Cover Page for Statistical Analysis Plan

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16.1.9 Documentation of statistical methods

List of contents

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

.

Statistical Analysis Plan

Trial ID: NN8022-4272

SCALE™ Insulin

Effect and safety of liraglutide 3.0 mg in subjects with overweight or obesity and type 2 diabetes mellitus treated with basal insulin

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Table of contents Page

List of abbreviations

AD	available drop-out
AE	adverse event
ANCOVA	analysis of covariance
AT	available on treatment
BMI	body mass index
DBL	Database Lock
ECG	Electrocardiogram
FAS	full analysis set
HbA_{1c}	glycosylated haemoglobin
HDL	high-density lipoprotein
IBT	Intensive behaviour therapy
ITT	intention- to-treat
IWQoL-Lite for CT	Impact of Weight on Quality of Life-Lite for Clinical Trials
LAO	last available observation
LAO-OT	last available observation (of body weight) on randomised treatment
LLOQ	lower limit of quantification
MCS	mental component summary
MD	missing drop-out
MedDRA	Medical Dictionary for Drug Regulatory Activities
MI	Multiple Imputation
MMRM	Mixed model for repeated measurements
MT	missing on treatment
OR	odds ratio
PCS	physical component summary
PYE	patient years of exposure
PYO	patient years of observation
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviations
SF-36	short form-36 version 2.0 acute

UNL	upper normal limit
UTN	Universal Trial Number
wANCOVA	weighted analysis of covariance
WC	waist circumference
WRSS	Weight related sign and symptom measure

1 Introduction

1.1 Trial information

Trial design

This is a 56-week randomised, double-blind, multi-national, multi-centre, placebo-controlled and two-armed trial in subjects with overweight or obesity and T2DM treated with basal insulin and up to two OADs (metformin, glitazone, SGLT-2 inhibitor, alpha glucosidase inhibitor, glinide or sulphonylurea).

Subjects will be randomised in a 1:1 manner to receive either liraglutide 3.0 mg or placebo, as an adjunct to reduced-calorie diet and increased physical activity delivered as part of a comprehensive lifestyle intervention program (in this document referred to as Intensive Behaviour Therapy [IBT]). Subjects treated with sulphonylurea will be stratified between the two arms.

It is recommended that the dose of basal insulin is reduced by 15-20 % for all subjects with HbA_{1c} ≤ 8 % (at the investigator's discretion) at randomisation, followed by weekly adjustment of insulin dose with the aim to achieve same pre-breakfast meal target plasma glucose as well as similar glycaemic control in the two treatment arms. Insulin dose should not be reduced for subjects with HbA1c > 8% to avoid unacceptable deterioration in glycaemic control.

Primary objective

To confirm superiority of liraglutide 3.0 mg vs. placebo, as an adjunct to a reduced-calorie diet and increased physical activity, on weight loss effectiveness in subjects with overweight or obesity and type 2 diabetes mellitus (T2DM) treated with a basal insulin and up to 2 oral antidiabetic (OAD) medications (metformin, glitazone, SGLT-2 inhibitor, alpha glucosidase inhibitor, glinide or sulphonylurea).

Secondary objectives

To establish the effects of liraglutide 3.0 mg vs. placebo, as an adjunct to a reduced-calorie diet and increased physical activity, on relevant efficacy endpoints in subjects with overweight or obesity and T2DM treated with basal insulin and up to 2 OADs (metformin, glitazone, SGLT-2 inhibitor, alpha glucosidase inhibitor, glinide or sulphonylurea)

To establish the safety and tolerability of liraglutide 3.0 mg vs. placebo, as an adjunct to a reduced-calorie diet and increased physical activity, in subjects with overweight or obesity and T2DM treated with basal insulin and up to 2 OADs (metformin, glitazone, SGLT-2 inhibitor, alpha glucosidase inhibitor, glinide or sulphonylurea)

1.2 Scope of the statistical analysis plan

This SAP is based on the protocol "SCALE™ Insulin. Effect and safety of liraglutide 3.0 mg in subjects with overweight or obesity and type 2 diabetes mellitus treated with basal insulin", version 4, and amendments 1, 2 and 3.

2 Statistical considerations

Results from the statistical analysis will generally be accompanied by two-sided 95% confidence intervals and two-sided p-values.

Superiority will be claimed if the two-sided p-value is less than 5% and the estimated treatment difference/ratio favours liraglutide 3.0 mg.

Primary endpoints

The two primary endpoints are defined as:

- Change in body weight (%) from baseline to week 56
- Proportion of subjects losing at least 5% of baseline body weight at week 56

The primary objective is met if superiority of liraglutide 3.0 mg vs. placebo is demonstrated for each of the primary endpoints.

Definition of primary endpoint: % weight change

Change in body weight (%) from baseline to week 56, denoted % weight change, is calculated as body weight at week 56 minus body weight at baseline divided by body weight at baseline and multiplied by 100; therefore

$$\%\ \text{weight change} = \frac{(\text{body weight at week 56} - \text{body weight at baseline})}{\text{body weight at baseline}} \times 100.$$

A negative value of % weight change indicates a body weight loss from baseline to week 56.

Definition of primary endpoint: 5% responders

The proportion of subjects having lost at least 5% of baseline body weight at week 56, denoted 5% responders, is defined as the proportion having

$$\%\ \text{weight change} \leq -5\%.$$

A 5% responder is defined as a subject fulfilling this, therefore

$$5\%\ \text{responder} = \begin{cases} 1 \text{ if } \%\ \text{weight change} \leq -5\% \\ 0 \text{ if } \%\ \text{weight change} > -5\% \end{cases}$$

Definition of Estimands

Effectiveness estimand

The primary estimand is an effectiveness estimand (*de facto*) quantifying the average effect of liraglutide 3.0 mg relative to placebo 56 weeks after randomisation, as adjunct to reduced caloric diet and increased physical activity, in all randomised subjects regardless of adherence to randomised treatment.

Efficacy estimand

In addition, an efficacy estimand (*de jure*) is quantifying the average effect of liraglutide 3.0 mg relative to placebo 56 weeks after randomisation, as adjunct to reduced caloric diet and increased physical activity, if all randomised subjects had adhered to the assigned treatment regimen for the entire planned duration of the trial.

Taxonomy of week 56 assessments being available or missing

A given assessment at week 56 may be available or missing. Table 2–1 describes the taxonomy for this. Note that this is done per assessment not per subject, as subjects may belong to different types for different assessments (a subject may have "available on treatment (AT)" for weight but "missing on treatment (MT)" for waist circumference).

