Cover Page for Statistical Analysis Plan

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Statistical Analysis Plan

Investigation of efficacy and safety of NNC0165-1875 as add-on to semaglutide for weight management in subjects with obesity

Substance: NNC0165-1875

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Version History

This Statistical Analysis Plan (SAP) for study NN9775-4708 is based on the protocol version 4.0 dated 05APR2022.

SAP Version	Date	Change	Rationale
1.0		Not Applicable	Original version
2.0		Updated endpoints accordingly to the newest version of the protocol. Updated the definition of treatment-adherent. Updated the definition of on-treatment. Updated the sensitivity analysis to not being applicable	Protocol was updated with new trial design and endpoints for part 2 of this trial

1 Introduction

Part 1
Part 1 is a 16-week, four-armed, double-blinded (within arms), randomised, placebo-controlled single-site trial comparing co-escalation of two doses of NNC0165-1875 as an add on to semaglutide s.c. 2.4 mg versus placebo added on to semaglutide s.c. 2.4 mg in subjects with obesity.

Part 2
Part 2 is a 48-week, randomised, double-blinded, placebo-controlled, two-armed, multi-centre, proof-of-principle trial comparing once weekly NNC0165-1875 as add on to once-weekly semaglutide s.c. 2.4 mg versus placebo as add on to once weekly semaglutide s.c. 2.4 mg in subjects with obesity.

1.1 Objectives, Endpoints, and Estimands

1.1.1 Primary, secondary and exploratory objectives and estimands

Part 1
Primary objective
To evaluate the safety and tolerability of co-escalation of once-weekly doses of NNC0165-1875 and semaglutide administered simultaneously as separate doses in subjects with obesity.

Part 2
Primary objective
To compare the effect of NNC0165-1875 1.0 mg added on to semaglutide s.c. 2.4 mg at steady state, versus continuing semaglutide s.c. 2.4 mg alone, on body weight in subjects with obesity.

Secondary objective
To compare the effect of NNC0165-1875 1.0 mg added on to semaglutide s.c. 2.4 mg at steady state versus continuing semaglutide s.c. 2.4 mg alone in subjects with obesity on:

- Glycaemic control
- Waist circumference
- Cardiovascular risk factors

To compare the safety and tolerability of NNC0165-1875 1.0 mg and NNC0165-1875 2.0 mg added on to semaglutide s.c. 2.4 mg versus continuing semaglutide s.c. 2.4 mg alone in subjects with obesity.

Estimands
Estimands apply for statistical analysis of Part 2.

Primary estimand
The estimand will quantify the average treatment of NNC0165-1875 1.0 mg as an add on to semaglutide 2.4 mg relative to placebo as an add on to semaglutide 2.4 mg in all randomised subjects regardless of treatment discontinuation and rescue interventions (anti-obesity drugs or devices, or bariatric surgery) with respect to percent change in body weight from week 32 to week 48 in all randomised subjects who are able to reach the target dose of semaglutide during 32 weeks of run-in with escalating semaglutide doses.

Attribute	
Treatment	NNC0165-1875 1.0 mg as an add on to semaglutide 2.4 mg versus placebo as an add on to semaglutide 2.4 mg
Population	All randomised subjects for whom semaglutide have escalated to the target dose with semaglutide 2.4 mg at week 28 and at target dose at the randomisation visit (week 32)
Endpoint	Percent change in body weight from week 32 to week 48
Intercurrent events	Treatment discontinuation: treatment policy strategy Rescue interventions (anti-obesity drugs or devices, or bariatric surgery): treatment policy/effectiveness policy strategy
Population-level summary	Difference in average percent change in body weight between NNC0165-1875 1.0 mg as an add on to semaglutide s.c. 2.4 mg and placebo as an add on to semaglutide s.c. 2.4 mg

Additional estimand

The estimand will quantify the average treatment of NNC0165-1875 1.0 mg as an add on to semaglutide 2.4 mg relative to placebo as an add on to semaglutide 2.4 mg in all subjects who remain on their randomised treatment for the entire planned duration of the treatment period and do not start any rescue intervention (anti-obesity drugs or devices, or bariatric surgery) with respect to percent change in body weight from week 32 to week 48 in all randomised subjects who are able to reach the target dose of semaglutide during 32 weeks of run-in with escalating semaglutide doses.

