estimates and draw inference.

In case of sparse data, defined as less than 5 participants, in some groups, the imputation model will be thinned by region followed by SGLT-2 inhibitor use (Y/N). If this is not sufficient the imputation will be based on participants randomised to the same treatment regardless of treatment status using the imputation model with SGLT-2 inhibitor use (Y/N) and region as factors and baseline HbA_{1c} as a covariate. Finally, if this is still not sufficient the imputation model may be thinned again in the aforementioned order.

4.2.2.1 Sensitivity analysis

A two-way tipping point sensitivity analysis will be performed by repeating the ANCOVA described in Section 4.2.2, however prior to analysis penalties of opposite sign are added to the imputed values at week 40 in both treatment arms simultaneously. It is assumed that participants with missing observations who are randomised to IGlar (reduced) + sema will receive a treatment that is less beneficial than participants with observed values who are randomised to IGlar (reduced) + sema, and the subjects with missing observations who are randomised to IGlar (titrated) will receive a treatment that is more beneficial than subjects with observed values who are randomised to IGlar (titrated). This sensitivity analysis evaluates the robustness of the conclusions to departures from the imputed change in HbA1c in both treatment groups.

The 500 complete datasets created for the primary analysis will be re-used for the two-way tipping-point analysis. Let (Δ_1, Δ_2) denote a pair of penalties to IGlar (reduced) + sema and IGlar (titrated) respectively. For each of these complete datasets (Δ_1, Δ_2) is added stepwise to the imputed missing end of treatment data for each treatment arm, followed by performing an ANCOVA, until a significant result in the corresponding non-inferiority/superiority analyses is no longer significant.

Then, for a given non-inferiority/superiority hypothesis that is confirmed, denote the corresponding 'one-way' tipping points with (Δ_{1tp},0) for IGlar (reduced) + sema and (0,Δ_{2tp}) for IGlar (titrated). It follows that the domain of penalties in a 'two-way' tipping point analysis should include a grid over (0,0) to (Δ_{1tp},Δ_{2tp}).

The impact on the conclusion will be assessed through a contour plot of the p-values. In this representation the contour line corresponding to 0.05 will partition the grid of penalties into two regions: a region where non-inferiority/superiority of IGlar (reduced) + sema is confirmed at a 5% significance level and a region where non-inferiority/superiority is no longer confirmed. Tipping point non-inferiority/superiority sensitivity analysis is only done if the corresponding primary non-inferiority or superiority analysis indicates statistical significance.

4.2.3 Additional Estimand Analysis

The additional estimand for the primary objective, presented in Section 1.1.1.1, will be estimated based on the FAS and DPS2 .

Missing end of treatment data will be imputed using MI assuming that missing data are MAR. The imputation will be performed separately within each treatment group. First, intermittent missing values are imputed using a Markov Chain Monte Carlo (MCMC) method, to obtain a monotone missing data pattern, generating 500 complete data sets. Secondly, a sequential conditional linear regression approach for imputing monotone missing values will be implemented starting with the first visit after baseline and sequentially continuing to the last planned visit. The imputation model will

include SGLT-2 inhibitor use (Y/N) and region as factors and baseline and post-baseline HbA_{1c} values observed prior to the visit in question as covariates. The seed for imputation will be set to 22071431.

The 500 complete datasets will be analysed using an ANCOVA with randomised treatment, SGLT-2 inhibitor use (Y/N) and region as factors and associated baseline HbA_{1c} as a covariate. Rubin's rule will then be applied to combine the estimates and draw inference.

4.2.3.1 Sensitivity Analysis

A two-way tipping point sensitivity analysis as described in Section 4.2.3 will be performed.