Table 2–1 Taxonomy of week 56 assessments being available or missing

Assessment at week 56	On randomised treatment at week 56	Type description	Type Abbreviation
Available	Yes	**Available on randomised treatment**: Subjects who did not discontinue randomised treatment prematurely. Include those that stop and restart trial product.	AT
	No	**Available drop-outs**: Subjects who discontinued randomised treatment prematurely but returned to have an assessment at week 56; so-called retrieved drop-outs.	AD
Missing	Yes	**Missing on randomised treatment**: Subjects who did not discontinue randomised treatment prematurely. Include those that stop and restart trial product.	MT
	No	**Missing drop-outs**: Subjects who discontinued randomised treatment prematurely and did not return to have an assessment at week 56; so-called non-retrieved drop-outs.	MD

2.1 Sample size calculation

The sample size calculation is based on the analysis approach addressing the primary estimand for the primary endpoints change in body weight (%) from baseline to week 56 (% weight change) and proportion of subjects losing ≥ 5% of baseline body weight at week 56 (5% responders).

The two primary endpoints and all confirmatory secondary endpoints will be tested in a hierarchical order.

The study design is a 1:1 randomisation, stratified by sulphonylurea (yes/no) with 400 subjects in total (200 subjects in each arm). The sample size calculation does not take stratification into account. Please see Table 2–2 for general specifications on sample size and power calculation.

Table 2–2 General specifications for sample size and power calculation

Endpoint	Statistical test	Minimum required power (%)
% weight change	Two-group Satterthwaite unpooled *t* test on the mean difference with α=0.05 assuming unequal variances	90.0 (marginal)
5% responders	Pearson chi-square test for two independent proportions with α=0.05	90.0 (marginal)

α: two-sided significance level

In the following paragraphs treatment differences and standard deviations (SD) are given without units.

Body weight measurements from returning discontinuing subjects will be used in the primary analysis. But for the sample size calculations, it is assumed that all subjects who discontinue will not return at week 56 and assume that they have a % weight change like placebo subjects who completed the trial. It is expected that % weight change for liraglutide 3.0 mg subjects who discontinue might be somewhere in between completing placebo subjects and completing liraglutide 3.0 mg subjects. The assumption is thus expected to lead to a conservative effect estimate. A 30% discontinuation is assumed based on findings in trial NN8022-1922.

Based on findings from NN8022-1922, a difference in % weight change between liraglutide 3.0 mg and placebo of –4 (–6% vs. –2%, SD= 6) is assumed among completing subjects. Adjusting for 30% discontinuation and using a mixture distribution, a difference of –2.8 is expected in the primary analysis. A sample size of 400 subjects (200 in each arm), gives a marginal power of 99.5%.

For the primary endpoint 5% responders, the expected proportions were calculated based on the same assumptions as above. Adjusting for 30% discontinuation gives an expected 5% responders proportion of 49% in the liraglutide 3.0 mg arm and 31% in the placebo arm. With 400 subjects, this results in a marginal power of 95.7%.

Given these assumptions, the sample size of 400 subjects (200 in each arm), results in a combined power (marginal powers multiplied) of 95.2%.

The tests of superiority of liraglutide 3.0 mg to placebo for each of the confirmatory endpoints are performed hierarchically in the order in which the endpoints are presented (see Sections **4.2.1** and **4.2.2.1** in the protocol). The two primary endpoints are included in the statistical testing hierarchy, and the primary objective will be met if superiority of liraglutide 3.0 mg vs. placebo is demonstrated for each of the primary endpoints. The test hierarchy is given in

Table **2–3** with underlying assumptions, marginal power and effective power. The effective power is calculated using a naïve and conservative approach, which assumes no correlation of endpoints by multiplying the respective marginal powers. Assumptions made to calculate the power for the two primary endpoints and all confirmatory secondary endpoints are also presented in

Table **2–3**.

Table 2–3 Assumptions, marginal power and effective power for each confirmatory endpoint in the hierarchical testing procedure given an anticipated number of 400 randomised subjects

	Assumed mean (±SD) / proportion for completers liraglutide 3.0 mg	placebo	Expected mean (±SD) / proportion liraglutide 3.0 mg #	Expected difference #	Marginal power (%)	Effective power (%)
% weight change	–6.0 (±6.0)	–2.0 (±6.0)	–4.8 (±6.3)	–2.8	99.5	99.5
5% responders	57%	31%	49%	18	95.7	95.2
10% responders	25%	9%	20%	11	89.0	84.7
WC	–6.0 (±5.9)	–3.1 (±5.9)	–5.1 (±6.0)	–2.0	92.4	78.3
HbA1c	–1.4 (±1.0)	–0.5 (±1.0)	–1.1 (±1.1)	0.6	99.9	78.2
Fasting glucose	–2.2 (±2.0)	–0.4 (±2.0)	–1.7 (±2.2)	1.3	99.9	78.1
SF-36 PF	3.7 (±8.0)	2.4(±8.0)	3.3 (±8.0)	0.9	20.5	16.0
IWQoL-Lite for CT PF *	15.0 (±14.5)	10.6 (±14.5)	13.7 (±14.6)	3.1	55.9	8.9

SD standard deviation, WC waist circumference, SF-36 PF Short Form-36 v2.0 acute physical functioning score, IWQoL-Lite for CT PF Physical function domain (5 items) score
Adjusted for 30% discontinuation; * IWQoL-Lite Clinical Trial Version;
Assumptions are based on findings from NN8022-1922.

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* includes all randomised subjects exposed to at least one dose of randomised treatment.

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

2.3 Primary endpoints

The two primary endpoints are as mentioned previously (see start of Section 2)

- % weight change
- 5% responders

2.3.1 Analytical methods addressing the effectiveness estimand for the primary endpoints

These analyses will use the FAS. The analyses of the primary endpoints use baseline body weight and body weight at week 56, and assessments at week 56 may be missing ("missing on treatment [MT]" and "missing drop-outs [MD]"). First, a description of the statistical models for the primary endpoints is given under the assumption of no missing values (i.e. all subjects have body weight measurements at baseline and week 56). Subsequently, handling of missing data is described.

2.3.1.1 Statistical model for the primary endpoint % weight change

The primary endpoint % weight change will be analysed using analysis of covariance (ANCOVA) including the factors and covariates listed in Table 2–4.