Attribute	
Treatment	NNC0165-1875 1.0 mg as an add on to semaglutide 2.4 mg versus placebo as an add on to semaglutide 2.4 mg
Population	All randomised subjects for whom semaglutide have escalated to the target dose with semaglutide 2.4 mg at week 28 and at target dose at the randomisation visit (week 32)
Endpoint	Percent change in body weight from week 32 to week 48
Intercurrent events	Treatment discontinuation: hypothetical strategy Rescue interventions (anti-obesity drugs or devices or bariatric surgery): hypothetical/efficacy strategy
Population-level summary	Difference in average percent change in body weight between NNC0165-1875 1.0 mg as an add on to semaglutide s.c. 2.4 mg and placebo as an add on to semaglutide s.c. 2.4 mg

1.1.2 Primary, secondary and exploratory endpoints

Primary endpoint

Part 1

Endpoint title	Time frame	Unit
Number of treatment-emergent adverse events (TEAEs)	From time of dosing (day 1) to follow-up (week 24)	Number of events

Part 2

Endpoint title	Time frame	Unit

Change in body weight	From randomisation (week 32) to end of treatment (week 48)	percentage

Supportive secondary endpoints

Part 2

Supportive secondary endpoints for NNC0165-1875 1.0 mg as an add on to semaglutide 2.4 mg versus placebo 1.0 mg as an add on to semaglutide 2.4 mg:

Endpoint title	Time frame	Unit
Change in body weight	From randomisation (week 32) to end of treatment (week 48)	kg
Change in $HbA1_c$	From randomisation (week 32) to end of treatment (week 48)	Percentage point
Change in fasting plasma glucose	From randomisation (week 32) to end of treatment (week 48)	mmol/l
Change in fasting insulin	From randomisation (week 32) to end of treatment (week 48)	pmol/l
Change in waist circumference	From randomisation (week 32) to end of treatment (week 48)	cm
Relative change in total cholesterol	From randomisation (week 32) to end of treatment (week 48)	ratio to baseline
Relative change in HDL cholesterol	From randomisation (week 32) to end of treatment (week 48)	ratio to baseline
Relative change in LDL cholesterol	From randomisation (week 32) to end of treatment (week 48)	ratio to baseline
Relative change in VLDL cholesterol	From randomisation (week 32) to end of treatment (week 48)	ratio to baseline
Relative change in Triglycerides	From randomisation (week 32) to end of treatment (week 48)	ratio to baseline
Relative change in Free fatty acids	From randomisation (week 32) to end of treatment (week 48)	ratio to baseline

Supportive secondary endpoints for NNC0165-1875 1.0 mg or 2.0 mg as an add on to semaglutide 2.4 mg versus placebo 1.0 mg or 2.0 mg as an add on to semaglutide 2.4 mg:

Endpoint title	Time frame	Unit
Number of emergent adverse events (TEAEs)	From baseline at (week 0) to end of trial (week 56)	Count of events
Number of serious treatment emergent adverse events (SAEs)	From baseline at (week 0) to end of trial (week 56)	Count of events

