Cover Page for Statistical Analysis Plan

Sponsor name:	Novo Nordisk A/S
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Official title of study:	Investigation of the safety and efficacy of semaglutide s.c. in combination with NNC0480-0389 in participants with type 2 diabetes – a dose finding study
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*Document date refers to the date on which the document was most recently updated.

Note: The date in the header of page 2 is the date of the compilation of the documents and not of an update to content.

9.1.9 Documentation of statistical methods

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Statistical Analysis Plan

Investigation of the safety and efficacy of semaglutide s.c. in combination with NNC0480-0389 in participants with type 2 diabetes – a dose finding study

Substance number/name: Semaglutide s.c. and NNC0480-0389

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Version History

This Statistical Analysis Plan (SAP) for study NN9389-4606 is based on the protocol version 4.0 dated 03SEP2021.

Version	Date	Change	Rationale
1.0	06-jul-21	Not applicable	The SAP contains additional descriptions and details of the planned analyses more detailed descriptions for deriving and calculation of endpoints.

2.0	08-nov-2022	Section 1.1.1: Updated text regarding the primary and additional estimand for the primary objective (definition of estimands are not changed), and added description of estimands for secondary objective 1, secondary objective 2, secondary objective 3, and for the parameter diastolic blood pressure. Section 3: Simplified text for the participant analysis sets and included both intercurrent events in the description of the data point sets. In the definition of the on-treatment data point set: "The date of last dose of randomised treatment + 35 days" is updated to "The date of last dose of randomised treatment + 49 days". Further, added specifications regarding estimands addressing the secondary objectives. Section 4.1: Added text specifying which treatment contrasts that will be reported. Corresponding text has been removed from subsequent sections. Section 4.1.1. Added text from protocol that specifies how missing baseline data will be handled. Corresponding text has been removed from subsequent sections. Section 4.1.2: Added section that specifies which stratification factors that are included in analyses. Section 4.1.3: added definition of rescue medication. Section 4.2.2.1: Description of analysis updated, and updated text regarding how to handle imputation model in case of sparse data. Section 4.8 also updated to elaborate on this update. Section 4.2.2.2: Description of analysis updated. Added text regarding how to thin the imputation model in case of sparse data. Section 4.2.3: Added section that specifies analyses addressing estimands for the secondary objective 1 and 2. Section 4.2.4: Text added to specify that that the estimated Hba1c	Section 1.1.1: To ensure a detailed description of the estimands. Section 3: To ensure a detailed and precise description of participant sets and data point sets. The update regarding addition of 49 days rather than 35 days is included to ensure that the observation period includes approximately five half-lives of the study product plus the visit window. Section 4.1: To avoid unnecessary repetition in each section. Section 4.1.1: To ensure that a detailed description of how to handle missing baseline data is included. Section 4.1.2: To avoid unnecessary repetition in each section. Section 4.1.3: To clarify what is defined as rescue medication. Section 4.2.2.1: Description updated to remove repetitions. Original text regarding thinning of imputation model was not precise considering the planned imputation approach for the hypothetical estimand. Section 4.2.2.2: Description updated to remove repetitions, and to clarify how to thin the imputation model in case of sparse data. Section 4.2.3: To clarify how estimands for secondary objective 1 and 2 will be estimated. Section 4.2.4: To ensure a detailed description of the analyses. Section 4.3.1: To further clarify on how to analyse supportive secondary endpoints. Section 4.5: To ensure detailed description of which data points set reporting of safety parameters will be based on. Adverse events removed from section as details regarding these are given in section 4.3.2.1. Section 4.6: Analysis added to further assess effect of treatment on cardio-metabolic as supporting evidence.

Version	Date	Change	Rationale
		changes will be weighted by their corresponding variances. Section 4.3.1: Text rephrased to align with the estimands that address the secondary objective (analyses not changed). Text also added regarding thinning of imputation models in case of sparse data. Also, additional analyses have been added for body weight endpoints similar to the analysis addressing the additional estimand. Section: 4.5: Specification of data point set added and specification of adverse events removed Section 4.6: Added description of statistical analysis for diastolic blood pressure. Section 4.6.2: : Specification of data point set added.	Section 4.6.2: To ensure detailed description of which data points set reporting of other variables/parameters will be based on.

List of abbreviations

AE	adverse event
ANCOVA	analysis of covariance
CI	confidence interval
DPS	defined data points sets
FAS	full analysis set
MAR	missing at random
PAS	participant analysis set
s.c.	subcutaneously
SAS	safety analysis set
SAP	statistical analysis plan
T2D	type 2 diabetes

1 Introduction

1.1 Objectives, Endpoints, and Estimands

Table 1: Objectives and endpoints

Objectives	Endpoints		
	Title	**Time frame**	**Unit**
	Primary		
To demonstrate superiority of subcutaneously co-administered semaglutide and NNC0480-0389 (in different dose ratios) versus placebo on change in HbA_{1c} (%-point) from baseline to week 34 in participants with T2D inadequately controlled on diet and exercise with or without metformin.	Change in HbA_{1c}	From baseline (week 0) to visit 24 (week 34)	%-point
Secondary			
Secondary objective 1: To demonstrate superiority of subcutaneously co-administered semaglutide and NNC0480 0389 (in different dose ratios) versus NNC0480-0389 and versus semaglutide on change in HbA_{1c} (%-point) from baseline to week 34 in participants with T2D inadequately controlled on diet and exercise with or without metformin.			
Secondary objective 2: To compare the effect of subcutaneously administered NNC0480-0389 monotherapy versus placebo on change in HbA_{1c} (%-point) from baseline to week 34 in participants with T2D inadequately controlled on diet and exercise with or without metformin.			
	Supportive secondary		
Secondary objective 3: To compare the effect of	Change in fasting plasma glucose (FPG)	From baseline (week 0) to visit 24 (week 34)	mmol/L