Table 2–4 Factors and covariates for the analysis of the primary endpoints

Factors and covariates at baseline	Type	Categories
Randomised tretment	Factor	Liraglutide 3.0 mg, placebo
Body weight (kg)	Covariate	*Not applicable*
BMI (kg/m^2)	Factor	[27,30[, [30,35[, [35,40[, ≥40
Gender	Factor	Male, female

The factors and covariates will be included in the model as main effects in an additive structure. The estimated treatment difference between liraglutide 3.0 mg and placebo will be reported together with the associated two-sided 95% CI and corresponding p-value.

The superiority test of liraglutide 3.0 mg vs. placebo will be carried out as follows:

Let $\mu_{liraglutide}$ and $\mu_{placebo}$ denote the true mean of % weight change for liraglutide 3.0 mg and placebo group, respectively. The hypothesis and the alternative are

H: $\mu_{liraglutide} \geq \mu_{placebo}$ against the alternative H_A: $\mu_{liraglutide} < \mu_{placebo}$.

The hypothesis will be rejected and superiority claimed, if the upper limit of the estimated two-sided 95% CI is below 0.

2.3.1.2 Statistical model for the primary endpoint 5% responders

This binary endpoint will be analysed using a logistic regression model. Factors and covariates will be those listed in Table 2–4. The estimated odds ratio (OR) between liraglutide 3.0 mg and placebo will be reported together with the associated two-sided 95% CI and corresponding p-value.

Let $OR_{liraglutide/placebo}$ denote the true odds ratio between liraglutide 3.0 mg and placebo. The hypothesis and the alternative are:

H: $OR_{liraglutide/placebo} \leq 1$ against the alternative H_A: $OR_{liraglutide/placebo} > 1$

The hypothesis will be rejected and superiority claimed, if the lower limit of the estimated two-sided 95% CI is above 1.

2.3.2 Handling of missing values for the effectiveness estimand

2.3.2.1 Handling of missing values at baseline

If an assessment has been made both at screening and randomisation, the value from the randomisation visit will be used as the baseline value. If the value measured at the randomisation visit is missing and the assessment was made at screening, the screening value will be used as the baseline value.

2.3.2.2 Handling of missing values at week 56

Missing values at week 56 will be imputed and the relevant endpoints will be derived from the imputed values. Several approaches for imputation of missing values at week 56 will be applied. First, a description of the primary imputation approach used to address the effectiveness estimand for the primary endpoints is given. This is followed by a description of a number of sensitivity analyses.

Primary approach for handling of missing values

The primary approach for multiple imputations of missing values of body weight at week 56 (type MT+MD) for both the liraglutide 3.0 mg and placebo group is by sampling among all available assessments at week 56 in the placebo group (type AT+AD). This approach is also known as jump to reference and makes the assumption that subjects instantly after discontinuation lose any effect of randomised treatment beyond what can be expected from placebo treatment as adjunct to diet and exercise[1]. Body weight measurements at visits between baseline and week 56 are not used for this imputation approach. The multiple imputation approach is done in three steps.

- **Imputation**: Step 1 defines an imputation model based on placebo subjects, which is used to impute missing body weight values at week 56 in both arms. This will be done 100 times

and results in 100 complete data sets. A more detailed explanation of this step is given below.

- **Analysis**: Step 2 analyses each of the 100 complete data sets, using the statistical model defined in Sections 2.3.1.1 and 2.3.1.2 , and saves the 100 estimation results.

- **Pooling**: Step 3 integrates the 100 estimation results into a final result using Rubin's formula.

The imputation model in step 1, uses placebo subjects from FAS with non-missing body weight measurements at baseline and week 56. The imputation model is a linear regression of body weight (kg) at week 56 on the factors and covariates listed in Table 2–4 (except randomised treatment arm) with no interactions. The estimated posterior distribution for the parameters (regression coefficients and variances) in the imputation model is then used to impute missing week 56 body weight values for both randomised treatment arms.

If 100 copies are not sufficient to establish stable results, a higher number will be used. The multiple imputations will be generated using Novo Nordisk trial number 80224272 as seed number.

Sensitivity analyses for the analysis of the primary endpoints for the effectiveness estimand

The sensitivity analyses will address the robustness of the primary approach for handling of missing values. In particular the sensitivity analyses address how assumptions on how body weight progresses after discontinuation of randomised treatment impact the estimated treatment difference between liraglutide 3.0 mg and placebo. The sensitivity analyses include the following.

- A multiple imputation approach as described by McEvoy[2] where missing body weight measurement at week 56 for non-retrieved drop-outs (type MD) are imputed by sampling from values obtained from retrieved drop-outs (type AD) in each randomised treatment arm and according to the timing (monthly) of last available observation (of body weight) on randomised treatment (LAO-OT). Missing body weight measurements at week 56 for subjects on drug treatment (type MT) are imputed by sampling from type AT in the relevant randomised treatment arm. Thus, the imputation model for each randomised treatment arm and timing of LAO-OT is a linear regression of body weight (kg) at week 56 on the factors and covariates listed in Table 2–4 (except randomised treatment arm) with no interactions and including LAO-OT of body weight as covariate. If timing by month is too restrictive, quarters, half-years, or excluding timing will be used.

- A weighted ANCOVA (wANCOVA) where returning drug discontinuing subjects (AD) are up-weighted relative to their proportion of all drug discontinuing subjects (AD+MD)

to account for the subjects not returning for assessments at week 56[44]. Similarly, AT subjects are up-weighted relative to their proportion of all drug continuing subjects (AT+MT). The up-weighing is done by randomised treatment arm and the timing of LAO-OT. Subjects who are missing the weight measurement at week 56 (MD+MT) are assigned a weight of 0 (zero).

- A single imputation approach as done by Sacks[3]. Missing weight measurement at week 56 for subjects who drop-out (type MD) are imputed using a weight regain rate of 0.3 kg/month after last available observation (LAO) of body weight. Change from baseline is truncated whenever the extrapolation would lead to a positive weight gain relative to baseline. LAO does not need to be the same as LAO-OT as subjects are allowed to come to scheduled visits after discontinuing randomised treatment. When a subject's LAO represents a gain in weight relative to baseline, no additional gain will be imputed, and the unfavourable gain is carried forward to week 56. Missing weight measurement at week 56 for subjects on treatment (type MT) will be imputed using the LAO. The weight regain imputation will be done for both randomised treatment arms. Additionally, a version where only the liraglutide 3.0 mg arm uses the regain rate while the placebo arm uses LAO (corresponding to a weight regain rate of 0 kg/month) will be performed.

