Cover Page for Statistical Analysis Plan

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16.1.9 Documentation of statistical methods

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Statistical Analysis Plan

Trial ID: NN9838-4433

Investigation of safety and efficacy of cagrilintide for weight management – a dose finding trial

Trial phase: 2

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

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List of abbreviations

Include the list of the abbreviations used in the document in alphabetical order. Do not include abbreviations that are not used in the SAP and do not include well known abbreviations such as mmHg.

ABPM:	*ambulatory blood pressure monitoring*
ANOVA	*analysis of variance*
AUC:	*area under the curve*
BMI	*body mass index*
CI	*confidence interval*
CRF	*case report form*
CTR	*clinical trial report*
DBP:	*Diatolic blood pressure*
EoT	*end-of-text*
FAS	*Full analysis set*
LOCF	*last observation carried forward*
MedDRA	*Medical Dictionary for Regulatory Activities*
MMRM	*Mixed model for repeated measurements*
OD	*Once daily*
OW	*Once weekly*
PD	*pharmacodynamics*
PK	*pharmacokinetics*
PP	*per protocol*
SAS	*Safety analysis set*
SBP	*Systolic blood pressure*
SAE	*serious adverse event*
SAP	*statistical analysis plan*
SD	*standard deviation*
SE	*standard error*

1 Introduction

1.1 Trial information

The primary objective is to compare the dose-response of increasing doses of cagrilintide once weekly (OW) versus placebo and versus liraglutide 3.0 mg once daily (OD) on body weight, in subjects with overweight or obesity, when added as an adjunct to a reduced-calorie diet and increased physical activity.
The primary estimand will quantify the average treatment effect of cagrilintide relative to placebo and liraglutide 3.0 mg after 26 weeks, as an adjunct to a reduced-calorie diet and increased physical activity, in all randomised subjects had they remained on their randomised treatment for the entire planned duration of the trial and not started any other weight loss intervention ('Trial product estimand'/'hypothetical estimand'). The secondary estimand will quantify the average treatment effect of cagrilintide relative to placebo and liraglutide 3.0 mg after 26 weeks, as an adjunct to a reduced-calorie diet and increased physical activity, in all randomised subjects regardless of adherence to treatment and regardless of starting any other weight loss intervention ('treatment policy estimand').
For more details on the trial, see the trial protocol.

1.2 Scope of the statistical analysis plan

This SAP is based on the protocol "Investigation of safety and efficacy of cagrilintide for weight management – a dose finding trial", version 2.0.

2 Statistical considerations

Treatment non-adherence
To address the primary estimand the concept of 'Treatment non-adherence' is defined as the occurrence of either one of the following events:

A subject is treatment adherent until first time of non-adherence, defined as:

- The subject has not been dosed with trial product within the prior 14 days.
- The subject has received other weight management drug or bariatric surgery
- The subject has not reached target dose at the following pre-specified evaluation week (relative to first dose administration):

Active treatment / placebo	Cagrilintide 0.3 mg	Cagrilintide 0.6 mg	Cagrilintide 1.2 mg	Cagrilintide 2.4 mg	Cagrilintide 4.5 mg	Liraglutide 3.0 mg
Evaluation week	2	2	3	6	9	8

- After the pre-specified evaluation week for the target dose, the subject has not received the target dose ±10% within the prior 14 days.

Taxonomy of week 26 assessments

To address the secondary estimand the following taxonomy is introduced: For each subject a given assessment at week 26 may be available or missing and the subject may be on randomised treatment or not (Table 2-1). 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 2-1 Taxonomy for subjects based on week 26 assessments

Assessment at week 26	Subjects on randomised treatment at week 26	Type description	Type Abbreviation
Available	Yes	**Available on randomised treatment**: Subjects who complete the trial on randomised treatment with an assessment at week 26. 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 26. 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 26. 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 26. These are also called non-retrieved subjects.	MD

2.1 Sample size determination

The sample size is based on the objective of finding the optimal dose of cagrilintide and is based on the primary endpoint. To characterise the shape of the curve for the dose-response relationship it is considered adequate to test 5 doses of cagrilintide and the sample size for each dose is determined in order to achieve a good precision on this relationship. Furthermore, sample size estimation is based on addressing assumptions corresponding to the analyses of both the primary and secondary estimands.