Objectives	Endpoints		
	Title	**Time frame**	**Unit**
subcutaneously co-administered semaglutide and NNC0480 0389 (in different dose ratios) versus placebo, versus NNC0480-0389 and versus semaglutide on change in fasting plasma glucose as well as body weight-related and cardio-metabolic parameters from baseline to week 34 in participants with T2D inadequately controlled on diet and exercise with or without metformin.	Change in body weight (kg)	From baseline (week 0) to visit 24 (week 34)	kg
	Change in body weight (%)	From baseline (week 0) to visit 24 (week 34)	%
	Change in waist circumference	From baseline (week 0) to visit 24 (week 34)	cm
	Change in systolic blood pressure (SBP)	From baseline (week 0) to visit 24 (week 34)	mmHg
	Relative change in total cholesterol	From baseline (week 0) to visit 24 (week 34)	Ratio
	Relative change in high-density lipoprotein (HDL) cholesterol	From baseline (week 0) to visit 24 (week 34)	Ratio
	Relative change in low-density lipoprotein (LDL) cholesterol	From baseline (week 0) to visit 24 (week 34)	Ratio
	Relative change in very-low-density lipoprotein (VLDL) cholesterol	From baseline (week 0) to visit 24 (week 34)	Ratio
	Relative change in triglycerides	From baseline (week 0) to visit 24 (week 34)	Ratio
	Relative change in free fatty acids	From baseline (week 0) to visit 24 (week 34)	Ratio
	Relative change in Apolipoprotein B (ApoB)	From baseline (week 0) to visit 24 (week 34)	Ratio
	Relative change in high sensitivity C-Reactive Protein (hsCRP)	From baseline (week 0) to visit 24 (week 34)	Ratio
Secondary objective 4: To compare the safety and tolerability of subcutaneously co-administered semaglutide and NNC0480 0389 (in different dose ratios) versus placebo, versus NNC0480-0389 and versus semaglutide in participants with T2D inadequately controlled on diet and exercise with or without metformin.	Number of treatment-emergent adverse events (TEAEs)	From baseline (week 0) to visit 25 (week 39)	Count of events

1.1.1 Estimands for the primary objective

For the primary objective, a primary estimand and an additional estimand are defined. Two intercurrent events are identified: premature discontinuation of randomised treatment and initiation of any rescue medication (anti-diabetic medication). The estimands are summarised below and the attributes of the estimands are presented in Table 2.

Primary estimand

The primary estimand addresses the main question of interest: What is the difference in mean change in HbA_{1c} (%-point) from baseline to week 34 of subcutaneously co-administered semaglutide and NNC0480-0389 versus placebo in patients with T2D, inadequately controlled on diet and exercise with or without metformin, had all participants remained on randomised treatment without use of rescue medication (anti-diabetic medications)?

The primary estimand aims at reflecting the achievable treatment effect if all patients remain on the randomised treatment without use of rescue medication. This is considered relevant to find the optimal dose ratio from an efficacy perspective. The primary estimand is also called the hypothetical estimand due to the strategy for handling intercurrent events.

Additional estimand for the primary objective

The additional estimand addresses an additional question of interest: What is the difference in mean change in HbA_{1c} (%-point) from baseline to week 34 of subcutaneously co-administered semaglutide and NNC0480-0389 versus placebo in patients with T2D, inadequately controlled on diet and exercise with or without metformin, regardless of premature discontinuation of randomised treatment and initiation of rescue medication (anti diabetic medications)?

The additional estimand aims to mirror the clinical practice scenario because the estimand considers both the efficacy and tolerability of subcutaneously co-administered semaglutide and NNC0480-0389. The additional estimand is also called the treatment policy estimand due to the strategy for handling intercurrent events.

Table 2: Attributes for the estimands for the primary objective

Estimand category	Treatment condition	Variable / endpoint	Population of interest	Remaining intercurrent events	Population-level summary
Primary	S.c. co-administered semaglutide and NNC0480-0389 (in different dose ratios) vs. placebo both as add-on to diet and exercise and with or without metformin had treatment not been discontinued and rescue medication not been initiated	Change in HbA_{1c} (% point) from baseline to week 34	Patients with T2D. Further details can be found in protocol section 5	None. The 2 intercurrent events: 'initiation of any rescue medication' and 'premature discontinuation of randomised treatment' are addressed in the treatment condition attribute and handled with the hypothetical strategy	Difference in means
Additional	S.c. co-administered semaglutide and NNC0480-0389 (in different dose ratios) vs. placebo, both with or without rescue medication, and both as add-on to diet and exercise with or without metformin regardless of treatment discontinuation			None. The 2 intercurrent events: 'initiation of any rescue medication' and 'premature discontinuation of randomised treatment' are addressed in the treatment condition attribute and handled with the treatment policy strategy	