- Tipping point analysis. In a similar manner as above for a range of weight regain rates (starting from 0.1 kg/month and in intervals of 0.1 kg/month) for MD in liraglutide 3.0 mg arm will be used to define a tipping point in which superiority of liraglutide 3.0 mg disappears. In this analysis, the placebo arm will be imputed by LAO.

Figure 2–1 and Table 2–5 give an overview of the handling of missing values at week 56 assessments.

Additional sensitivity analyses

Additional analyses will investigate how sensitive the primary statistical models (for primary endpoints) are to the choice of factors and covariates in the model as follows. A model resembling the primary analysis models using the same imputation method (jump to reference) adjusting only for baseline body weight and randomised treatment arm. The imputation model (step 1) will be same as for the primary approach.

In addition, a model resembling the primary analysis models using the same imputation method (jump to reference) including treatment, BMI groups, sex, sulphonylurea (Yes, No), insulin type (Insulin detemir, Other basal insulin) and HbA1c groups (<=8%, >8%) as factors and baseline body weight in kg and total daily basal insulin dose in U as covariates will be conducted. The imputation model (step 1) will be same as for the primary approach.

For the binary primary endpoint, the risk difference (unadjusted for any factors and covariates) and corresponding 95% CI will also be calculated.

2.3.3 Analysis method addressing the efficacy estimand for the primary endpoints

The efficacy estimand for % weight change will be assessed using a mixed model for repeated measurements (MMRM). The MMRM will use assessments only from subjects who are taking the randomised treatment until end of trial or at first discontinuing of trial drug (either temporarily or permanently). A pause of less than eight consecutive days is not regarded as discontinuation for this analysis. This means that assessments at week 56 for retrieved drop-outs (type AD) will be discarded. The MMRM will be fitted using % weight change and the same factors and covariates (see Table 2–4) as for the primary analyses all nested within visit. An unstructured covariance matrix for measurements within the same subject will be employed, assuming that measurements for different subjects are independent.

The efficacy estimand for 5% responders will be assessed using the same MMRM. From the MMRM individually predicted values for % weight change at week 56 will be used to classify each subject as 5% responder or not. This classification will then be analysed using a logistic regression model with treatment and sulphonylurea (yes/no) as the only factors.

2.3.4 Subgroup analyses for primary endpoints

For the effectiveness estimand, subgroup analyses will be done for the factors listed and categorised as in Table 2–4. For baseline weight, categories based on quartiles will be used.The subgroup analyses will be done separately for each of these by including interaction term(s) with randomised treatment arm in the respective models (ANCOVA or logistic regression).

2.3.5 Exploratory analysis of change in body weight

Two exploratory analyses of change in body weight (%) taking into account the change in total daily insulin use from baseline (week 0) to week 56 will be conducted. Change in total daily insulin dose (U) is calculated by subtracting the total daily basal insulin dose (U) at baseline from the average total daily insulin dose (U) from baseline or week 44 to week 56. The change in total daily insulin dose will also be grouped into 4 groups based on the median for subjects with a change < 0 and the median for subjects with a change ≥ 0. Change in body weight will be analysed using a analysis of covariance (ANCOVA) including treatment, gender, BMI group and grouped change in total daily insulin as factors and baseline body weight in kg as a covariate and an interaction between change in total daily insulin dose and the grouped change in total daily insulin dose.