4.2.4 Supplementary Analysis

Not applicable

4.3 Secondary Endpoints Analysis

4.3.1 Confirmatory Secondary Endpoints

4.3.1.1 Definition of Endpoints

Type	Title	Time frame	Unit	Details
Confirmatory secondary endpoint	Change in body weight	From baseline (week 0) to end of treatment (week 40)	kg	Related to the secondary objective (see Table 1-1.
	Relative change in daily insulin dose	From baseline (week 0) to end of treatment (week 40)	%	
	Change in HbA_{1c}	From baseline (week 0) to end of treatment (week 40)	%-point	
	Score of DTSQc	At end of treatment (week 40)	Score points (range -18 to +18)	

4.3.1.2 Main Analytical Approach

For each endpoint mentioned in Section 4.3.1.1 an analysis similar to the one described in Section 4.2.2 will be performed (with values of body weight/insulin doses/DTSQc instead of HbA_{1c} for three of the endpoints). Furthermore, the model will assume a different residual variance across the two treatment arms when the endpoint considered is relative change in daily insulin dose. Additionally, for the relative change in daily insulin dose endpoint, pre-randomized dose will be considered as baseline whereas for DTSQc endpoint, baseline of DTSQs will be considered as baseline.

Relative change from baseline to week 40 in insulin dose (%) is computed as

$$\frac{[[\text{insulin dose at week 40}] - [\text{insulin dose at baseline}]] * 100}{[\text{insulin dose at baseline}]}$$

4.3.1.2.1 Sensitivity Analysis

For each endpoint mentioned in Section 4.3.1.1 a two-way tipping point sensitivity analysis similar to the one described in Section 4.2.3 will be performed (with values of body weight/insulin doses/DTSQc instead of HbA_{1c} for two of the endpoints).

4.3.1.3 Additional estimand analysis

For each endpoint mentioned in Section 4.3.1.1 an analysis similar to the one described in Section 4.2.3 will be performed (with values of body weight/insulin doses/DTSQc instead of HbA_{1c} for three of the endpoints). Furthermore, the model will assume a different residual variance across the two treatment arms when the endpoint considered is relative change in daily insulin dose. Additionally, for the relative change in daily insulin dose endpoint, pre-randomized dose will be considered as baseline whereas for DTSQc endpoint, baseline of DTSQs will be considered as baseline Furthermore, for the DTSQc endpoint, the visit window days will be extended by +30 days for Visit 42 to account for any potential delays in responding to the end-of-treatment questionnaire.

4.3.1.3.1 Sensitivity Analysis

For each endpoint mentioned in Section 4.3.1.1 a two-way tipping point sensitivity analysis similar to the one described in Section 4.2.3 will be performed (with values of body weight/insulin doses/DTSQc instead of HbA_{1c} for two of the endpoints).

4.3.1.4 Supplementary Analysis

Not applicable

4.3.2 Supportive Secondary Endpoints

For each supportive secondary endpoint mentioned in Sections 4.3.2.1, 4.3.2.2, and 4.3.2.3 the primary estimand, presented in Section 1.1.1.1, will be estimated. To account for missing data, an imputation similar to the one described in Section 4.2.2 will be performed with (values of body weight/insulin doses/DTSQs/SF-36 v2 instead of HbA_{1c} for three of the endpoints). Imputations are done on the continuous scale.

4.3.2.1 Binary Endpoints

The binary supportive secondary endpoints (listed below) will be analysed using a logistic regression model with a logit link function, randomised treatment, SGLT-2 inhibitor use (Y/N) and region as categorical effects, and relevant baseline value as covariate (i.e. baseline HbA_{1c} for binary HbA_{1c} endpoint, baseline insulin dose for binary insulin dose endpoint and baseline of HbA_{1c},body weight and insulin dose for composite binary endpoint. From the model, the estimated odds ratio (IGlar (reduced) + sema vs IGlar (titrated)) will be presented together with the corresponding two-sided 95% confidence interval and the unadjusted two-sided p-value for testing the null-hypothesis of no difference. This analysis will be based on the FAS and DPS1.

Otherwise, in case of missing data the binary endpoints will be subsequently dichotomized based on the 500 imputed datasets on which the imputations are done on the continuous scale for HbA_{1c}, body weight, insulin dose respectively and no imputations will be done for the missing hypoglycaemic episodes. Furthermore, for the binary endpoint insulin dose 0U, any imputed values with less than 0 will be set to 0. For the odds ratio, the multiple analysis results will be combined on the logarithmic

scale (using Rubin's rule as for the primary endpoint). 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.