Abbreviations: s.c.: subcutaneously; T2D : type 2 diabetes

1.1.2 Estimands for secondary objective 1 and secondary objective 2

Estimands, similar to the primary and additional estimands for primary objective, will be used to address secondary objective 1 and secondary objective 2, respectively, the only difference pertaining to the treatment conditions attribute as reflected in the two secondary objectives in Table 2 instead of 'co-administered semaglutide and NNC0480-9389 (in different dose ratios) vs. placebo':

- 'co-administered semaglutide and NNC0480-0389 (in different dose ratios) vs. NNC0480-0389
- 'co-administered semaglutide and NNC0480-0389 (in different dose ratios) vs. semaglutide'
- 'NNC0480-9389 monotherapy vs. placebo'

1.1.3 Estimands for secondary objective 3

1.1.3.1 Body weight

Estimands, similar to the primary and additional estimands for primary objective, will be used to address secondary objective 3 of the body weight endpoints. The differences pertaining to the endpoint attribute as reflected in the two secondary objectives in Table 2. Instead of 'change in HbA1c (% point) from baseline to week 34':

- 'Change in body weight (kg) from baseline to week 34'
- 'Change in body weight (%) from baseline to week 34'

In addition, differences pertaining to the treatment conditions attribute will also be considered, instead of 'co-administered semaglutide and NNC0480-9389 (in different dose ratios) vs. placebo':

- 'co-administered semaglutide and NNC0480-0389 (in different dose ratios) vs. NNC0480-0389
- 'co-administered semaglutide and NNC0480-0389 (in different dose ratios) vs. semaglutide'
- 'NNC0480-9389 monotherapy vs. placebo'

1.1.3.2 Remaining secondary endpoints

Estimands, similar to the primary estimand for primary objective, will be used to address secondary objective 3 for the remining secondary endpoints. The differences pertaining to the endpoint attribute as reflected in the primary estimand for primary objective in Table 2. Instead of 'change in HbA1c (% point) from baseline to week 34':

- 'Change in fasting plasma glucose from baseline to week 34'
- 'Change in waist circumference from baseline to week 34'
- 'Change in systolic blood pressure from baseline to week 34'
- 'Relative change in total cholesterol from baseline to week 34'
- 'Relative change in high-density lipoprotein (HDL) cholesterol from baseline to week 34'
- 'Relative change in low-density lipoprotein (LDL) cholesterol from baseline to week 34'
- 'Relative change in very-low-density lipoprotein (VLDL) cholesterol from baseline to week 34'

- 'Relative change in triglycerides from baseline to week 34'
- 'Relative change in free fatty acids from baseline to week 34'
- 'Relative change in Apolipoprotein B (ApoB) from baseline to week 34'
- 'Relative change in high sensitivity C-Reactive Protein (hsCRP) from baseline to week 34'

In addition, for each secondary endpoint differences pertaining to the treatment condition attribute will also be considered, instead of 'co-administered semaglutide and NNC0480-9389 (in different dose ratios) vs. placebo':

- 'co-administered semaglutide and NNC0480-0389 (in different dose ratios) vs. NNC0480-0389
- 'co-administered semaglutide and NNC0480-0389 (in different dose ratios) vs. semaglutide'

1.1.4 Estimands for other variables

An estimand, similar to the primary estimand for primary objective, will be used to address the parameter diastolic blood pressure. The differences pertaining to the endpoint attribute as reflected in the primary estimand for primary objective in Table 2. Instead of 'change in HbA1c (% point) from baseline to week 34':

- 'Change in diastolic blood pressure from baseline to week 34'

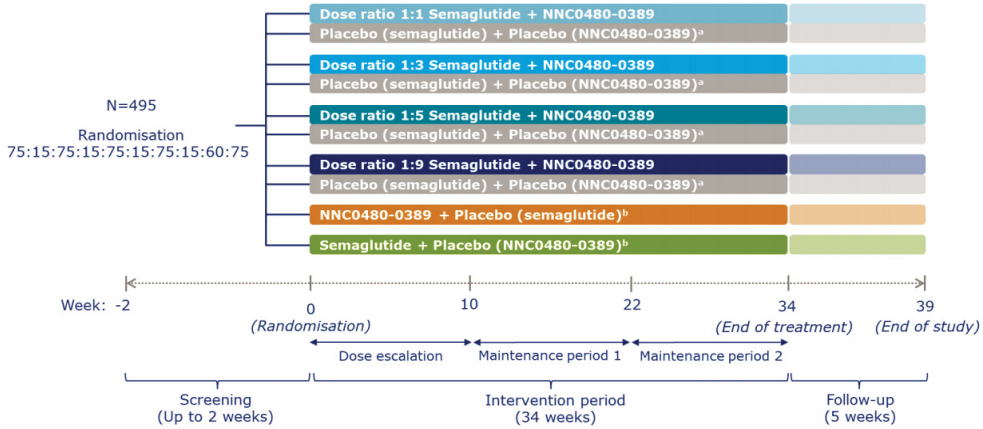
In addition, differences pertaining to the treatment condition attribute will also be considered, instead of 'co-administered semaglutide and NNC0480-9389 (in different dose ratios) vs. placebo':

- 'co-administered semaglutide and NNC0480-0389 (in different dose ratios) vs. NNC0480-0389
- 'co-administered semaglutide and NNC0480-0389 (in different dose ratios) vs. semaglutide'

1.2 Study design

This is an interventional, 34-week, randomised, parallel-group, volume-matched placebo-controlled, ten-armed, multi-centre, multi-national dose finding phase 2 study (Figure 1). It will be double-blinded between each dose ratio arm and volume-matched placebo arm or volume-matched active comparator arm. The study will compare four different dose ratios of semaglutide and NNC0480-0389 (using a fixed dose of semaglutide and varying doses of NNC0480-0389) versus placebo, versus NNC0480-0389 and versus semaglutide, respectively, as an adjunct to diet and exercise ± metformin in participants with T2D.