Figure 2–1 Illustration of imputation approaches

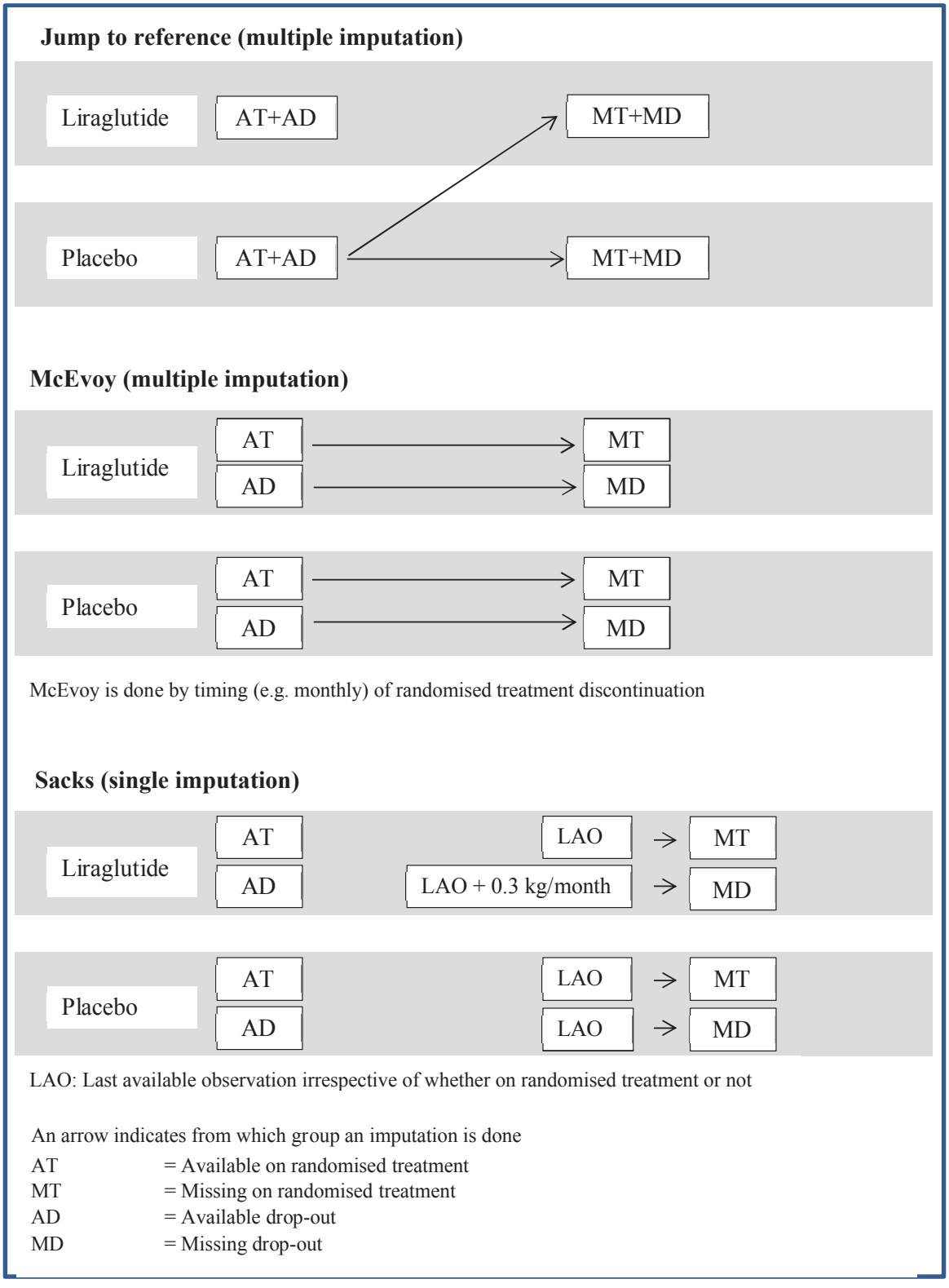


Table 2–5 Overview of handling of missing values

Approach	Description	Assumptions
Jump to reference (multiple imputation)	Liraglutide and placebo MT+MD imputed from placebo AT+AD (i.e., all available placebo assessments at week 56)	- Liraglutide MD lose any treatment effect instantly after drop-out - Placebo AT and placebo AD are assumed to have same weight loss
McEvoy (multiple imputation)	Separately for the two randomised treatment arms: MD imputed from AD by matching on time (month) of drop-out MT imputed from AT	- AD is representative of the MD for each randomised treatment arm - AT is representative of the MT for each randomised treatment arm
Weighted ANCOVA (wANCOVA)	No imputation. Separately for the two randomised treatment arms: AD subjects are up-weighted relative to their proportion of AD+MD and timing of drop-out AT subjects are up-weighted relative to their proportion of AT+MT	- AD is representative of the MD for each randomised treatment arm - AT is representative of the MT for each randomised treatment arm
Sacks (single imputation)	Liraglutide MD imputed by minimum of LAO+0.3 kg and baseline value for each month from drop-out to week 56 and either a) Placebo MD imputed by minimum of LAO+0.3 kg and baseline value for each month from drop-out to week 56 or b) MT (both randomised treatment arms) and placebo MD are imputed by LAO	a) Liraglutide and placebo MD lose any treatment effect linearly after drop-out. b) Only liraglutide MD lose any treatment effect linearly after drop-out. No change in treatment effect since LAO for others.
Tipping point (single imputation)	Liraglutide MD imputed by minimum of LAO+X kg (X in steps of 0.1) and baseline value for each month from drop-out to week 56. MT (both randomised treatment arms) and placebo MD are imputed by LAO	Only liraglutide MD lose any treatment effect linearly after drop-out. No change in treatment effect since LAO for others

AT available on randomised treatment, MT missing on randomised treatment, AD available drop-out, MD missing drop-out, LAO last available observation, LAO-OT last available observation on randomised treatment.

2.4 Secondary endpoints

2.4.1 Confirmatory secondary endpoints

Confirmatory secondary endpoints are listed in Section **4.2.2.1** in the protocol.

All confirmatory secondary endpoints are planned to be assessed at week 56 and will be analysed using the same MI approach as used for the primary endpoints and to address the effectiveness estimand. The statistical models for continuous endpoints will be ANCOVA with factors and covariates listed in Table 2–4 with baseline body weight replaced by baseline measurement of endpoint to be analysed. The statistical model for 10% responders will be analysed using logistic regression in the same way as for 5% responders.

Sensitivity analyses will be carried out for all confirmatory secondary endpoints. See Table 2–6 for details on planned analysis methods, multiple imputation approach and sensitivity analyses.

The efficacy estimand will also be assessed for confirmatory secondary endpoints using MMRM as described for the primary endpoints.

2.4.2 Description of the testing procedure to address the effectiveness estimand for primary and confirmatory secondary endpoints

The tests of superiority of liraglutide 3.0 mg to placebo for each of the endpoints are tested in a hierarchical manner in the order in which the endpoints are presented. The two primary endpoints are included in the statistical testing hierarchy below, even though the primary objective will only be met if superiority of liraglutide 3.0 mg vs. placebo is demonstrated for each of the primary endpoints. The test hierarchy is given in Table 2–6. The first endpoints to be tested are all assessing aspects of weight loss (e.g., relative change in body weight, achieving a certain magnitude of weight loss, and change in waist circumference); these endpoints are followed by endpoints assessing change in weight-related comorbidities and/or consequences of excess body weight and 'feeling and function' indicators.

Table 2–6 Hierarchical order and type of statistical model to address the effectiveness estimand for primary and confirmatory secondary endpoints

Test order	Endpoint	Endpoint type	Statistical model	MI approach	Sensitivity analyses #
	Primary endpoint				
1	Change in body weight (%) from baseline to week 56	Continuous	ANCOVA	Jump to reference	McEvoy wANCOVA Sacks Tipping point Unadjusted ANCOVA
2	Proportion of subjects losing at least 5% of baseline body weight at week 56	Binary	Logistic Regression	Jump to reference	McEvoy Sacks Tipping point Risk difference
	Confirmatory secondary endpoints				
3	Proportion of subjects losing more than 10% of baseline body weight at week 56	Binary	Logistic Regression	Jump to reference	McEvoy Tipping point
4	Change from baseline to week 56 in waist circumference (cm)	Continuous	ANCOVA	Jump to reference	McEvoy wANCOVA Tipping point
5	Change from baseline to week 56 in HbA1c (%)	Continuous	ANCOVA	Jump to reference	McEvoy wANCOVA Tipping point
6	Change from baseline to week 56 in fasting glucose (%)	Continuous	ANCOVA	Jump to reference	McEvoy wANCOVA Tipping point
7	Change from baseline to week 56 in Short Form-36 (SF-36) v2.0 acute physical functioning score	Continuous	ANCOVA	Jump to reference	McEvoy wANCOVA Tipping point
8	Change from baseline to week 56 in impact of Weight on Quality of Life-Lite (IWQoL-Lite for CT), physical function domain (5-itmes) score	Continuous	ANCOVA	Jump to reference	McEvoy wANCOVA Tipping point

MI Multiple Imputation;
See Table 2–5

2.4.3 Supportive secondary endpoints

2.4.3.1 Efficacy endpoints

Supportive secondary endpoints are listed in Section **4.2.2.2** in the protocol. The questionnaire for Weight related sign and symptom (WRSS) measure will not be validated until after DBL. Therefore the total score cannot be calculated and the supportive secondary endpoint "Weight related sign and symptom (WRSS) measure, total score" will not be analysed. Instead frequencies for categorical responses will be presented for each item and by visit.

Supportive secondary endpoints will be evaluated to address the effectiveness estimand. These endpoints will be analysed using the same MI approach as used for the primary and confirmatory secondary endpoints.