1.2 Trial Design

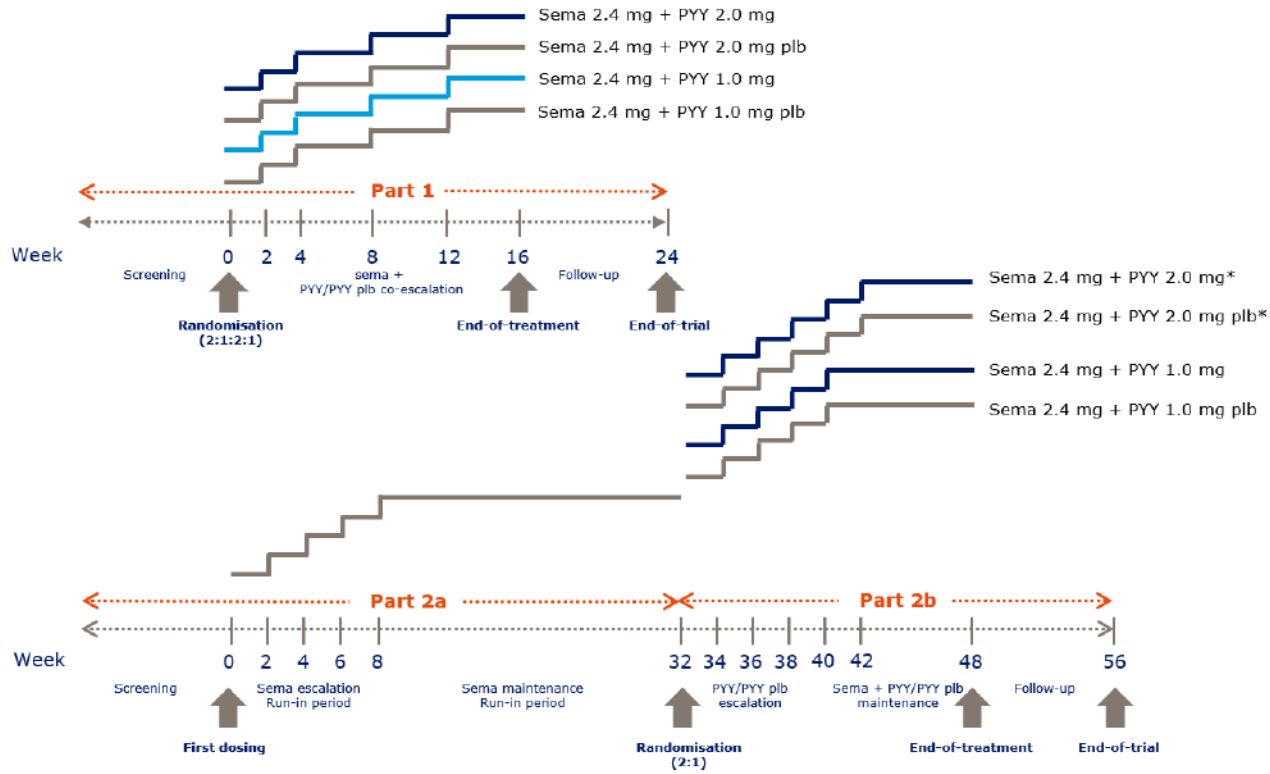
Part 1 is a 16-week, four-armed, double-blinded (within arms), randomised, placebo-controlled, single-site trial comparing co-escalation of two doses of NNC0165-1875 as an add on to semaglutide s.c. 2.4 mg versus placebo added on to semaglutide s.c. 2.4 mg in subjects with obesity.

Part 2 is a 48-week, four-armed, double-blinded (within arms), randomised, placebo-controlled, multi-centre, proof-of-principle trial comparing once weekly NNC0165-1875 as add on to once-weekly semaglutide s.c. 2.4 mg versus placebo as add on to once-weekly semaglutide s.c. 2.4 mg in subjects with obesity. Part 2 will evaluate efficacy and safety for NNC0165-1875 1.0 mg, and safety for NNC0165-1875 2.0 mg.

Part 2 consists of two parts: an open-label run-in part (Part 2a) where all subjects are treated with once-weekly semaglutide and a second part (Part 2b) where once-weekly NNC0165-1875 or NNC0165-1875 placebo is added to semaglutide s.c. 2.4 mg.