Figure 1: Schematic design of study



[a]The 4 placebo arms will be pooled into one placebo group in the main analysis

[b]Volume-matched to the dose ratio 1:9 arm

For each dose ratio, participants will be randomised 75:15 to the active treatment arm and the corresponding placebo matched arm. Moreover, participants will be randomised 60:75 to the NNC0480-0389 monotherapy arm and the semaglutide monotherapy arm. This will result in an overall randomisation scheme of 75:75:75:75:60:75:60 for the four dose ratios, NNC0480-0389 monotherapy, semaglutide monotherapy, and the pooled placebo group. Randomisation will be stratified according to treatment with metformin at screening (yes/no), country (Japan/Other), and HbA1c at screening (<8.5%/≥8.5%).

For further study design information, see the protocol section 4.1.

2 Statistical Hypotheses

For the primary estimand with primary endpoint, change from baseline to week 34 in HbA_{1c} (%-point), the following hypotheses are planned to be tested.

The primary hypotheses of superiority for the four dose ratios versus placebo are defined as follows; Let x denote the NNC0480-0389 dose in the dose ratio 1:x, let $\mu_{Ratio1:x}$ denote the true mean of change in HbA_{1c} (%-point) from baseline to week 34 for dose ratio 1:x, and let $\mu_{placebo}$ denote the true mean of change in HbA_{1c} (%-point) from baseline to week 34 for the pooled placebo group. The null and alternative hypotheses tested are:

$$H_0: \mu_{Ratio1:x} \geq \mu_{placebo} \text{ vs. } H_A: \mu_{Ratio1:x} < \mu_{placebo}$$

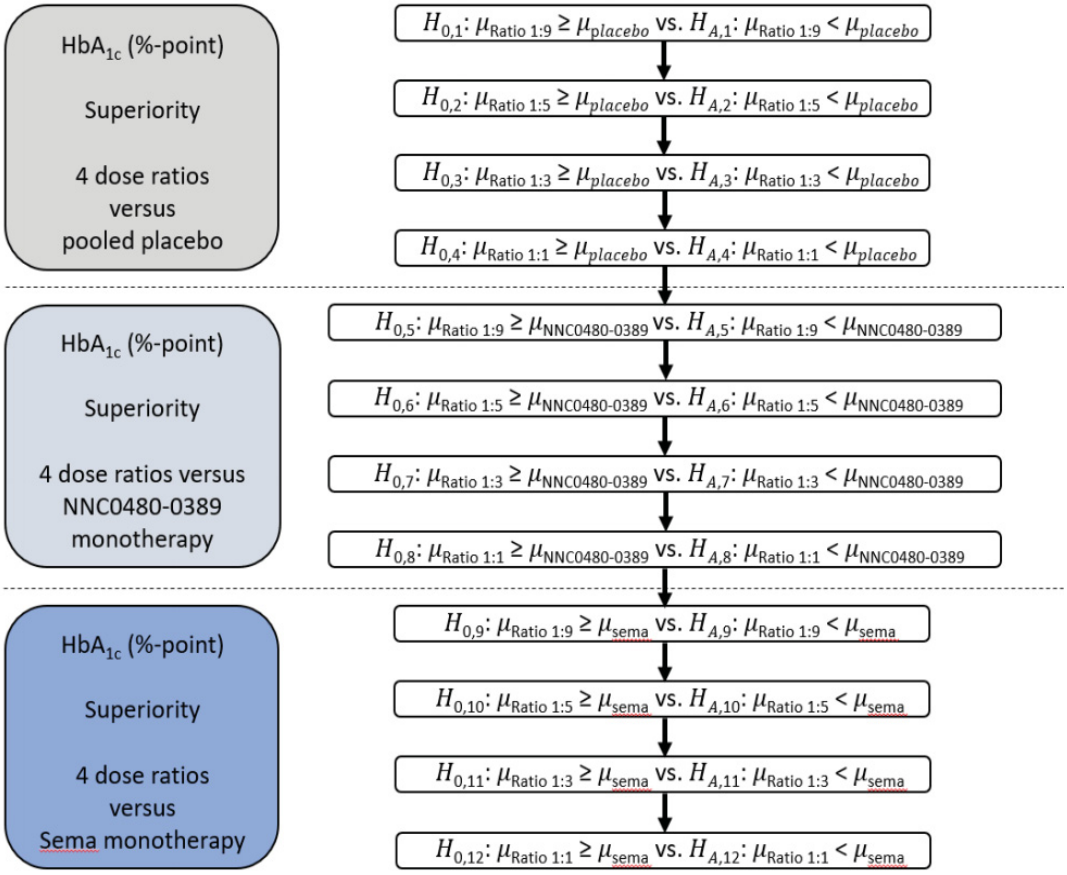
Furthermore, the secondary hypothesis of superiority for each of the four dose ratios versus NNC0480-0389 monotherapy ($\mu_{NNC0480-0389}$) will be evaluated, and finally evaluated versus semaglutide monotherapy (μ_{sema}). In total, this results in a hierarchical testing procedure with 12 tests for change in HbA_{1c} from baseline to week 34 (see section 2.1).