Table 4-1 Binary Supportive Secondary Endpoints

Type	Title	Time frame	Unit	Details
Supportive secondary endpoint	Participants achieving: • Insulin dose = 0U	At end of treatment (week 40)	Y/N	Related to the secondary objective (see Table 1-1).
	Participants achieving: • Insulin dose reduced from baseline by at least 50%	At end of treatment (week 40)	Y/N	
	Participants achieving: • HbA_{1c} < 7%	At end of treatment (week 40)	Y/N	
	Participants achieving all of the following targets: • HbA_{1c} reduced from baseline by at least 0.3%-point • Insulin dose reduced from baseline • No hypoglycaemic episodes (<3.9 mmol/L (70 mg/dL) confirmed by BG meter) • No weight gain	At end of treatment (week 40)	Y/N	

4.3.2.2 Count Endpoints

The count supportive secondary endpoints (listed below) will be analysed using a negative binomial regression model with a log-link function, and the logarithm of the participant's 'on-treatment' observation period as offset. The model will include randomised treatment, SGLT-2 inhibitor use (Y/N) and region as fixed factors and baseline HbA_{1c} as a covariate. This analysis will be based on the SAS and DPS2 with no imputation. The results will be described by the ratio between treatments and the associated 95% confidence interval and p-value for no treatment difference.

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

Table 4-2 Count Supportive Secondary Endpoints

Type	Title	Time frame	Unit	Details
Supportive secondary endpoint	Number of severe hypoglycaemic episodes (level 3)	From baseline (week 0) to end of treatment (week 40)	Number of episodes	Related to the secondary objective (see Table 1-1).

Type	Title	Time frame	Unit	Details
	Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL) confirmed by BG meter)	From baseline (week 0) to end of treatment (week 40)	Number of episodes	See above for details on the statistical analysis.
	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) to end of treatment (week 40)	Number of episodes	

4.3.2.3 Other Endpoints

Each of the PRO endpoints like the other continuous endpoints will be analysed separately using a similar model approach as for the primary estimand with the relevant baseline value as covariate instead of HbA1c. These analyses will be based on the FAS and DPS1. For change in score of SF-36 endpoint, scores from the 8 domains and summary scores (physical component and mental component) will be analysed using norm-based scores derived using the Optum's PRO CoRE software.

36-item Short Form Health Survey version 2 (SF-36 v2)

- Physical Component Summary (PCS) score (range: 5.0-79.8)
- Mental Component Summary (MCS) score (range: -4.0-80.1)
- Physical Functioning (PF) domain score (range: 19.3-57.5)
- Role-Physical (RP) domain score (range: 21.2-57.2)
- Bodily Pain (BP) domain score (range: 21.7-62.0)
- General Health (GH) domain score (range: 19.0-66.5)
- Vitality (VT) domain score (range: 22.9-70.4)
- Social Functioning (SF) domain score (range: 17.2-57.3)
- Role-Emotional (RE) domain score (range: 14.4-56.2)
- Mental Health (MH) domain score (range: 11.6-63.9)

Type	Title	Time frame	Unit	Details
Supportive secondary endpoint	Change in score of DTSQs	From baseline (week 0) to end of treatment (week 40)	Score points (range: 0 to 36)	Related to the secondary objective (see Table 1-1).
	Change in score of SF-36 v2	From baseline (week 0) to end of treatment (week 40)	Score points	

4.4 Exploratory Endpoints Analysis

Not applicable, as there are no exploratory endpoints in this study.

4.5 Other Safety Analysis

All safety analyses will be based on the safety analyses set. The standard safety assessments (AEs, safety laboratory parameters, vital signs, etc.) will be reported descriptively based on the DPS2 and modified DPS2; including any notable changes of clinical interest in laboratory parameters.

4.5.1 Extent of Exposure

Duration of exposure will be summarized categorically by treatment group for all observed data points from first date of study product until permanent discontinuation of treatment. In addition, time on study product and treatment pause will be summarized descriptively just like the other continuous endpoints.

4.5.2 Adverse Events

Adverse events (AEs) will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) coding. A treatment-emergent AE is defined as an AE with onset in all observed data points from first date of study product until permanent discontinuation of treatment.