In the imputation approach used for the sample size calculations addressing the primary estimand missing values (MT and MD) and assessments from retrieved subjects (AD) are assumed to be similar to treatment completers (AT) within the same treatment group. In the imputation approach

used for the sample size calculations addressing the secondary estimand, missing values (MT and MD) are assumed to be similar to placebo subjects regardless of treatment arm.

The five different injection volumes in each of the cagrilintide placebo arms and the one liraglutide placebo arm will be pooled into one placebo group in the main analyses. This pooling assumes that there is no substantial effect of different placebo volumes or different dose escalation on the efficacy and safety endpoints. This is consistent with findings from previous obesity trials (NN8022-1922 and NN9536-4153).

The assumptions for the sample size calculations are:

- The significance level is 5%

- 100 subjects are included in each of the cagrilintide arms, 100 subjects in the liraglutide 3.0 mg OD arm and 100 subjects in total in the pool of cagrilintide placebo and liraglutide placebo arms

- Assumptions corresponding to the primary estimand:
    - Standard deviation of 5.2% for relative change in weight loss at week 26 (based on data from trial NN9536-4153)
    - Treatment effect versus the pooled placebo group of at least 8% for the optimal dose among completers (based on data from trial NN9536-4153)
    - Treatment effect versus liraglutide 3.0 mg of at least 3% among completers (based on data from trial NN9536-4153 and NN8022-1839)

- Assumptions corresponding to the secondary estimand:
    - Standard deviation of 5.6% for relative change in weight loss at week 26 (based on data from trial NN9536-4153)
    - 13% of subjects discontinue randomised treatment permanently and 60% of these are retrieved (AD) at week 26 (Based on data from trial NN9536-4153)
    - All subjects in the pooled placebo group are assumed to have the same effect as subjects who complete the trial on placebo (AT)
    - Retrieved subjects (AD) in any of the active arms are assumed to have an effect corresponding to half the treatment difference (compared to the pooled placebo group) of subjects who complete the trial in that arm (AT)
    - Non-retrieved subjects (MD) in any of the active arms are assumed to have an effect corresponding to the pooled placebo group
    - Treatment effect versus the pooled placebo group of at least 7.3% for the optimal dose after adjustment for treatment discontinuation and missing data

- The treatment differences are analysed by two-sided t-tests which is a simplification of the main analyses including explanatory variables

The probabilities and power calculations beneath are based on assumptions for the secondary estimand (primary estimand for the treatment effect versus liraglutide 3.0 mg). However, both the primary and secondary estimands will be covered, since the probabilities and power for the primary estimand are higher compared to the secondary estimand.

To characterise the dose-response relationship well, the precision of the mean difference between any cagrilintide dose and the pooled placebo group is evaluated by calculating the probability of the half-width of the confidence interval (CI) to be equal to or below a given value. Table 2-2 gives this probability for different number of subjects and values for the CI half-width.

Table 2-2 Probability of desired CI half-width

N per active arm/N for pooled placebo group	CI half-width (%)	Probability
100	1.7	96%
80	1.7	32%
100	1.6	69%
80	1.6	7%

A sample size of 100 subjects in each active treatment arm compared with a pooled placebo group of 100 subjects allows the 95% CI for the treatment difference between any active arm and placebo to be contained within +/-1.7% of the estimate with 96% probability. This is considered to be a sufficient precision to characterize the dose-response relationship. In total this requires a sample size of 700 subjects.

For the primary endpoint, change from randomisation at week 0 to week 26 in body weight (%), a sample size of 100 subjects in each active treatment arm results in a power of more than 99% for a significant difference between the optimal dose of cagrilintide and the pooled placebo group.

For the primary endpoint a sample size of 100 subjects in each active treatment arm results in a power of 98% for detecting a significant difference between the optimal dose of cagrilintide and liraglutide 3.0 mg for the primary estimand.

