Cover Page for Statistical Analysis Plan

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Official title of study:	LIRA-ADD2SGLT2i – liraglutide versus placebo as add-on to SGLT2 inhibitors
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16.1.9 Documentation of statistical methods

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

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Statistical Analysis Plan

Trial ID: NN2211-4315

LIRA-ADD2SGLT2i – liraglutide versus placebo as add-on to SGLT2 inhibitors

Author:

[redacted]

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List of abbreviations

ADA	American Diabetes Association
AE	adverse event
ANCOVA	analysis of covariance
BG	blood glucose
BMI	body mass index
CI	confidence interval
CRF	case report form
CTR	clinical trial report
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomular filtration rate
EoT	end-of-text
FAS	full analysis set
GI	gastro-intestinal
HbA_{1c}	glycosylated haemoglobin
HDL	high-density lipoprotein
IWRS	interactive voice/web response sytem
LDL	low-density lipoprotein
LLoQ	lower limit of quantification
LOCF	last observation carried forward
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model repeated measurements
PD	pharmacodynamics
PK	pharmacokinetics
PP	per protocol
REML	restricted maximum likelihood
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
SD	standard deviation
SE	standard error
SGLT2	sodium-glucose co-transporter 2
SMPG	self-measured plasma glucose
T2DM	type 2 diabetes mellitus
TE	Treatment effect
VLDL	very low density lipoprotein

1 Introduction

1.1 Trial information

This is a 26-week, 2:1 randomised, placebo controlled, double blind, multicentre, multinational, confirmatory, two arm trial investigating the effect and safety of liraglutide versus placebo as addon to an SGLT2 inhibitor with or without metformin in subjects with type 2 diabetes mellitus who have not achieved adequate glycaemic control despite stable treatment with SGLT2 inhibitor ± metformin. Refer to the protocol for further details.

1.2 Scope of the statistical analysis plan

This Statistical Analysis Plan (SAP) is based on the statistical analyses of NN2211-4315 as planned in the trial protocol.

Changes to the statistical methods proposed in this SAP and the reason for the change must be reported in the clinical trial report (CTR).

This SAP is based on the protocol version 3.0 (dated 01 September 2017).

2 Statistical considerations

The blinding of the randomised treatments will be maintained until the database has been released for statistical analysis. No interim analyses or other analyses of unblinded data will be performed before the database is locked.

Data from all sites will be analysed and reported together.

In statistical analyses where stratification is included, anti-diabetic background medication at randomisation (metformin use: yes vs no) will be included based on the actual information collected through the eCRF. In case of missing eCRF information concerning the stratification, the information collected from the IWRS will be used.

The latest available measurement, at or prior to the randomisation visit, will be used as the baseline measurement. If no measurement(s) have been obtained, at or prior to randomisation, the baseline value will be left missing.

Laboratory values below the lower limit of quantification (LLoQ) will be set to ½LLoQ. The number of values below LLoQ by treatment and visit will be summarised if deemed relevant.

Results from a statistical analysis will, at a minimum be presented by the estimated treatment contrasts for the comparison between liraglutide and placebo with associated two-sided 95% confidence intervals and p-values corresponding to two-sided tests of no difference.

Primary and secondary estimands

Two estimands addressing different aspects of the trial objective will be defined; a primary de-facto (effectiveness) estimand and a secondary de-jure (efficacy) estimand:

1. Primary estimand

- de-facto treatment difference at week 26 for all randomised subjects

The primary de-facto estimand assesses the average glycaemic benefit in a future population with T2DM with inadequate glycaemic control that results from adding treatment with liraglutide to a stable regimen of either SGLT2 inhibitor monotherapy or in combination with metformin including potential rescue medication(s) as compared to a continuing stable regimen of either SGLT2 inhibitor monotherapy or in combination with metformin including potential rescue medication(s). Generalisation of this estimand depends among other things on the extent to which the use of rescue medication and treatment adherence in this trial reflects clinical practice. All post-baseline scheduled visit data will be included in the analysis, including data collected after discontinuation of trial product or initiation of rescue medication(s).