The following assessments will be done and summarized by means of the number of patients with at least one event (N), the proportion of patients with at least one event (%), the number of events (E) and the event rate (R) per 100 patient years of exposure time for all observed data points from first date of study product until permanent discontinuation of treatment (resp. per 100 patient years of observation time for all observed data points from first date of study product until permanent discontinuation of treatment):

- Serious adverse events (SAEs)
- Adverse events (AEs) leading to discontinuation of randomized treatment
- AEs of COVID-19, irrespective of seriousness. Note: Suspected COVID-19 should be reported if the clinical presentation is suggestive of COVID-19, even in the absence of a COVID-19 test or without a positive COVID-19 test result. In the absence of clinical symptoms, a positive COVID-19 test (antigen or antibody) should be reported, if available.
- Medication errors, misuse, and abuse

Summaries will be presented as overall, by relationship to study product, by severity, by seriousness, by outcome, by treatment discontinuation status and by action taken to study product. Total exposure time and observation time, as explained above, in years will be presented in the summary as well.

In addition, treatment emergent SAEs and AEs leading to discontinuation of randomized treatment will be summarized by system organ class and preferred term (All observed data points from first date of study product until permanent discontinuation of treatment.).

The development over time in AEs leading to discontinuation will be presented graphically.

Data on pregnancies in female patients and pregnancy outcome (until age 1 month) and AEs in the fetus or newborn infant will be presented in a listing.

Additional data collected regarding medication errors, misuse and abuse of randomized treatment will be presented in listings.

4.5.3 Additional Safety Assessments

Not Applicable

4.6 Other Analysis

Exploratory analyses of CGM derived variables. Additionally, exploratory analyses of cardiovascular and renal risk markers will be performed. Descriptive summary (continuous/ categorical) for the additional estimand will be given for the variables/ parameters specified in section 4.6.1.

4.6.1 Other Variables and/or Parameters

Endpoint	Time frame	Unit	Details
CGM Endpoints			
Time In Range			
Change in time in tight range (TITR) 3.9–7.8 mmol/L (70–140 mg/dL)*	From baseline (week -2 to week 0) to end of treatment(week 38 to week 40)	% -pts	
Change in time in range (TIR) 3.9-10.0 mmol/L (70-180 mg/dL)*	From baseline (week -2 to week 0) to end of treatment(week 38 to week 40)	% -pts	
Time Below Range			
Change in time below range (TBR)[1] < 3.9 mmol/L (70 mg/dL)*	From baseline (week -2 to week 0) to end of treatment (week 38 to week 40)	% -pts	
Change in time below range[1]< 3.0 mmol/L (54 mg/dL)*	From baseline (week -2 to week 0) to end of treatment (week 38 to week 40)	% -pts	
Time Above Range			
Change in time above range > 10.0 mmol/L (>180 mg/dL)*	From baseline (week -2 to week 0) to end of treatment (week 38 to week 40)	% -pts	
Change in time above range > 13.9 mmol (>250 mg/dL)*	From baseline (week -2 to week 0) to end of treatment (week 38 to week 40)	% -pts	
Change in mean sensor glucose*	From baseline (week -2 to week 0) to end of treatment (week 38 to week 40)	mmol/L (mg/dL)	
Change in glucose management indicator (GMI)[2]	From baseline (week -2 to week 0) to end of treatment (week 38 to week 40)	%-pts (mmol/mol)	
Binary outcomes			