The null hypothesis will be rejected if the upper limit of the estimated two-sided 95% confidence interval (CI) for the treatment difference is below 0, thereby demonstrating that the lowering of HbA_{1c} for the dose ratio is superior to the comparator.

2.1 Multiplicity Adjustment

Confirmation of superiority in lowering of HbA_{1c} for each of the four dose ratios versus placebo will be evaluated using a hierarchical testing procedure starting with the treatment difference between the highest dose ratio (1:9) and placebo and ending with the treatment difference between the lowest dose ratio (1:1) and placebo. Likewise, the hierarchical testing procedure continues with confirmation of superiority in lowering of HbA_{1c} for each of the four dose ratios versus NNC0480-0389 monotherapy, and lastly versus semaglutide monotherapy. If a study arm is discontinued due to safety/tolerability concerns, the tests associated with that study arm will be omitted from the testing hierarchy. In case of a statistically non-significant treatment difference, the testing procedure will stop. This will protect the family wise type 1 error in the strong sense on a 5% (two-sided) level of significance. The hierarchical testing procedure is shown in Figure 2.

Figure 2: Hierarchical testing procedure for showing superiority for each of the four dose ratios vs pooled placebo, NNC0480-0389 monotherapy and semaglutide monotherapy, respectively, on change in HbA1c (%-point) from baseline to week 34



3 Analysis Sets

Two participant analysis sets are defined, see Table 3.

Table 3: Participant analysis sets

Participant analysis set (PAS)	Description
Full analysis set (FAS)	All randomised participants
Safety analysis set (SAS)	All participants who are exposed to randomised treatment

For the efficacy analyses, participants will be included in the analyses according to the randomised treatment; whereas for safety analyses, participants will be included in the analyses according to the treatment they actually received.

Three data points sets are defined, see Table 4.

Table 4: Data points sets

Defined data points sets (DPS)	Description
DPS1 – in-study	All observed data from date of randomisation to date of last planned contact with study site including data collected after treatment discontinuation or initiation of rescue medication will be included in the data point set.
DPS2 – on-treatment	All observed data for which participants are considered exposed to randomised treatment including data collected after initiation of rescue medication will be included in the data point set. More specifically, this includes observed data from DPS1 excluding data observed after the first date of any of the following: • The date of last dose of randomised treatment + 49 days • The date of the last planned contact with study site
DPS3 – on-treatment without rescue medication	All observed data for which participants are considered exposed to randomised treatment and have not initiated any rescue medication will be included in the data point set. More specifically this includes observed data from DPS2 excluding data observed after the first date of any of the following: • Initiation of rescue medication. • The date of last dose of randomised treatment + 14 days

FAS and DPS3 are used to estimate the primary estimand for the primary objective and secondary estimands (hypothetical strategy) for the secondary objective 1, secondary objective 2, and secondary objective 3. Further, FAS and DPS3 will be used to estimate the estimand for the variable diastolic blood pressure.

FAS and DPS1 are used to estimate the additional estimand for the primary objective and for the additional estimands (treatment policy strategy) for secondary objectives 1 and 2. Further, FAS and DPS1 will be used to estimate the secondary estimand (treatment policy strategy) for secondary objective 3 for the body weight endpoints.

SAS and DPS2 are used to analyse safety data.

4 Statistical Analyses

4.1 General Considerations

For all analyses and reporting, the four placebo arms will be pooled.

Results from all statistical analysis will be presented by the following estimated treatment contrast together with the associated two-sided 95% CI and corresponding two-sided p-value:

- each dose ratio of semaglutide and NNC0480-0389 versus placebo
- each dose ratio of semaglutide and NNC0480-0389 versus NNC0480-0389
- each dose ratio of semaglutide and NNC0480-0389 versus semaglutide
- NNC0480-0389 versus placebo

4.1.1 Handling of missing baseline data

The latest available measurement at or prior to randomisation is used as the baseline measurement. If no measurement(s) have been obtained at or prior to randomisation, the mean value at randomisation across all participants is used as the baseline value.

4.1.2 Stratification factors

In statistical analyses where stratification is accounted for, the treatment with metformin (yes/no) at screening and country (Japan/Other) will be included based on the actual information collected through the eCRF. Information regarding HbA_{1c} at screening (<8.5%/≥8.5%) will be included based on the actual value from the central laboratory. In case of missing information from the eCRF or central laboratory, the information collected from the IWRS system will be used. The statistical analyses will account for all three stratification factors as well as the interaction between the three strata. For analyses of the primary endpoint, change in HbA_{1c}, the stratification factor HbA_{1c} at screening (<8.5%/≥8.5%) will not be included as the statistical model will contain baseline HbA_{1c} as a covariate.

4.1.3 Definition of rescue medication

Rescue medication is any intensification of background anti-diabetic medication (metformin) and/or initiation of new anti-diabetic treatment initiated at or after randomisation and before latest date of randomised treatment.

The following rules will be applied based on the concomitant medication data reported by the investigator, to determine whether the recorded anti-diabetic medication is 1. New anti-diabetic medication or 2. Intensification of anti-diabetic medication (metformin).