2.2 Definition of analysis sets

Two analysis sets are defined:

The *full analysis set* (FAS) includes all randomised subjects according to the intention-to-treat principle.

The *safety analysis set* (SAS) includes all randomised subjects exposed to at least one dose of randomised treatment.

Any observation excluded from the analysis will be documented before database lock with the reason for exclusion provided.

2.2.1 Observation periods

Three observation periods are defined for each subject:

Period	Characteristics	Definition	Purpose
In-trial	Observation period: Patient Years of Observation (PYO)	The *in-trial period* is defined as the uninterrupted time interval from date of randomisation to date of last contact with trial site. Follow-up time for positive antibodies is not included in the in-trial period.	Used for reporting of adverse events (AEs)
On-treatment	Exposure period using 6-weeks ascertainment window irrespective of rescue interventions: Patient Years of Exposure (PYE)	A time-point is considered as 'on-treatment' if any dose of trial product has been administered within the prior 6 weeks. The on-treatment period is defined as all times which are considered on-treatment. The on-treatment period will therefore be from the date of first trial product administration to date of last trial product administration excluding potential off-treatment time intervals triggered by at least 6 consecutive missed doses for cagrilintide or 6 consecutive weeks of missed dosing with liraglutide.	Used for reporting of treatment emergent adverse events (TEAEs)
Treatment-adherent	Treatment period using 2-weeks ascertainment window with no rescue interventions	A subject is treatment adherent until the first time of non-adherence defined as • The subject has not been dosed with trial product within the prior 14 days. • The subject has received other weight management drug or bariatric surgery • The subject has not reached target dose at a pre-specified week (section 2) • After the pre-specified evaluation week for the target dose, the subject has not received the target dose ±10% within the prior 14 days.	Use for determining the primary estimand

2.3 Statistical analyses

Efficacy endpoints will be analysed using the FAS; safety endpoints will be analysed using the SAS.

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 subjects is used as the baseline value.

2.3.1 Primary endpoint

Definition of primary endpoint: % weight change

Change from randomisation at week 0 to week 26 in body weight (%) is defined as:

$$\% \text{ weight change} = \frac{(\text{body weight at week } 26 - \text{body weight at baseline})}{\text{body weight at baseline}} \times 100\%$$

2.3.1.1 Analyses addressing the primary estimand

The primary estimand for % weight change addresses the efficacy of cagrilintide and will be estimated based on the FAS using post-baseline measurements up to and including week 26 from the treatment-adherent observation period.

The primary analysis for the primary estimand for % weight change is an analysis of covariance (ANCOVA) with randomised treatment as factor and baseline body weight (kg) as a covariate.

Handling of missing week 26 values for the primary estimand
Observations outside the treatment-adherent observation period such as week 26 assessments for retrieved drop-outs (AD) will be handled as if they were missing and will be imputed using multiple imputation assuming that missing data is missing at random (MAR). Missing data will be imputed using observed data within the same randomised treatment group. This approach makes the assumption that subjects with missing data and subjects with dose non-adherence or weight loss intervention have the same effect as subjects adhering to randomised treatment without initiating any other weight loss intervention.

If the definition of treatment non-adherence is too restrictive then excluding observations due to dose lowering will not be implemented. If this is also too restrictive then a higher number of allowed missed dose will be considered.

The multiple imputation is done in three steps:

1. **Imputation:**
    a. 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. 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 26. A model used to impute missing values at each planned visit will be fitted for each of the treatment groups (each cagrilintide dose, liraglutide 3.0 mg or pooled placebo) using observed data. The model will include gender (male/female) and region (Europe, North America, and rest of the world) as factors and baseline and post-baseline body weight (kg) values observed prior to the visit in question as covariates.

2. **Analysis:** An ANCOVA with treatment as categorical effects and baseline body weight (kg) as a covariate will be used to analyse body weight % change at week 26 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.

The proportion of missing weight change data at week 26 is estimated to be 5% (based on data from trial NN9536-4153) and is expected to be similar in all treatment arms.