An overview of the trial design for Part 1 and Part 2 is presented in Figure 1-1

Figure 1-1 Overview of the trial design



PYY: NNC0165-1875; Sema: semaglutide; Plb: placebo
* 12 subjects will be randomised 2:1 to receive sema 2.4 mg + PYY 2.0 mg or sema 2.4 mg + PYY 2.0 mg plb

2 Statistical Hypotheses

Part 1

There is no formal hypothesis testing for Part 1.

Part 2

For the primary endpoint percentage weight change from randomisation (week 32) to end-of-treatment (week 48), the superiority test for NNC0165-1875 1.0 mg and semaglutide s.c. 2.4 mg versus placebo 1.0 mg and semaglutide s.c. 2.4 mg will be carried out as follows. As all subjects will receive semaglutide s.c. 2.4 mg and to ease notation, semaglutide s.c. 2.4 mg is ignored in the notation. Let $\mu_{\text{NNC0165-1875 ,1.0 mg}}$ and $\mu_{\text{placebo, 1.0 mg}}$ denote the true mean of percentage weight change for dose level NNC0165-1875 1.0 mg and the placebo 1.0 mg group, respectively.

The null and alternative hypotheses tested are

$$H_0: \mu_{\text{NNC0165-1875 ,}x} \geq \mu_{placebo} \text{ vs. } H_A: \mu_{\text{NNC0165-1875 ,}x} < \mu_{placebo}$$

The null hypothesis will be rejected if the upper limit of the estimated two-sided 95% CI for the treatment difference is below 0.

3 Analysis Sets

The following populations are defined:

Population	Description
Full analysis set	Full analysis set (FAS): All subjects randomised. Exclusion of data from analyses should be used restrictively, and normally no data should be excluded from the FAS. Subjects will be analysed according to the randomised treatment
Safety analysis set	Safety analysis set (SAS): All subjects randomly assigned to trial treatment and who take at least one dose of trial product. Subjects are analysed according to the treatment they actually received.

The subjects or observations to be excluded, and the reasons for their exclusion must be documented before unblinding. The subjects and observations excluded from analysis sets, and the reason for this, will be documented in the CTR.

Treatment periods

Three observation periods are defined for each subject in Part 2:

- In-trial: The in-trial period is defined as the uninterrupted time interval from date of randomisation to date of last contact with trial site.
- On-treatment: A time-point is considered as 'on-treatment' if any dose of trial products has been administered within the prior 8 weeks. The on-treatment period is defined as all times which are considered on-treatment.
- Treatment-adherent: A time-point is considered as 'treatment-adherent' if trial product has been administered within the prior 2 weeks with NNC0165-1875/placebo and semaglutide and only before the first event of 'treatment non-adherence'. The derived date of the missed dose causing treatment non-adherence (second consecutive with NNC0165-1875/placebo or semaglutide) will be used as the latest date for including assessments in this observation period. For subjects who initiate any other weight loss intervention before this date, the date of starting other weight management drugs or undergoing bariatric surgery will be used as latest date for using assessments in this observation period. Thus, the assessment closest in time and before the date of starting any weight loss intervention will be used as last assessment on randomised treatment. For subjects not reaching target dose according to the escalation regimen no post-baseline assessments will be included.

The in-trial and on-treatment periods define the patient years of observation (PYO) and patient years of exposure (PYE), respectively, as the total time duration in the periods.

4 Statistical Analyses

This section is only applicable for part 2.

4.1 General Considerations

Handling of missing baseline data

The last available and eligible observation at or before randomisation is used as the baseline value. If no assessments are available, the mean value at randomisation across all eligible subjects is used as the baseline value.