Endpoint	Time frame	Unit	Details
Achievement of ≥ 5 %-points improvement in time in range (TIR) 3.9-10.0 mmol/L (70-180 mg/dL)	From baseline (week -2 to week 0) to end of treatment (week 38 to week 40)	Count of participants	
Achievement of time in range (TIR) 3.9–10.0 mmol/L (70–180 mg/dL) for >70% of time	From week 38 to end of treatment (week 40)	Count of participants	
Achievement of time above range(TAR) >10.0 mmol/L (>180 mg/dL) for < 25% of time	From week 38 to end of treatment (week 40)	Count of participants	
Achievement of time above range(TAR) >13.9 mmol/L (>250 mg/dL) for < 5% of time	From week 38 to end of treatment (week 40)	Count of participants	
Achievement of time below range (TBR) < 3.9 mmol/L (<70 mg/dL) <4% of time	From week 38 to end of treatment (week 40)	Count of participants	
Achievement of time below range (TBR) < 3.0 mmol/L (<54 mg/dL) < 1% of time	From week 38 to end of treatment (week 40)	Count of participants	
Coefficient of variation, total	From week 38 to end of treatment (week 40)	%	
Coefficient of variation, total	From baseline (week -2) to week 0	%	
Coefficient of variation, intraday	From baseline (week -2) to week 0	%	
Coefficient of variation, intraday	From week 38 to end of treatment (week 40)	%	
Composite			
Achievement of >0.5%-points improvement in HbA1c without an increase in time below range (TBR) <3.0 mmol/L (<54 mg/dL) of >0.5%	From baseline (week -2) to week 0 to during week 38 to end of treatment (EoT) week 40	Count of participant	
Achievement of >10%-points improvement in time in range (TIR) 3.9-10.0 mmol/L (70-180 mg/dL) without an increase in time below range (TBR) <3.0 mmol/L (<54 mg/dL) of > 0.5%	From baseline (week -2) to week 0 to during week 38 to end of treatment (EoT) week 40	Count of participant	
Achievement of mean glucose <8.6 mmol/L (<154 mg/dL) and <1% time below range (TBR) <3.0 mmol/L (<54 mg/dL)	From week 38 to end of treatment (week 40)	Count of participant	
Achievement of >70% time in range (TIR) 3.9-10.0 mmol/L (70-180 mg/dL) and <4% time below range (TBR) <3.9 mmol/L (<70 mg/dL)	From week 38 to end of treatment (week 40)	Count of participant	

Endpoint	Time frame	Unit	Details
Achievement of >70% time in range (TIR) 3.9-10.0 mmol/L (70-180 mg/dL) and <1% time below range (TBR) <3.0 mmol/L (<54 mg/dL)	From week 38 to end of treatment (week 40)	Count of participant	
Other Variables			
Change in FPG	From baseline (week 0) to end of treatment (week 40)		
Change in C-peptide	From baseline (week 0) to end of treatment (week 40)		
Change in e-GFR	From screening (V1B) to end of treatment (week 40)		
Change in total cholesterol	From baseline (week 0) to end of treatment (week 40)	mmol/L	
Change in LDL cholesterol	From baseline (week 0) to end of treatment (week 40)	mmol/L	
Change in HDL cholesterol	From baseline (week 0) to end of treatment (week 40)	mmol/L	
Change in triglycerides	From baseline (week 0) to end of treatment (week 40)	mmol/L	
Change in apolipoprotein B	From baseline (week 0) to end of treatment (week 40)	mmol/L	
Change in urinary albumin	From baseline (week 0) to end of treatment (week 40)	mg/24h	
Change in urinary albumin to creatinine ratio	From baseline (week 0) to end of treatment (week 40)	mg/g	
Change in high sensitivity c-reactive protein	From baseline (week 0) to end of treatment (week 40)	mg/L	
Change in systolic blood pressure	From baseline (week 0) to end of treatment (week 40)	mmHg	
Change in diastolic blood pressure	From baseline (week 0) to end of treatment (week 40)	mmHg	
Participants achieving all of the following targets: • HbA_{1c} < 7%	From baseline (week 0) to end of treatment (week 40)	Y/N	