In exception, the endpoints total daily basal insulin dose (% of pretrial dose in U), total daily basal insulin dose (U/kg) and total daily insulin dose (U/kg) will not be analysed but only summarised in tables. Endpoint at baseline and change of endpoint will be summarised by week and treatment.

The endpoint mean daytime glucose value will be calculated from the 7-point SMPG profile as area under the curve (AUC) divided by length of time-interval. AUC will be calculated using the linear trapezoidal method. Missing points in the 7-point SMPG profile are ignored for the calculation.

The statistical model for continuous endpoints will be ANCOVA with factors and covariates listed in Table 2–4 with baseline body weight replaced by baseline measurement of endpoint to be analysed. The statistical model for proportions will be analysed using logistic regression.

In addition to the supportive secondary efficacy endpoints regarding IWQoL-Lite for CT listed in the protocol, analyses and outputs for the IWQoL-Lite for CT physical domain (not to be confused with IWQoL-Lite for CT physical function domain) will be made.

2.4.3.2 Safety endpoints

Descriptive statistics for all safety endpoints will be provided with the aim to compare liraglutide 3.0 mg and placebo. All analyses and tabulations will be done using the safety analysis set. Unless otherwise stated, no formal statistical analyses are planned for the safety endpoints.

Adverse events and hypoglycaemic episodes will be classified and analysed as 'in trial' and 'on drug' defined in terms of patient years of observation (PYO) and patient years of exposure (PYE), respectively. For each subject PYO is defined as number of days from date of randomisation until and including date of follow-up visit or date of last contact. For each subject PYE is defined as time intervals of exposure to trial drug including an ascertainment window of 14 days for each exposure interval.

Adverse events

AEs will be coded using the current version of Medical Dictionary for Regulatory Activities (MedDRA). All AEs will be presented based on system organ class, high level group term and preferred terms.

AEs, which occurred while the subject was in trial or on drug will be summarised descriptively, whereas AEs, which occurred before first exposure to trial drug or after the follow-up visit will only be presented in listings. AEs will be displayed in terms of the number of subjects with at least one event (N), the percentage of subjects with at least one event (%), the number of events (E) and the event rate per 100 years (R). Furthermore, AEs will be summarised by seriousness, severity, relation to trial drug, premature treatment discontinuation due to AE and outcome.

Summary tables by system organ class, high level group term and preferred term will be made for all AEs, SAEs, AEs possibly or probably related to trial drug, severe AEs, AEs occurring in at least 5% of the subjects in any arm, and AEs occurring in at least 1% of the subjects in any treatment arm.

AEs requiring completion of specific event forms will be presented in tables and listings. In addition, time to occurrence of these AEs will be presented in cumulative incidence plots.

Hypoglycaemic episodes

All hypoglycaemic episodes will be summarised in terms of N, %, E, rate as on drug (PYE) and in trial (PYO) and using same ascertainment window of 14 days as for AEs.

In addition to summary tables for hypoglycaemic episodes, an analysis and outputs for number of hypoglycaemic episodes will be made. The number of hypoglycaemic episodes occurring on-drug after 56 weeks of treatment will be analysed using a negative binomial regression model with a log - link function and the logarithm of the on drug time period as offset. The model will include treatment, sex, BMI group and sulphonylurea (Yes, No) as fixed factors and baseline body weight in kg and HbA1c in % as covariates."

Classification of Hypoglycaemia:

Treatment emergent: hypoglycaemic episodes will be defined as treatment emergent if the onset of the episode occurs during on drug time intervals.

Nocturnal hypoglycaemic episodes: are episodes occurring between 00:01 and 05.59 both inclusive.

Hypoglycaemic episodes are classified according to the Novo Nordisk classification of hypoglycaemia (see Figure 2–2) and the ADA classification of hypoglycaemia (see Figure 2–3).

Novo Nordisk classification of hypoglycaemia

In normal physiology, symptoms of hypoglycaemia occur below a plasma glucose level of 3.1 mmol/L (56 mg/dL)[20] Therefore, Novo Nordisk has included hypoglycaemia with plasma glucose levels below this cut-off point in the definition of blood glucose (BG) confirmed hypoglycaemia.

Novo Nordisk uses the following classification (see **Figure 2–2 Novo Nordisk classification of hypoglycaemia**Figure 2–2) in addition to the ADA classification:

Severe hypoglycaemia according to the ADA classification[11].

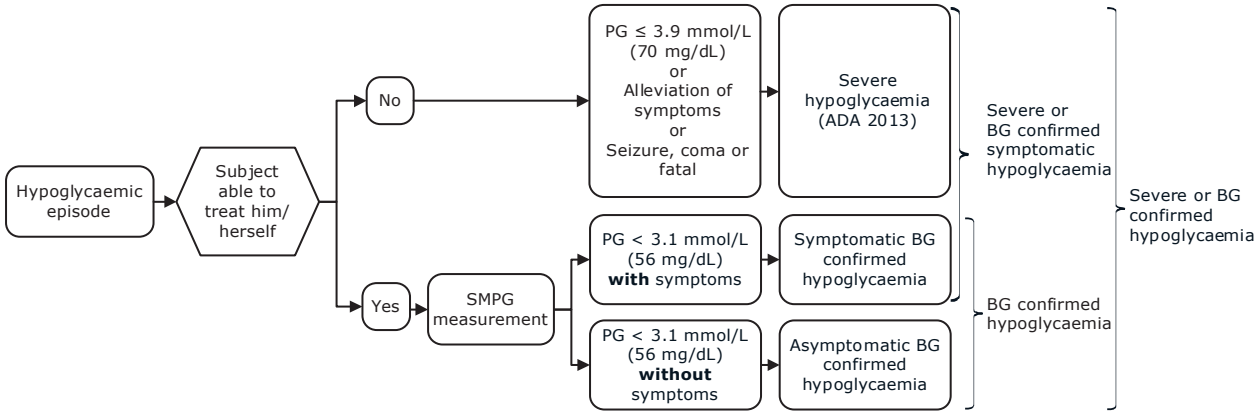
Symptomatic BG confirmed hypoglycaemia: An episode that is BG confirmed by plasma glucose value <3.1 mmol/L (56 mg/dL) **with** symptoms consistent with hypoglycaemia.

Asymptomatic BG confirmed hypoglycaemia: An episode that is BG confirmed by plasma glucose value <3.1 mmol/L (56 mg/dL) **without** symptoms consistent with hypoglycaemia.