Of relevance for the estimation of the primary estimand, the combined proportion of missing data and subjects with treatment non-adherence is estimated to be 13%. This is based on data on proportion of subjects discontinuing treatment from trial NN9536-4153 and a very low expected proportion of subjects undergoing bariatric surgery or starting other weight management interventions. cagrilintide treatment is expected to be effective with regard to weight loss, and this should reduce the number of missed doses due to ineffective therapy. A higher rate of missed doses due to GI AEs is expected in the high cagrilintide dose treatment arms and the liraglutide 3.0 mg arm compared to placebo. Apart from this, the rate of missed doses due to AEs is expected to be similar across groups. Based on previous experience, a higher rate of treatment discontinuation due to other reasons is expected in the placebo group compared to active treatment. This difference may be due to lack of efficacy with placebo treatment.

The estimated treatment difference between individual cagrilintide doses and pooled placebo group will be reported together with the associated two-sided 95% CI and corresponding two-sided p-value. The pooled placebo group will include all subjects on cagrilintide placebo as well as liraglutide placebo.

Confirmation of superiority for each cagrilintide dose vs. placebo will be evaluated using a hierarchical testing procedure starting with the treatment difference between the highest cagrilintide dose and placebo and ending with the lowest dose. In the case of a 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% level of significance.

The superiority test for cagrilintide vs. placebo will be carried out as follows. Let $\mu_{\text{cagrilintide},x}$ and μ_{placebo} denote the true mean of % weight change for dose level x of cagrilintide and the pooled placebo group, respectively. The null and alternative hypotheses tested are

$$H_0: \mu_{\text{NNC0174-0833},x} \geq \mu_{placebo} \text{ vs. } H_A: \mu_{\text{NNC0174-0833},x} < \mu_{placebo}$$

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

Dose-response modelling

In order to evaluate the effect of cagrilintide dose vs. placebo on % weight change and to characterise the dose-response relationship the mean % weight change will be estimated using dose as a continuous variable.

The dose-response candidate models in Table 2-3 will be fit if feasible.

Table 2-3 Dose-response candidate models

Model	Functional form f(dose,θ)
E_{max}	$E_0 + E_{max}\frac{dose}{ED_{50} + dose}$
Sigmoidal E_{max}	$E_0 + E_{max}\frac{dose^{\lambda}}{{ED_{50}}^{\lambda} + dose^{\lambda}}$
Linear	$a + b \cdot dose$
Linear log-dose	$a + b \cdot \log(dose + 1)$
Quadratic	$a + b \cdot dose + c \cdot dose^2$

The candidate models will be fit to the estimated % weight change means at week 26 for the employed cagrilintide doses and placebo from the primary analysis model described above. Thus all subjects in the FAS will be included and the same assumptions regarding missing values and the impact of explanatory variables will be applied. When fitting the models estimated % weight change means 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.

Dose-response curves will be estimated and plotted using the fitted dose-response model.

Analysis addressing the effect of cagrilintide vs. liraglutide 3.0 mg
This analysis will evaluate the treatment difference between cagrilintide and liraglutide 3.0 mg using the same analysis as the primary analysis for the primary estimand described above. However, the treatment differences between cagrilintide doses and liraglutide will be estimated and no confirmatory testing will be carried out.

Sensitivity analyses
The below sensitivity analyses will be conducted:

- A mixed model for repeated measurements (MMRM) comparing the change from baseline in body weight (%) at 26 weeks between treatments. All post randomisation measurements at planned visits up to week 26 and obtained during treatment adherence will be included in the model as dependent variables. Treatment will be included as fixed factors and the baseline body weight will be included as a covariate both nested within the factor visit. The

within subject covarance structure will be unstructured. Subjects without post randomisation measurements of weight will be excluded from the analysis.

- Post-baseline measurements excluded for subjects with treatment non-adherence: This sensitivity analysis will evaluate the robustness to the assumption that post-baseline data for subjects with treatment non-adherence is informative for the weight change had the subjects adhered. The same analysis model and multiple imputation approach as for the primary analysis will be carried out, but for subjects with dose treatment non-adherence all post-baseline measurements will be handled as missing and imputed using multiple imputation.