4.2 Primary endpoint

Definition of primary endpoint: % weight change
Change from randomisation at week 32 to week 48 in body weight (%) is defined as:

$$\%\ \text{weight change} = \frac{(\text{body weight at week 48} - \text{body weight at week 32})}{\text{body weight at week 32}} \times 100\%$$

4.2.1 Analyses addressing the primary estimand

The following statistical analyses and imputation methods are designed to address the primary estimand, i.e., to assess the effectiveness of NNC0165-1875 1.0 mg.

The analysis model for % weight change is an ANCOVA with randomised treatment as factor and baseline body weight (kg) as a covariate.

Primary imputation approach for the primary estimand (RS-MI)

The primary analysis of the primary estimand is a retrieved subjects-based multiple imputation approach (RS-MI) which is simplified but similar to the one described by McEvoy. Missing body weight measurement at week 48 for non-retrieved subjects (MD) are imputed using assessments from retrieved subjects (AD). Missing body weight measurements at week 48 for subjects on randomised treatment (MT) are imputed using available measurements at week 48 from subjects on randomised treatment (AT).

The multiple imputation approach is done in three steps:

1. **Imputation**: An imputation model is defined using retrieved subjects (AD) from the FAS. The model will be a linear regression of body weight (kg) at week 48 with treatment as factor and baseline body weight (kg), last available treatment-adherent observation of body weight (kg) and number of days in the treatment-adherent observation period as covariates[1]. No interactions will be included. If any subjects are MT, an imputation model for missing body weight measurements at week 48 for MT subjects will also be defined using AT subjects in a similar way. The estimated posterior distribution for the parameters (regression coefficients and

[1] If this is not feasible then remove last available treatment-adherent observation of body weight and number of days in the treatment-adherent observation period from the model.

variances) in the imputation models are then used to impute missing week 48 body weight values. This will be done 1000 times, resulting in 1000 complete data sets.

2. **Analysis**: Analysis of each of the 1000 complete data sets using the ANCOVA with treatment as factor and baseline body weight as covariate[2], resulting in 1000 estimates for each treatment comparison.

3. **Pooling**: The 1000 estimation results are integrated into a final result using Rubin's formula.

The estimated treatment difference between NNC0165-1875 1.0 mg dose as add on to semaglutide s.c. 2.4 mg and placebo group will be reported together with the associated two-sided 95% CI and corresponding two-sided p-value.

Sensitivity Analysis

Given a small amount of data and that the trial is not an confirmatory trial. A sensitivity analysis is not applicable.

4.2.2 Analyses addressing the additional estimand

The following statistical analysis is designed to address the additional estimand, i.e., to assess the effectiveness of NNC0165-1875 1.0 mg in subjects who remain on their randomised treatment for the entire planned duration of the treatment period and do not start any rescue intervention.

The analysis model for % weight change will be analysed using MMRM with the same factor and covariate as for the primary analysis all nested within visit. In the analysis all the data from the subjects who remain on their randomised treatment for the entire planned duration of the treatment period or until before the start of rescue intervention (anti-obesity drugs or bariatric surgery) or until first discontinuing of randomised treatment. The estimated treatment difference between individual NNC0165-1875 1.0 mg doses as add on to semaglutide s.c. 2.4 mg and placebo group will be reported together with the associated two-sided 95% CI and corresponding two-sided p-value.

4.3 Secondary endpoint

4.3.1 Confirmatory secondary endpoint

Not applicable for this trial

4.3.2 Supportive secondary endpoints

Supportive secondary endpoints are listed in Section 1.1.2

Efficacy endpoints

Change from randomisation at week 32 to week 48 in:

- Body weight (kg)

[2] If this is not feasible then remove treatment as factor.

- Waist circumference (cm)
- $HbA1_c$ (%-point)
- Fasting Plasma Glucose (mmol/l)
- Fasting insulin (pmol/l)

These continuous supportive secondary efficacy endpoints will be analysed using the same analysis model as the primary analysis for the primary endpoint addressing the primary estimand. The outcome variable % weight change and the covariate baseline body weight will be replaced by the corresponding outcome and baseline assessments of the endpoint to be analysed. The estimated treatment difference between individual NNC0165-1875 1.0 mg doses as add on to semaglutide s.c. 2.4 mg and placebo group will be reported together with the associated two-sided 95% CI.