Severe or BG confirmed symptomatic hypoglycaemia: An episode that is severe according to the ADA classification[11] or BG confirmed by a plasma glucose value <3.1 mmol/L (56 mg/dL) **with** symptoms consistent with hypoglycaemia.

BG confirmed hypoglycaemia: An episode that is BG confirmed by a plasma glucose value <3.1 mmol/L (56 mg/dL) **with** or **without** symptoms consistent with hypoglycaemia.

Severe or BG confirmed hypoglycaemia: An episode that is severe according to the ADA classification[11] or BG confirmed by a plasma glucose value <3.1 mmol/L (56 mg/dL) **with** or **without** symptoms consistent with hypoglycaemia.



Note: Glucose measurements are performed with capillary blood calibrated to plasma equivalent glucose values

Figure 2–2 Novo Nordisk classification of hypoglycaemia

ADA classification[11] of hypoglycaemia

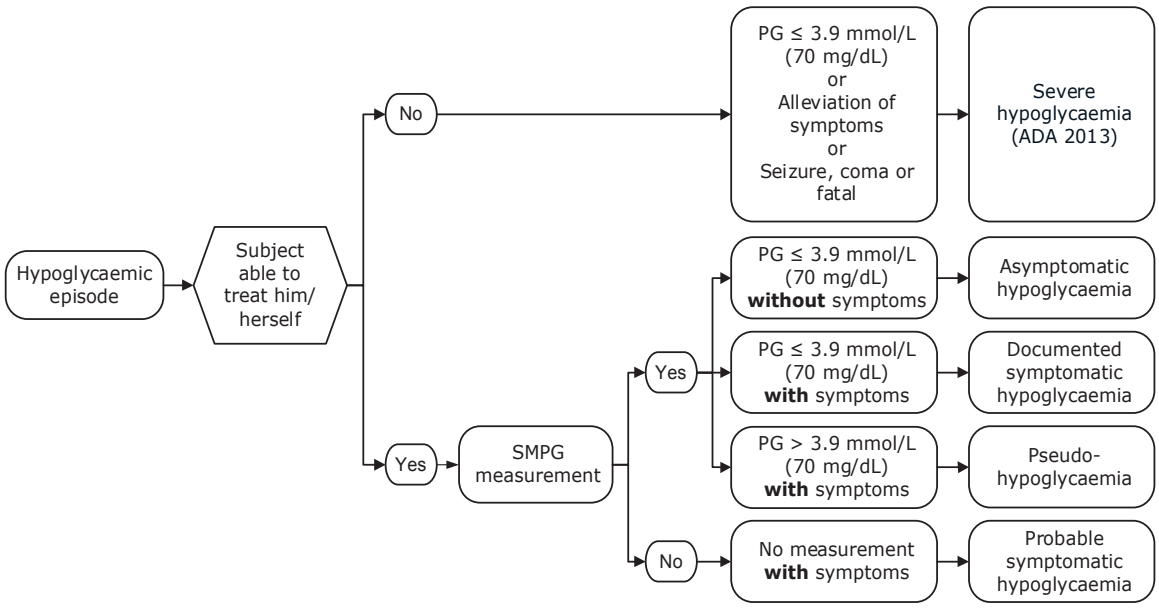
Severe hypoglycaemia: An episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

Asymptomatic hypoglycaemia: An episode not accompanied by typical symptoms of hypoglycaemia, but with a measured plasma glucose concentration ≤ 3.9 mmol/L (70 mg/dL).

Documented symptomatic hypoglycaemia: An episode during which typical symptoms of hypoglycaemia are accompanied by a measured plasma glucose concentration ≤ 3.9 mmol/L (70 mg/dL).

Pseudo-hypoglycaemia: An episode during which the person with diabetes reports any of the typical symptoms of hypoglycaemia with a measured plasma glucose concentration > 3.9 mmol/L (70 mg/dL) but approaching that level.

Probable symptomatic hypoglycaemia: An episode during which symptoms of hypoglycaemia are not accompanied by a plasma glucose determination but that was presumably caused by a plasma glucose concentration ≤ 3.9 mmol/L (70 mg/dL).



Note: Glucose measurements are performed with capillary blood calibrated to plasma equivalent glucose values

Figure 2–3 ADA classification of hypoglycaemia

Physical examination

Outcome of the physical examination at screening and change in the physical examination category at week 56 will be summarised in tables.

Pulse

Pulse (beats/min) at baseline and change of pulse at week 56 will be summarised in tables by week and treatment. Categories based on the maximum change from baseline until week 56 (>0, >5, >10, >20 beats/min) and categories based on the maximum value until week 56 (>80, >90, >100 beats/min) will be included in summary tables. Additionally, change in pulse from baseline to week 56 will be evaluated in the in trial observation period similar as in the primary analysis for the primary estimand but using the safety analysis.

ECG

Shifts in the ECG category from screening to week 56 will be summarised in tables.

Laboratory measurements

Laboratory values below the lower limit of quantification (LLOQ) will be set to ½LLOQ.

Laboratory safety parameters are measured throughout the trial and comprise haematology and biochemistry as defined in the flow chart.

The distribution of each continuous laboratory parameter will be presented using box plots by treatment and week. Continuous laboratory parameters will be compared to the relevant reference ranges and results will be presented.

Amylase and lipase

Shifts from baseline to highest value in trial period to UNL, 2xUNL and 3xUNL will be summarised in tables.

Mean plots, geometric mean plots and box plots by gender, visit and treatment will be prepared. Change from week 0 to week 56 will also be presented by empirical distribution plots.

Number and percentage of subjects with amylase and lipase levels ≥UNL, ≥2xUNL or ≥3xUNL will be tabulated by week and treatment. Subjects with values ≥2xUNL will additionally be presented with spaghetti plots.

Additionally, change in amylase and lipase from baseline to week 56 will be evaluated in the in trial observation period similar to the primary analysis for the primary estimand but using the safety analysis set.

Calcitonin

Number, percentage and incidence of subjects with persistent (all post-baseline measurements) and incidental (at least one post-baseline measurement) increases in calcitonin for the criteria below will be tabulated for all subjects, males and females.

From baseline <UNL to ≥UNL
From baseline <UNL to ≥20 ng/L
From baseline <UNL to ≥50 ng/L
From baseline <20 ng/L to ≥20 ng/L
From baseline <50 ng/L to ≥50 ng/L
Number and percentage of subjects with calcitonin levels ≥UNL, ≥1.5xUNL or ≥20 ng/L and ≥50 ng/L will be tabulated by visit and treatment.