New anti-diabetic medication: Anti-diabetic medication (4th-level ATC code) that is initiated after randomisation and is new compared to the anti-diabetic background medication at randomisation and with a dosing duration of more than 21 days.

Intensification of anti-diabetic medication: A more than 20% increase in the dose of anti-diabetic medication after randomisation as compared to the anti-diabetic medication dose at randomisation (5th-level ATC code not changed) and with a dosing duration of more than 21 days.

More than 21 days is chosen as a minimum duration for the medication to be considered as 'anti-diabetic medication'. This threshold is set to ensure that the short-term durations (i.e. ≤ 21 days) of anti-diabetic medication (e.g. in connection with concurrent illnesses) are not included because such intensifications are not likely to affect the efficacy endpoints.

4.2 Primary Endpoint Analysis

4.2.1 Definition of Endpoint

Definition of primary endpoint: Change in HbA_{1c} (%-point)

Change from baseline (week 0) to week 34 in HbA_{1c} (%-point) is defined as:

$$\text{Change in } HbA_{1c} \text{ (\%-point)} = HbA_{1c} \text{ (\%) at week 34} - HbA_{1c} \text{ (\%) at baseline}$$

4.2.2 Main Analytical Approach

4.2.2.1 Analysis addressing the primary estimand

The primary estimand will be estimated based on the FAS using the on-treatment without rescue medication data point set (DPS3). The primary analysis for the primary estimand is an analysis of covariance (ANCOVA) with randomised treatment and strata as factors and baseline HbA_{1c} as a covariate.

Handling of missing week 34 values for the primary estimand

Missing data and observations outside the period covered by DPS3 will be imputed using multiple imputation assuming missing at random (MAR).

The multiple imputation is done in three steps:

1. **Imputation:**

    a. First, intermittent missing values are imputed using a Markov Chain Monte Carlo (MCMC) method, in order to obtain a monotone missing data pattern. This imputation is done for each of the treatment groups separately and 1000 copies of the dataset will be generated.

    b. Next, a sequential regression approach for imputing monotone missing values at planned visits will be implemented starting with the first visit after baseline and sequentially continuing to the last planned visit at week 34. The imputation model used to impute missing values at each planned visit will be fitted for each of the treatment groups using observed and imputed data prior to the visit in question. The imputation model will

include strata as factors and baseline and post-baseline HbA_{1c} values prior to the visit in question as covariates.

2. **Analysis:** An ANCOVA with randomised treatment and strata as factors and baseline HbA_{1c} as a covariate will be used to analyse HbA_{1c} change at week 34 for each of the 1000 complete data sets generated as part of the imputation of missing values.

3. **Pooling:** Rubin's rule will be used to combine the analysis results in order to draw inference.

In case of sparse data in some of the groups, the imputation model will be thinned in the following order, starting with the one that will be removed first; interaction between stratification factors, metformin at screening (yes/no), and country (Japan/Other). In case the imputation model needs to be thinned for one of the treatment groups, the imputation model will be thinned in the same way for the remaining treatment groups.

The proportion of HbA_{1c} change data at week 34 that will not be included in the analysis is assumed to be no more than 20%. Initiation of rescue medication is expected to be more frequent with placebo and NNC0480-0389 monotherapy than for the remaining study arms. A higher proportion of participants are expected to discontinue randomised treatment due to adverse events (AEs) in the dose ratio arms and with semaglutide monotherapy compared to the other arms. So, overall, the frequency of data not included in the analysis is expected to be similar across arms

4.2.2.2 Analyses addressing the additional estimand

The analysis model for change in HbA_{1c} (%-point) is an ANCOVA with randomised treatment and strata as factors and baseline HbA_{1c} as a covariate. The additional estimand will be estimated based on the FAS using week 34 measurements from the in-study data point set (DPS1).

Handling of missing week 34 values for the additional estimand

Missing week 34 data will be imputed using multiple imputation assuming NMAR. Imputation will be done based on the placebo group. The imputation model will include strata as factors and baseline HbA_{1c} as covariate.

More specifically, the multiple imputation is done in three steps:

1. **Imputation:** An imputation model is defined using participants with available week 34 data from the placebo group in FAS. The model will be an ANCOVA of HbA_{1c} at week 34 with strata as factors and baseline HbA_{1c} as covariate. The estimated posterior distribution for the parameters (regression coefficients and variance) in the imputation model are then used to impute missing week 34 HbA_{1c} values. This will be done 1000 times, resulting in 1000 complete data sets.

2. **Analysis:** An ANCOVA with randomised treatment and strata as factors and baseline HbA_{1c} as a covariate will be used to analyse HbA_{1c} change at week 34 for each of the 1000 complete data sets generated as part of the imputation of missing values.
3. **Pooling** Rubin's rule will be used to combine the analysis results in order to draw inference.

In case of sparse data in the placebo group, the imputation model will be thinned in the following order, starting with the one that will be removed first; interaction between stratification factors, metformin at screening (yes/no), and country (Japan/Other).

4.2.3 Analysis addressing estimands for secondary objective 1 and secondary objective 2

The estimands for the secondary objective 1 and secondary objective 2 will be estimated similar to analyses described in section 4.2.2.1 and section 4.2.2.2.