Relative change from randomisation at week 32 to week 48 in following lipids:

- Total cholesterol
- HDL cholesterol
- LDL cholesterol
- VLDL cholesterol
- Triglycerides
- Free Fatty acids

For lipids, a multiplicative model will be used, i.e., the ratio between post-randomisation measurements and baseline will be analysed as the outcome variable instead of differences, and both the outcome variable and the baseline assessment will be log-transformed prior to analysis.

These endpoints will be summarised by descriptive statistics using the FAS.

4.4 Exploratory endpoint

Not applicable in this trial

4.5 Safety Analyses

All safety analyses will be made on the safety analysis set. The standard safety assessments (AEs, safety laboratory parameters, vital signs, etc.) will be reported descriptively.

Safety Endpoints

Part 1

A TEAE is defined as an event that either:

- Has onset after administration of trial product and no later than the follow-up visit
- Is present before trial product administration and increases in after the first dose of trial product and no later than the follow-up visit.
- No formal statistical inference will be carried out based on the number of TEAEs and SAEs. TEAEs and treatment-emergent SAEs will be summarised by descriptive statistics.

Part 2

Adverse events will be defined as 'treatment-emergent' (TEAE), if the onset of the event occurs in the on-treatment period, see Section 3. No formal statistical inference will be carried out based on the number of TEAEs and SAEs. TEAEs and treatment emergent SAEs will be summarised by descriptive statistics.

4.6 Other Analyses

Pharmacokinetic and/or pharmacodynamic modelling
Population PK and exposure-response analyses will be used as supportive evidence for the evaluation of efficacy and safety as well as to support the dose selection of s.c. NNC0165-1875 for future clinical development in subjects with obesity. Firstly, plasma NNC0165-1875 concentrations will be analysed using a population PK model, quantifying covariate (such as baseline body weight, age, sex, race, ethnicity) effects on NNC0165-1875 exposure. Secondly, model-based estimates of steady-state average concentrations will be derived for each subject, to facilitate subsequent exposure-response analyses. Relevant efficacy and safety endpoints will be related to steady-state average concentrations and subjected to model-based analysis.

4.7 Interim Analyses

Not applicable in this trial

4.8 Changes to Protocol-planned Analyses

The sensitivity analysis for the primary estimand has been removed due to a small amount of data and that the trial is not a confirmatory trial.
The analysis described in protocol section 9.4.3.2 does not belong to the secondary endpoint, but is the analysis described for the additional estimand. This error has been corrected in this SAP.

4.9 Handling of pharmacokinetic concentration values below lower limit of quantification (LLOQ)

Timing of values below LLOQ	Imputation	Use of imputed values
Values below LLOQ obtained before the first administration	Set to 0 (zero)	Plots
Values below LLOQ obtained after the first administration	Set to LLOQ/2	Plots

5 Sample size determination

Part 1

Part 1 is exploratory in nature, as the primary objective is to assess safety and tolerability following multiple s.c. once-weekly doses of NNC0165-1875 and semaglutide. Therefore, the sample size is not based on a formal statistical assessment but is considered to be sufficient to evaluate the safety and tolerability based on summaries of results. Specifically, in Part 1, 32 subjects will be randomised 2:1:2:1 to receive NNC0165-1875 1.0 mg, NNC0165-1875 1.0 mg placebo, NNC0165-1875 2.0 mg or NNC0165-1875 2.0 mg placebo. All subjects will receive semaglutide.

Approximately 75 subjects will be screened to achieve 32 subjects randomly assigned to trial product.