2.3.1.2 Analyses addressing the secondary estimand

The following statistical analyses and imputation methods are designed to address the secondary estimand, i.e. to assess the effectiveness of cagrilintide.

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

Handling of missing week 26 values for the secondary estimand
All available data at week 26 (AT and AD) are used. Missing values (MT and MD) at week 26 will be imputed and the endpoints will be derived from the imputed values. First, a description of the primary imputation approach to address the secondary estimand for the primary endpoints is given followed by a description of the sensitivity analyses used to assess the robustness of the primary analysis results. The sensitivity analyses investigate how assumptions on body weight development after discontinuation of randomised treatment impact the estimated treatment contrasts between active doses and placebo.

Primary imputation approach for the secondary estimand (RS-MI)
The primary analysis of the secondary estimand is a retrieved subjects based multiple imputation approach (RS-MI) which is simplified but similar to the one described by McEvoy (reference 44 in the protocol). Missing body weight measurement at week 26 for non-retrieved subjects (MD) are imputed using assessments from retrieved subjects (AD). Missing body weight measurements at week 26 for subjects on randomised treatment (MT) are imputed using available measurements at week 26 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 26 with treatment as factor and baseline body weight (kg), last available treatment-adherent observation of body weight (kg) and time spent in the treatment-adherent observation period as covariates. No interactions will be included. If any subjects are MT, an imputation model for missing body weight measurements at week 26 for MT subjects will also be defined using AT subjects in a similar

way. The estimated posterior distribution for the parameters (regression coefficients and variances) in the imputation models are then used to impute missing week 26 body weight values. This will be done 1000 times, resulting in 1000 complete data sets.

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

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

Treatment comparisons for cagrilintide doses vs. placebo will be carried out as described for the primary analysis addressing the primary estimand. However, no confirmatory testing will be carried out.

Dose-response modelling
The selected model shape for the primary estimand will also be estimated based on mean estimates and their variances for % weight change from the ANCOVA model using the primary imputation approach for the secondary estimand.

Analysis addressing the effect of cagrilintide vs. liraglutide 3.0 mg
This analysis will evaluate the treatment difference between cagrilintide and liraglutide 3.0 mg using the same analysis as the primary analysis for the secondary estimand described above. However, the treatment differences between cagrilintide doses and liraglutide will be estimated.

Sensitivity analyses
Multiple imputation approach using retrieved subjects (J2R-MI): A jump to reference multiple imputation approach will be applied. Missing values of body weight at week 26 (MT and MD) for all treatment groups are imputed by using available assessments at week 26 in the placebo group (AT and AD). This approach makes the assumption that subjects with missing data (MT and MD) lose any effect of randomised treatment beyond what can be expected from placebo treatment as adjunct to diet and physical activity. The multiple imputation approach is done in three steps. The imputation step is described below and step two and three are similar to the primary analysis for the secondary estimand.

An imputation model is defined using all placebo subjects from FAS with a week 26 measurement (AT and AD). The model will be a linear regression of body weight (kg) at week 26 on gender (male/female) and region as factors and baseline body weight (kg) as covariate. No interactions will be included. The estimated posterior distribution for the parameters (regression coefficients and variances) in the imputation models are then used to impute missing week 26 body weight values for each randomised treatment arm. This will be done 1000 times and results in 1000 complete data sets.

Treatment comparisons for cagrilintide doses vs. placebo and liraglutide will be carried out as described for the analyses addressing the primary estimand.

2.3.2 Secondary endpoints

2.3.2.1 Supportive secondary endpoints

Supportive secondary endpoints are listed in the protocol. All supportive secondary endpoints will be analysed to address the primary estimand.

Efficacy endpoints

Continuous efficacy endpoints
Change from randomisation at week 0 to week 26 in:

- Body weight (kg)
- Waist circumference (cm)
- Fasting lipids (mg/dL)
  - Total cholesterol
  - HDL cholesterol
  - LDL cholesterol
  - VLDL cholesterol
  - Triglycerides

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 described in Section 2.3.1.1. 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. Treatment differences will be estimated comparing each cagrilintide dose with placebo and liraglutide.

For fasting 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.