4.2.4 Dose-response modelling

The mean HbA_{1c} (%-point) change from baseline to week 34 will be estimated using dose of NNC0480-0389 as a continuous variable. This is done to evaluate the effect of the four dose ratios versus semaglutide monotherapy on change in HbA_{1c} (%-point) and to characterise the dose-response relationship, where dose is the NNC0480-0389 dose in the given dose ratio and response is the treatment difference in change in HbA_{1c} between the dose ratio and treatment with semaglutide monotherapy. The dose-response candidate models in Table 5 will be fitted.

Table 5: Dose-response candidate models

Model	
E_{max}	$E_0+E_{max}\frac{d}{ED_{50}+d}$
Linear	$E_0+\beta d$

E_0: The expected effect on HbA1c with semaglutide monotherapy, ED_{50}: The dose, which produces half of E_{max}, E_{max}: Maximum effect attributable to the drug,

d: NNC0480-0389 dose

The candidate models will be fitted to the estimated difference in mean change in HbA_{1c} (%-point) at week 34 between each of the four dose ratios and semaglutide monotherapy. The estimated differences are obtained from an analysis similar to the one for estimating the primary estimand described above. In the fitting procedure the estimated changes in HbA_{1c} will be weighted by their inverse estimated variances. The model used to evaluate dose-response will be selected among the candidate models based on the best fit to data. The best fit will be evaluated based on convergence, model complexity, Akaike information criterion (AIC) value and visual evaluation.

4.3 Secondary endpoint Analyses

4.3.1 Analysis addressing estimands for secondary objective 3

The following supportive secondary endpoints, change from baseline to week 34 in

- Fasting plasma glucose
- Body weight (kg)
- Waist circumference
- Systolic blood pressure

are computed similar to the primary endpoint. That is, for each of the four parameters, the change from baseline (week 0) to week 34 is defined as:

$$\text{Change in parameter} = \text{parameter value at week 34} - \text{parameter value at baseline}$$

For each of the following supportive secondary endpoints, relative change from baseline (ratio to base) to week 34 in

- Total cholesterol
- High-density lipoprotein (HDL) cholesterol
- Low-density lipoprotein (LDL) cholesterol
- Very-low-density lipoprotein (VLDL) cholesterol
- Triglycerides
- Free fatty acids
- Apolipoprotein B (ApoB)
- High sensitivity C-Reactive Protein

the relative change from baseline (week 0) to week 34 is defined as:

$$\text{Relative change in parameter} = \frac{\text{parameter value at week 34}}{\text{parameter value at baseline}}$$

The endpoint change in body weight (%) will be calculated as

$$\text{Change in body weight (\%)} = \frac{\text{body weight at week 34} - \text{body weight at baseline}}{\text{body weight at baseline}} \times 100\%$$

4.3.1.1 Body weight

The estimands for secondary objective 3 of the secondary endpoints

- Change in body weight (kg)
- Change in body weight (%)

will be estimated similar to analyses described in section 4.2.2.14.2.2.2. The endpoint change in HbA_{1c} from baseline to week 34 will be replaced by the corresponding endpoint, and the covariate baseline HbA_{1c} will be replaced by baseline body weight.

In case of sparse data, the imputation model will be thinned in the following order, starting with the one that will be removed first: interaction between stratification factors, treatment with metformin at screening (Yes/No), HbA_{1c} at screening (<8.5%/≥8.5%), and country (Japan/Other)
In case the imputation model needs to be thinned for one of the treatment groups, the imputation model will be thinned in the same way for the remaining treatment groups

4.3.1.2 Remaining secondary endpoints

Estimands for secondary objective 3 of for each of the remining supportive secondary endpoints (fasting plasma glucose, waist circumference, systolic blood pressure, lipid parameters, and hsCRP)

will be analysed separately using the same analysis model as the primary analysis of the primary estimand described in section 4.2.2.1. The endpoint change in HbA_{1c} from baseline to week 34 and the covariate baseline HbA_{1c} will be replaced by the corresponding endpoint and baseline assessment of it to be analysed.

For lipid parameters and hsCRP a multiplicative model will be used, i.e., estimated treatment ratios will be reported instead of differences, and both the outcome variable and the baseline assessment will be log-transformed prior to analysis.

In case of sparse data, the imputation model will be thinned in the following order, starting with the one that will be removed first:

- Fasting plasma glucose: interaction between stratification factors, treatment with metformin at screening (Yes/No), country (Japan/Other), and HbA_{1c} at screening (<8.5%/≥8.5%).
- Waist circumference, systolic blood pressure, lipid parameters, and hsCRP: interaction between stratification factors, treatment with metformin at screening (Yes/No), HbA_{1c} at screening (<8.5%/≥8.5%), and country (Japan/Other)

In case the imputation model needs to be thinned for one of the treatment groups, the imputation model will be thinned in the same way for the remaining treatment groups.

4.3.1.3 Treatment-emergent adverse events

The secondary endpoint 'number of TEAE' is the number of AEs recorded during the on-treatment period (DPS2). All AEs will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA).

Summaries of TEAEs are presented as an overview including all AEs, serious AEs, AEs leading to premature treatment discontinuation, AEs by severity, AEs by relation to treatment and outcome of AEs. Furthermore, summary tables based on system organ class and preferred term are made for:

- All TEAEs
- Serious TEAEs

4.4 Exploratory Endpoints Analyses

Not applicable.

4.5 Other Safety Analyses

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

4.6 Other Analyses

4.6.1 Analyses addressing the estimand for diastolic blood pressure

The estimand for the parameter diastolic blood pressure will be estimated similar to analyses of systolic blood pressure as described in section 4.3.1.2.