Endpoint	Time frame	Unit	Details
• No hypoglycaemic episodes (<3.9 mmol/L (70 mg/dL) confirmed by BG meter) • No weight gain			
Participants achieving all of the following targets: • HbA_{1c} < 7% • No hypoglycaemic episodes (<3.9 mmol/L (70 mg/dL) confirmed by BG meter)	From baseline (week 0) to end of treatment (week 40)	Y/N	
Participants achieving all of the following targets: • HbA_{1c} < 6.5% • No hypoglycaemic episodes (<3.9 mmol/L (70 mg/dL) confirmed by BG meter)	From baseline (week 0) to end of treatment (week 40)	Y/N	
Participants achieving: • Body weight reduced from baseline by at least 5%	From baseline (week 0) to end of treatment (week 40)	Y/N	
Participants achieving: • Body weight reduced from baseline by at least 10%	From baseline (week 0) to end of treatment (week 40)	Y/N	
Number of clinically significant nocturnal hypoglycaemic episodes (level 2) confirmed by BG meter) or severe nocturnal hypoglycaemic episodes (level 3)	From baseline (week 0) to end of treatment (week 40)	Number of episodes	
Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL) confirmed by BG meter) or severe hypoglycaemic episodes (level 3)	From baseline (week 0) to week 20	Number of episodes	
Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL) confirmed by BG meter) or severe hypoglycaemic episodes (level 3)	From week 21 to end of treatment (week 40)	Number of episodes	

* CGM derived

1, It is often the case for TBR that neither change in TBR nor TBR fulfils the model requirements for an ANCOVA. In that case TBR can be analysed by a negative binomial model with baseline TBR as covariate and treatment contrast reported as Estimated Treatment Ratios (ETR); 2, GMI = Glucose Management Indicator, GMI (%)= 3.31 + 0.02392 x [mean glucose in mg/dL (mmol/L)]

CGM data from the two pre-planned periods will be used without prior cleaning of outliers. The CGM endpoints (change from baseline in) TIR, TITR, TBR and TAR will be calculated for each subject and period as "% -pts" in the relevant range with a coverage of at least 48 hrs (from the relevant 10/14-day period).

Intra-day glycaemic variability will be calculated for each subject and period as the average of the within-day (10 days at period 1 and 14 days at period 2) CVs. Parameters involving change in time below range, change in time above range, change in time in range and change in time in tight range will be analysed using additional estimand without imputation of missing data. That is, similar to that

used for the primary endpoints, where the relevant parameter is substituted for HbA1c. Furthermore, the latest available and eligible measurement, at or prior to the randomisation visit, will be used as the baseline value. However, missing data will not be imputed in this case.

4.6.2 Subgroup Analysis

To assess consistency of treatment effect for HBA1c and Daily insulin dose at week 40 across ethnic groups (Not Hispanic or Latino, Hispanic or Latino), age (<65, ≥ 65 years), gender (Male, Female) and BMI ($\leq 30, > 30$), a Subgroup analysis will be performed.

The analysis will be based on the primary estimand. That is, similar to that used for the primary endpoint. The treatment by subgroup interaction will be added to the ANCOVA model specified in section 4.2.2.The independent effects included in the model will be treatment, SGLT-2 inhibitor use (Y/N), region, subgroup and treatment by subgroup as categorical fixed effects and baseline value as a covariate.

From the ANCOVA model the treatment difference at week 40 by subgroup will be estimated and the corresponding 95% confidence interval. Level of significance for treatment by subgroup interaction will be 5%. The estimated treatment difference with confidence interval by subgroup will be displayed in a forest plot.

4.7 Interim Analys*is*

This study will be subject to a partial database lock (DBL) at the end of the treatment period for all participants, i.e. after the date of the last participant last treatment (LPLT) visit. A full DBL will be performed, as per the usual procedures, after last participant last visit. Only Novo Nordisk employees from Medical & Science and Biostatistics will be blinded during this open-label study. These skill areas will be unblinded at the partial DBL. All efficacy analyses will be performed based on the data from the partial DBL. No efficacy assessments are collected after LPLT. In turn, efficacy results cannot be biased by the early unblinding. The impact on safety is considered minor, as most participants will have completed the follow-up visit. Analysis of safety will be performed after the full DBL.

4.8 Changes to Protocol-planned Analys*is*

- The protocol specified that the endpoint for the change in score of Short Form 36 version 2 (SF-36 v2) ranges from 0 to 100 scores. However, since it is recommended to use norm-based scores which do not fall within the 0-100 score range, a detailed description has been provided in section 4.3.2.3.

5 Sample size determination

Please refer to the protocol.

6 Supporting Documentation

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

Not Applicable

7 References

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