Change from randomisation at week 0 to week 26 in:

- HbA_{1c} (%-point, mmol/mol)
- FPG (mg/dL)
- Fasting insulin (µIU/mL)
- HOMA-IR (%-point)
- HOMA-β (%-point)

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

Binary efficacy endpoints
Subjects who after 26 weeks achieve (yes/no):

- Body weight reduction ≥ 5% from randomisation
- Body weight reduction ≥ 10% from randomisation

The analysis model for the 5% and 10% body weight reduction endpoints is a logistic regression using randomised treatment as a factor and baseline body weight (kg) as covariate.

The analysis will be based on FAS using the treatment-adherent observation period and observations outside this observation period will be handled as missing. Missing values of body weight at week 26 are imputed under the same assumption of MAR as for the primary analysis for the primary endpoint addressing the primary estimand using multiple imputation. The imputed data sets for continuous weight change % as described in Section 2.3.1.1 will be used to derive the binary weight reduction endpoints. The logistic regression model will be used to estimate log odds ratios comparing each cagrilintide dose with placebo and liraglutide for each complete data set and Rubin's rule will be used to draw inference. The results after applying Rubin's rule will be back-transformed and described by the odds ratio.

Composite strategy
The following composite variables are defined by subjects who after 26 weeks achieve (yes/no):

Body weight reduction ≥ 5% from randomisation and no treatment non-adherence
Body weight reduction ≥ 10% from randomisation and no treatment non-adherence

The analysis approach is the same as the logistic regression model including multiple imputation described above addressing the primary estimand except that for subjects with treatment non-adherence no imputation of missing data will be used. Instead they will be considered not achieving the composite body weight variable.

Dose-response modelling for body weight reduction endpoints
The dose-response analysis of 5% and 10% body weight reduction endpoints will be carried out on the mean estimates of treatment log odds for each cagrilintide dose and placebo obtained via the logistic regression with treatment as factor addressing the primary estimand described above. Candidate shapes listed in Table 2-4 will be fit and evaluated based on the best fit. Normal distribution of the mean estimates for the specific model will be assumed. Mean estimates will be weighted by the inverse of the estimated variances of the mean log odds.

Table 2-4 Binary dose-response candidate models

Model	Link function for probability p	Functional form f(d,θ)
Logistic	$\log[p/(1-p)]$	$E_0 + b \cdot dose$
E_{max}	log[p/(1-p)]	$E_0 + E_{max}\frac{dose}{ED_{50} + dose}$
Sigmoidal Emax	log[p/(1-p)]	$E_0 + E_{max}\frac{dose^{\lambda}}{{ED_{50}}^{\lambda} + dose^{\lambda}}$

Sensitivity analyses for supportive secondary endpoints
For supportive secondary endpoints no sensitivity analysis will be carried out.

Safety endpoints

Adverse events and anti-drug antibodies
Number of TEAEs from randomisation at week 0 to week 32 ('end of trial')
Number of SAEs from randomisation at week 0 to week 32 ('end of trial')
Occurrence (yes/no) of anti-drug antibodies towards cagrilintide from randomisation at week 0 to week 32 ('end of trial').

Adverse events will be defined as 'treatment-emergent' (TEAE), if the onset of the event occurs in the on-treatment period, see definition in Section 2.2.1. TEAEs and treatment emergent SAEs will be summarised by descriptive statistics, such as frequencies and rates, using the SAS. No formal statistical inference will be carried out based on the number of TEAEs and SAEs.

Occurrence of anti-drug antibodies towards cagrilintide will be summarised by descriptive statistics using the SAS.

Dose-response modelling for GI AEs
Analyses of the dose-response for the probability of subjects meeting two different response criteria:

- Having a treatment emergent GI adverse event (yes/no)
- Having a moderate or severe treatment emergent GI adverse event (yes/no)

Dose-response modelling will be done on the SAS with binary response status (yes/no) for each subject during the on-treatment observation period as the outcome variable and dose as a continuous covariate. Candidate shapes listed in Table 2-4 will be fit and evaluated based on the best fit.