4.6.2 Other Variables and/or Parameters

The following parameters will be summarised by descriptive statistics using FAS and DPS3:

- Fasting insulin
- Fasting glucagon
- Fasting C-peptide
- Fasting proinsulin
- HOMA2-B
- HOMA2-IR
- CTx
- P1NP
- Total adiponectin
- High-molecular weight adiponectin
- GFAP

4.7 Interim Analyses

See the protocol section 9.4.

4.8 Changes to Protocol-planned Analyses

In the protocol section 9.3.2 regarding analysis of the primary estimand, the following text was included on how to handle sparse data in the imputation model:

In case of sparse data in some of the groups, a common treatment discontinuation group across randomised treatments will be created, and randomised treatment will be added to the imputation model as a factor. If this is still not sufficient, the model will be thinned in the following order, starting with the one that will be removed first; strata, randomised treatment, and baseline value.

This text has been updated to (see section 4.2.2.1):

In case of sparse data in some of the groups, the imputation model will be thinned in the following order, starting with the one that will be removed first; interaction between stratification factors, metformin at screening (yes/no), and country (Japan/Other). In case the imputation model needs to be thinned for one of the treatment groups, the imputation model will be thinned in the same way for the remaining treatment groups.

The reason for this update is that the original text regarding a common treatment discontinuation group across randomised treatments is not precise considering the planned imputation approach for

the hypothetical estimand (primary estimand). Thus, the text has been updated to further clarify on how specify the imputation model in case of sparse data.

5 Sample size determination

See the protocol section 9.5.

6 Supporting Documentation

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

Type	Title	Time frame	Unit	Details
Primary endpoint	Change in HbA_{1c}	From baseline (week 0) to visit 24 (week 34)	%-point	Change in HbA_{1c} = HbA_{1c} (%) at week 34 - HbA_{1c} (%) at baseline (week 0)
Supportive secondary endpoint	Change in fasting plasma glucose (FPG)	From baseline (week 0) to visit 24 (week 34)	mmol/L	Change in FPG = FPG (mmol/L) at week 34 - FPG (mmol/L) at baseline (week 0)
	Change in body weight (kg)	From baseline (week 0) to visit 24 (week 34)	kg	Change in body weight (kg) = body weight (kg) at week 34 - body weight (kg) at baseline (week 0)
	Change in body weight (%)	From baseline (week 0) to visit 24 (week 34)	%	Change in body weight (%) $= \frac{\text{body weight (kg) at week 34} - \text{body weight (kg) at baseline}}{\text{body weight (kg) at baseline (week 0)}} \times 100\%$
	Change in waist circumference	From baseline (week 0) to visit 24 (week 34)	cm	Change in waist circumference = waist circumference (cm) at week 34 - waist circumference (cm) at baseline (week 0)
	Change in systolic blood pressure (SBP)	From baseline (week 0) to visit 24 (week 34)	mmHg	Change in SBP = SBP (mmHg) at week 34 - SBP (mmHg) at baseline (week 0)
	Relative change in total cholesterol	From baseline (week 0) to visit 24 (week 34)	Ratio	Relative change in total cholesterol $= \frac{\text{total cholesterol at week 34}}{\text{total cholesterol at baseline (week 0)}}$

	Relative change in high-density lipoprotein (HDL) cholesterol	From baseline (week 0) to visit 24 (week 34)	Ratio	Relative change in HDL cholesterol $= \frac{\text{HDL cholesterol at week 34}}{\text{HDL cholesterol at baseline (week 0)}}$
	Relative change in low-density lipoprotein (LDL) cholesterol	From baseline (week 0) to visit 24 (week 34)	Ratio	Relative change in LDL cholesterol $= \frac{\text{LDL cholesterol at week 34}}{\text{LDL cholesterol at baseline (week 0)}}$
	Relative change in very-low-density lipoprotein (VLDL) cholesterol	From baseline (week 0) to visit 24 (week 34)	Ratio	Relative change in VLDL cholesterol $= \frac{\text{VLDL cholesterol at week 34}}{\text{VLDL cholesterol at baseline (week 0)}}$
	Relative change in triglycerides	From baseline (week 0) to visit 24 (week 34)	Ratio	Relative change in triglycerides $= \frac{\text{triglycerides at week 34}}{\text{triglycerides at baseline (week 0)}}$
	Relative change in free fatty acids	From baseline (week 0) to visit 24 (week 34)	Ratio	Relative change in free fatty acids $= \frac{\text{free fatty acids at week 34}}{\text{free fatty acids at baseline (week 0)}}$
	Relative change in Apolipoprotein B (ApoB)	From baseline (week 0) to visit 24 (week 34)	Ratio	Relative change in ApoB $= \frac{\text{ApoB at week 34}}{\text{ApoB at baseline (week 0)}}$
	Relative change in high sensitivity C-Reactive Protein (hsCRP)	From baseline (week 0) to visit 24 (week 34)	Ratio	Relative change in hsCRP $= \frac{\text{hsCRP at week 34}}{\text{hsCRP at baseline (week 0)}}$
Assessment	Change in diastolic blood pressure (DBP)	From baseline (week 0)	mmHg	Change in DBP = DBP (mmHg) at week 34 - DBP (mmHg) at baseline (week 0)

		to visit 24 (week 34)		

7 References