Part 2

Taxonomy of week 48 assessments

For each subject, a given assessment at week 48 may be available or missing and the subject may be on randomised treatment or not. Table 5-1 describes the taxonomy for this. Note that this is done per assessment and per subject; subjects may be a different type for different assessments (a subject may have 'available on randomised treatment (AT)' for body weight but 'missing on randomised treatment (MT)' for waist circumference).

Table 5-1 Taxonomy for subjects based on week 48 assessments

Assessment at week 48	Subjects on randomised treatment at week 48	Type description	Type Abbreviation
Available	Yes	Available on randomised treatment: Subjects who complete the trial on randomised treatment with an assessment at week 48. This includes those that stop and restart trial product.	AT
	No	Available but discontinued Subjects who discontinue randomised treatment prematurely but return to have an assessment at week 48. These are also called retrieved subjects.	AD
Missing	Yes	Missing on randomised treatment: Subjects who complete the trial on randomised treatment without an assessment at week 48. This includes those that stop and restart trial product.	MT
	No	Missing and discontinued: Subjects who discontinue randomised treatment prematurely and do not return to have an assessment at week 48. These are also called non-retrieved subjects.	MD

Sample size assumptions

The assumptions for the sample size calculations are:

- The two-sided significance level is 5%

- 50 subjects are randomised to the NNC0165-1875 1.0 mg added on to semaglutide arms
- 25 subjects are randomised to the NNC0165-1875 1.0 mg placebo added on to semaglutide arms

Assumptions corresponding to the primary estimand:

- Non-retrieved subjects (MD) in any of the active arms are assumed to have a 11% body weight gain compared to subject completing treatment with placebo added on to semaglutide s.c. 2.4 mg
- Retrieved subjects (AD) in any of the active arms are assumed to have an effect corresponding to half the treatment difference between non-retrieved subjects and subjects who complete the trial in that arm (AT)
- The groups of non-retrieved subjects, retrieved subjects and completers are assumed to have a standard deviation for body weight change of 4.8%
- 10% of subjects are assumed to discontinue randomised treatment permanently and 60% of these are retrieved (AD) at week 48 (based on data from trial NN9536-4153)
- Standard deviation after adjustment for treatment discontinuation and missing data is 5.9%
- The treatment differences are analysed by two-sided t-tests which is a simplification of the main analyses including explanatory variables.

Given the assumptions above, a treatment difference of NNC0165-1875 1.0 mg added on to semaglutide s.c. 2.4 mg compared to placebo added on to semaglutide s.c. 2.4 mg for completers of 4.5% corresponds to a treatment difference of 4.2% for targeting the treatment policy estimand. Standard deviation after adjustment for treatment discontinuation and missing data is 5.9%.

Furthermore, 50 subjects randomised to NNC0165-1875 1.0 mg added on to semaglutide arm and 25 randomised to the NNC0165-1875 1.0 mg placebo added on to semaglutide arms, gives a power of 81% for the test of difference between high dose of NNC0165-1875 combined with semaglutide and placebo group under the assumption of a 4.5%-point difference in weight loss for completers.

Based on NN9536-4376, it is expected that 11% subjects will drop out by week 32. To account for this, it is planned to enrol 90 subjects. Further, approximately 106 subjects will be screened to ensure 90 subjects for enrolment.

The probabilities and power calculations beneath are based on assumptions for the primary estimand. However, both the primary and secondary estimands will be covered, since the probabilities and power for the secondary estimand are higher compared to the primary estimand.

Table 5-2 lists the power for different choices of sample size and assumed treatment difference for completers.