Continuous safety endpoints

Change from randomisation to week 26 in:

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Pulse (bpm)
- hsCRP (mg/L)
- PAI-1 activity (mg/L)
- Renin activity (ng/mL/h)
- Aldosterone (ng/dL)

These continuous safety endpoints will be summarised by descriptive statistics based on observed data from subjects in the SAS that are on drug at week 26.

2.3.3 Exploratory endpoints

Subjects who after 26 weeks achieve (yes/no):

- Body weight reduction ≥ 15% from randomisation
- Body weight reduction ≥ 20% from randomisation

These endpoints will be analysed using a logistic regression model with randomised treatment as a factor and baseline body weight (kg) as covariate as described for body weight reduction ≥ 5% and ≥ 10% in Section 2.3.2.1.

Change from randomisation at week 0 to week 26 in:

- Endogenous amylin
- Soluble leptin receptor
- Leptin
- SF-36 v2.0 acute:
  - Physical component summary score
  - Mental component summary scores
  - Scores on the individual sub-domains:
    - Physical functioning
    - Role functioning
    - Bodily pain
    - General health
    - Vitality
    - Social functioning
    - Role emotional
    - Mental health
- TFEQ-R18v2: Transformed scale scores for the three scales measured: Uncontrolled Eating, Cognitive Restraint and Emotional Eating.

Time to permanent discontinuation of randomised trial product (weeks)

Date of permanent discontinuation of randomised trial product is evaluated by the investigator in the 'end of treatment' form and used to derive the time to permanent discontinuation.

Physical functioning score will be analysed using the same analysis model as the primary analysis for the primary endpoint addressing the primary estimand described in Section 2.3.1.1. The outcome variable % weight change and the covariate baseline body weight will be replaced by the corresponding outcome and baseline assessments of the physical functioning score. Treatment differences will be estimated comparing each cagrilintide dose with placebo and liraglutide. The remaining endpoints will be summarised by descriptive statistics.

2.3.4 Explorative statistical analysis for pharmacogenetics and biomarkers

No statistical analyses are planned for genetic data. Planned analyses for biomarkers are handled in Section 2.3.1, 2.3.2 and 0.

2.3.5 Other analyses

Ambulatory blood pressure measurements (ABPM) are carried out during 24 hours at screening visit 1 (baseline) and visit 11 (end of treatment) for the cagrilintide and placebo groups for subjects on treatment at visit 11. If a subject is not on treatment at visit 11, the ABPM endpoints for the subject will be set to missing. Hourly ABPM averages with standard deviation bars for SBP, DBP, and heart rate at baseline and at visit 11 will be graphically displayed by treatment (cagrilintide dose or placebo). Invalid ABPM profiles (as judged by the investigator) will not be included in any statistical or descriptive analysis.

The following endpoints will be calculated based on ABPM:

- ΔSBP_{av}, change from baseline in average 24 hour systolic blood pressure
- ΔDBP_{av}, change from baseline in average 24 hour diastolic blood pressure
- ΔHR_{av}, change from baseline in average 24 hour heart rate
- $\Delta SBP_{av,day,}$ change from baseline in average day time (6:00 am – 00:00 pm) systolic blood pressure
- $\Delta DBP_{av,day}$, change from baseline in average day time (6:00 am – 00:00 pm) diastolic blood pressure
- $\Delta HR_{av,day}$, change from baseline in average day time (6:00 am – 00:00 pm) heart rate
- $\Delta SBP_{av,night,}$ change from baseline in average day time (00:01 am – 05:59 pm) systolic blood pressure
- $\Delta DBP_{av,night,}$ change from baseline in average night time (00:01 am – 05:59 pm) diastolic blood pressure

- $\Delta HR_{av,night}$, change from baseline in average night time (00:01 am – 05:59 pm) heart rate

The above endpoints are calculated as AUC (using the linear trapezoidal method) during the respective time period divided by the duration of the observed time period.