A summary table showing number and percentage of observations < and ≥ LLOQ, minimum, Q25, median, Q75, maximum and geometric mean will be prepared by gender, visit and treatment.

The distribution of the calcitonin values across treatment group and time will be shown in plots by gender and total actual levels. Geometric means will be plotted by visit and treatment in order to assess the pattern of the longitudinal changes.

In addition, a scatter plot of baseline vs. maximum post-baseline calcitonin value will be prepared.

Longitudinal changes with calcitonin ≥20ng/L will be evaluated with spaghetti plots.

Subjects with at least one post-baseline calcitonin value above 20 ng/L will be listed.

The listings will include treatment, age, gender, smoking habits at baseline, risk factor information (use of relevant concomitant medication at time of assessment [proton pump inhibitors and H2 blockers] and medical history of thyroid disorder) and calcitonin values.

3 Changes to the statistical analyses planned in the protocol

3.1 Deviation from analyses as described in the protocol

- Factors and covariates to be included in the statistical modelling of the efficacy related endpoints has been reduced to only include treatment, gender and BMI group as factors and

baseline body weight in kg as a covariate to align with the current modelling strategy in obesity projects at Novo Nordisk A/S.

The following table (**Table 2–4** in the protocol):

Factors and covariates at baseline	**Type**	**Categories**
Randomised tretment	Factor	Liraglutide 3.0 mg, placebo
Sulphonylurea	Factor	Yes, no
Body weight (kg)	Covariate	*Not applicable*
BMI (kg/m^2)	Factor	[27,30[, [30,35[, [35,40[, ≥40
Gender	Factor	Male, female
Insulin type	Factor	Insulin detemir, other basal insulin
Insulin dose	Covariate	*Not applicable*
HbA1c	Factor	≤ 8.0%, > 8.0%

has been replaced by:

Factors and covariates at baseline	**Type**	**Categories**
Randomised tretment	Factor	Liraglutide 3.0 mg, placebo
Body weight (kg)	Covariate	*Not applicable*
BMI (kg/m^2)	Factor	[27,30[, [30,35[, [35,40[, ≥40
Gender	Factor	Male, female

- A MMRM is used for the efficacy estimand and only assessments from subjects who are taking the randomised treatment until end of trial or until first discontinuing of trial drug (either temporarily or permanent) are included. In the protocol, a trial drug pause of more than two days is defined as a treatment discontinuation, but a treatment discontinuation should have been defined as a trial drug pause of more than 7 days, which is also the information collected in the eCRF.

The following text:

”A pause of less than three consecutive days is not regarded as discontinuation for this analysis.”

has been replaced by:

"A pause of less than eight consecutive days is not regarded as discontinuation for this analysis."

- Since subgroup analyses are only planned to be done for factors and covariates included in the statistical modelling of efficacy related endpoints, a subgroup analysis for baseline insulin dose is no longer required as per protocol.

The following text:

"For baseline weight and insulin dose, categories based on quartiles will be used."

has been replaced by:

"For baseline weight, categories based on quartiles will be used."

- The WRSS questionnaire will not be validated until after DBL. Therefore the total score cannot be calculated and the supportive secondary endpoint "Weight related sign and symptom (WRSS) measure, total score" cannot be analysed.

The following text has been added:

"The questionnaire for Weight related sign and symptom (WRSS) measure will not be validated until after DBL. Therefore the total score cannot be calculated and the supportive secondary endpoint "Weight related sign and symptom (WRSS) measure, total score" will not be analysed. Instead frequencies for categorical responses will be presented for each item and by visit."

- The following three supportive secondary efficacy endpoint Total daily basal insulin dose (% of pre-trial dose in U), Total daily basal insulin dose (U/kg) and Total daily insulin dose (U/kg) will not be analysed but only summarised in tables, as no additional relevant information will be gained from analysing four endpoints all concerning change in insulin dose from baseline to week 56

The following text has been added:'

"In exception, the endpoints total daily basal insulin dose (% of pretrial dose in U), total daily basal insulin dose (U/kg) and total daily insulin dose (U/kg) will not be analysed but only summarised in tables. Endpoint at baseline and change of endpoint will be summarised by week and treatment."

3.2 Additional analyses not described in the protocol

The following text has been added:

"In addition, a model resembling the primary analysis models using the same imputation method (jump to reference) including treatment, BMI groups, sex, sulphonylurea (Yes, No), insulin type (Insulin detemir, Other basal insulin) and HbA1c groups (<=8%, >8%) as factors and baseline body weight in kg and total daily basal insulin dose in U as covariates will be conducted. The imputation model (step 1) will be same as for the primary approach."

"Two exploratory analyses of change in body weight (%) taking into account the change in total daily insulin use from baseline (week 0) to week 56 will be conducted. Change in total daily insulin dose (U) is calculated by subtracting the total daily basal insulin dose (U) at baseline from the average total daily insulin dose (U) from baseline or week 44 to week 56. The change in total daily insulin dose will also be grouped into 4 groups based on the median for subjects with a change < 0 and the median for subjects with a change ≥ 0. Change in body weight will be analysed using a analysis of covariance (ANCOVA) including treatment, gender, BMI group and grouped change in total daily insulin as factors and baseline body weight in kg as a covariate and an interaction between change in total daily insulin dose and the grouped change in total daily insulin dose."

"In addition to the supportive secondary efficacy endpoints regarding IWQoL-Lite for CT listed in the protocol, analyses and outputs for the IWQoL-Lite for CT physical domain (not to be confused with IWQoL-Lite for CT physical function domain) will be made."

"In addition to summary tables for hypoglycaemic episodes, an analysis and outputs for number of hypoglycaemic episodes will be made. The number of hypoglycaemic episodes occurring on-drug after 56 weeks of treatment will be analysed using a negative binomial regression model with a log-link function and the logarithm of the on drug time period as offset. The model will include treatment, sex, BMI group and sulphonylurea (Yes, No) as fixed factors and baseline body weight in kg and HbA1c in % as covariates."

4 References

1. Carpenter JR, Roger JH, Kenward MG. Analysis of longitudinal trials with protocol deviation: a framework for relevant, accessible assumptions, and inference via multiple imputation. J Biopharm Stat. 2013;23(6):1352-71.

2. McEvoy BW. Missing data in clinical trials for weight management. J Biopharm Stat. 2016;26(1):30-6.

3. Sacks FM, Bray GA, Carey VJ, Smith SR, Ryan DH, Anton SD, et al. Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. N Engl J Med. 2009;360(9):859-73.