Table 5-2 Power when comparing NNC0165-1875 added on to semaglutide s.c. 2.4 mg versus placebo added on to semaglutide s.c. 2.4 mg

N subjects randomised 2:1	Treatment difference	Power
60	4.0	63%
75	4.0	73%
90	4.0	80%
60	4.5	72%
75	4.5	81%
90	4.5	88%
60	5.0	80%
75	5.0	88%
90	5.0	93%

6 Supporting Documentation

6.1 Appendix 1: List of abbreviations

AD	Available but discontinued
AE	adverse event
ANCOVA	analysis of covariance
AT	Available on randomised treatment
BMI	body mass index
CI	confidence interval
FAS	Full analysis set
HDL	High density lipoprotein
LDL	Low density lipoprotein
MD	Missing and discontinued
MMRM	Mixed model with repeated measurement
MT	Missing on randomised treatment
PK	Pharmacokinetic
PYE	Patient years of exposure
PYO	Patient years of observation
RS-MI	Retrieved subjects-based multiple imputation
SAE	Serious treatment emergent adverse event
SAS	Safety analysis set
TEAE	Treatment emergent adverse event
VLDL	Very low-density lipoprotein

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

For part 1

Type	Title	Time frame	Unit	Details
Primary endpoint	Number of treatment emergent adverse events (TEAEs)	From time of dosing (day 1) to follow-up (week 24)	Number of events	No further details.

For part 2

Type	Title	Time frame	Unit	Details
Primary endpoint	Change in body weight	From randomisation (week 32) to end of treatment (week 48)	%	Calculated by subtraction of baseline body weight from body weight at end of treatment.
Supportive secondary endpoint	Change in body weight	From randomisation (week 32) to end of treatment (week 48)	kg	Calculated by subtraction of baseline body weight from body weight at end of treatment.
Supportive secondary endpoint	Change in $HbA1_c$	From randomisation (week 32) to end of treatment (week 48)	Percentage point	Calculated by subtraction of baseline $HbA1_c$ from $HbA1_c$ at end of treatment.
Supportive secondary endpoint	Change in fasting plasma glucose	From randomisation (week 32) to end of treatment (week 48)	mmol/l	Calculated by subtraction of baseline fasting plasma glucose from fasting plasma glucose at end of treatment.
Supportive secondary endpoint	Change in fasting insulin	From randomisation (week 32) to end of treatment (week 48)	pmol/l	Calculated by subtraction of baseline fasting insulin from fasting insulin at end of treatment.
Supportive secondary endpoint	Change in waist circumference	From randomisation (week 32) to end of treatment (week 48)	cm	Calculated by subtraction of baseline waist circumference from waist circumference at end of treatment.
Supportive secondary endpoint	Relative change in total cholesterol	From randomisation (week 32) to end of treatment (week 48)	ratio to baseline	Calculated by dividing total cholesterol at end of treatment by total cholesterol at baseline
Supportive secondary endpoint	Relative change in HDL cholesterol	From randomisation (week 32) to end of treatment (week 48)	ratio to baseline	Calculated by dividing HDL cholesterol at end of treatment by HDL cholesterol at baseline
Supportive secondary endpoint	Relative change in LDL cholesterol	From randomisation (week 32) to end of treatment (week 48)	ratio to baseline	Calculated by dividing LDL cholesterol at end of treatment by LDL cholesterol at baseline
Supportive secondary endpoint	Relative change in VLDL cholesterol	From randomisation (week 32) to end of treatment (week 48)	ratio to baseline	Calculated by dividing VLDL cholesterol at end of treatment by VLDL cholesterol at baseline
Supportive secondary endpoint	Relative change in triglycerides	From randomisation (week 32) to end of treatment (week 48)	ratio to baseline	Calculated by dividing triglycerides at end of treatment by triglycerides at baseline
Supportive secondary endpoint	Relative change in free fatty acids	From randomisation (week 32) to end of treatment (week 48)	ratio to baseline	Calculated by dividing free fatty acids at end of treatment by free fatty acids at baseline

Type	Title	Time frame	Unit	Details
Supportive secondary endpoint	Number of emergent adverse events (TEAEs)	From baseline at (week 0) to end of trial (week 56)	Count of events	No further details.
Supportive secondary endpoint	Number of serious treatment emergent adverse events (SAEs)	From baseline at (week 0) to end of trial (week 56)	Count of events	No further details.