The endpoint ΔSBP_{av} will be analysed using ANCOVA model with treatment as factor and baseline SBP_{av} as covariate (without interaction) and the treatment difference vs. placebo will be estimated with 95% CI for each dose level of cagrilintide. Two approaches to handling missing data will be used:

1) Single imputation of missing baseline SBP_{av} will be done using linear regression on baseline office SBP. A multiple imputation approach will be performed where missing SBP at visit 11 are imputed from a regression model with baseline SBP_{av} as covariate (separately for each treatment group). The targeted population is subjects adhering to treatment from the SAS. 1000 datasets will be imputed and Rubins rule will be used to combine the analysis results in order to draw inference.

2) A completers analysis where subjects with missing baseline or visit 11 BP and subjects who are not adhering to treatment are excluded

The remaining ABPM endpoints will be analysed using the same approach as for ΔSBP_{av}.. A subgroup analysis for subjects with hypertension will be done if possible including subjects according to one of the below criteria:

- Pre-existing hypertension
- Age >60 years
- Black-American race

All collected data that were not defined as endpoints will be summarised by descriptive statistics.

2.4 Pharmacokinetic and/or pharmacodynamic modelling

Population PK and exposure-response analyses will be used as supportive evidence for the evaluation of efficacy and safety and further to support the dose selection of cagrilintide for future clinical development in subjects with obesity. First, plasma cagrilintide concentrations will be analysed using a population PK model, quantifying covariate (such as baseline body weight, age, gender, race, ethnicity, and injection site) effects on cagrilintide exposure. Second, model based estimates of steady-state average concentrations will be derived for each subject, in order 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.

A modelling analysis plan will be prepared before database lock, outlining details of the analyses. The modelling will be performed by Quantitative Clinical Pharmacology at Novo Nordisk and will be reported separately from the clinical trial report.

3 Changes to the statistical analyses planned in the protocol

The following supportive safety endpoints based on ABPM have been added after protocol finalisation on request from regulatory authorities:

Endpoint title	**Timeframe**	**Description/metric used**
Change from baseline in average 24 hour systolic blood pressure	From visit 1 (week -1) to visit 11 (week 26)	mmHG
Change from baseline in average 24 hour diastolic blood pressure	From visit 1 (week -1) to visit 11 (week 26)	mmHG
Change from baseline in average 24 hour heart rate	From visit 1 (week -1) to visit 11 (week 26)	beats/min
Change from baseline in average day time (6:00 am – 00:00 pm) systolic blood pressure	From visit 1 (week -1) to visit 11 (week 26)	mmHG
Change from baseline in average day time (6:00 am – 00:00 pm) diastolic blood pressure	From visit 1 (week -1) to visit 11 (week 26)	mmHG
Change from baseline in average day time (6:00 am – 00:00 pm) heart rate	From visit 1 (week -1) to visit 11 (week 26)	beats/min
Change from baseline in average night time (00:01 am – 05:59 pm) systolic blood pressure	From visit 1 (week -1) to visit 11 (week 26)	mmHG
Change from baseline in average night time (00:01 am – 05:59 pm) diastolic blood pressure	From visit 1 (week -1) to visit 11 (week 26)	mmHG
Change from baseline in average night time (00:01 am – 05:59 pm) heart rate	From visit 1 (week -1) to visit 11 (week 26)	beats/min

The statistical analysis of these endpoints is described in section 2.3.5.
In addition the following changes to the protocol were made:

- The definition of treatment adherence has been updated since the original definition was not feasible to implement.
- A mixed model for repeated measurements (MMRM) comparing the change from baseline in body weight (%) at 26 weeks between treatments has been added as a sensitivity analysis to the primary analysis using the primary estimand.
- A tipping point analysis for body weight will not be done due to computational infeasibility.
- Dose-response curves will be plotted without placebo-adjustments but with dose=0 corresponding to placebo.
- Dose response modelling of Treatment discontinuation due to a treatment emergent GI adverse event (yes/no) is not done due to too few cases of discontinuation
- Dose response modelling of having a moderate or severe treatment emergent GI adverse event (yes/no) has been added
- Assessments pertaining to endogenous amylin, PAI-1 and DNA sequencing were not performed in this trial and thus no descriptive statistics of these parameters could be done
- Wording has been updated various places to increase readability.