2. Secondary estimand

- de-jure treatment difference at week 26 for all randomised subjects if all subjects adhered to treatment and did not initiate rescue medication

The secondary de-jure estimand assesses the glycaemic benefit a future subject with inadequate glycaemic control is expected to achieve if adding treatment with liraglutide to a stable regimen of either SGLT2 inhibitor monotherapy or in combination with metformin as compared to a stable regimen of either SGLT2 inhibitor monotherapy or in combination with metformin. It is considered a clinically relevant estimand as it provides information to treating clinicians about the expected glycaemic efficacy of liraglutide compared to placebo for purposes of treating individual subjects. Generalisation of this estimand depends among other things on the extent to which the compliance to trial product administration in this trial reflects clinical practice. Only post-baseline scheduled visit data collected prior to discontinuation of trial product or initiation of rescue medication will be included in the analysis. This will avoid confounding from rescue medication.

Missing data considerations at week 26

When estimating the primary estimand, the proportion of missing data, (i.e., data that do not exist even though subjects are intended to stay in the trial regardless of treatment status and initiation of rescue medication(s)), is expected to be at a maximum 10% based on previous experience in T2DM trial NN2211-4059[1]. Missing data will mainly be due to withdrawal from trial or loss to follow-up.

The proportion of missing data when estimating the secondary estimand is expected to be higher (25%), since data collected after discontinuation of trial product or initiation of rescue medication(s) will be set to missing. This assumption of 25% missing data is based on previous observations in the T2DM trial NN2211-4059[1]. Across treatment arms, the main reasons for missing data are expected to be: early treatment discontinuation due to GI AEs and initiation of rescue medication. Initiation of rescue medication is expected to be more frequent in the placebo arm, whereas a higher proportion of subjects are expected to discontinue treatment due to AEs in the liraglutide arm when compared to the other treatment arm. Overall, the frequency of missing data is expected to be similar across treatment arms.

To document the extent and reason for missing data, descriptive summaries and graphical representation of extent, reason(s) for and pattern of missing data will be presented by treatment arm.

2.1 Sample size calculation

The primary endpoint is change from baseline to week 26 in HbA_{1c}. The confirmatory secondary endpoint is change from baseline to week 26 in body weight.

The sample size has been determined in order to demonstrate superiority of liraglutide vs. placebo both as add-on to SGLT2 inhibitor +/- metformin, with respect to both the primary and confirmatory secondary endpoints. The two pre-specified confirmatory tests are assumed to be independent. Since the tests are expected to be positively correlated, the assumption of independence is viewed as conservative. The hypotheses and testing procedure are described in Section 2.2.

The sample size assumptions for treatment effects, adjusted treatment effects and the standard deviations (SD) are given in Table 2–1. These are based on results from previous trials in the liraglutide Phase 3a clinical development program[2345][6][7], and are supported by trial NN2211-4059[1].

They are as follows:

- Change in HbA_{1c}: a minimal treatment effect (TE) of 0.5% for liraglutide vs. placebo both as add-on to SGLT2i +/- metformin; standard deviation (SD) assumed to be 1.1%.

- The proportion of subjects either discontinuing treatment, initiating rescue medication, or not completing the week 26 HbA_{1c} assessment is expected to be 25% equally distributed among the two treatment arms. The TE among these 25% of subjects is expected to be 0.25%, leading to an adjusted TE of 0.4375% in the entire trial population.

- Change in body weight: a minimal treatment effect of 2.0 kg for liraglutide vs. placebo both as add-on to SGLT2i +/- metformin; SD assumed to be 4.0 kg.

- Similarly as for HbA_{1c}, the TE among the 25% of subjects either discontinuing treatment, initiating rescue medication, or not completing the week 26 body weight assessment is expected to be reduced to 1.0 kg, leading to an adjusted TE of 1.75 kg in the entire trial population.

Table 2–1 Assumptions used in the sample size calculation

Liraglutide vs. placebo	HbA_{1c}	Body weight
TE	-0.50%	-2.0 kg
Adjusted TE	-0.4375%	-1.75 kg
SD	1.1%	4.0 kg

* TE: treatment effect

Based on these assumptions, the sample size is set to 202 in the liraglutide arm and 101 in the placebo arm for the full analysis set in order to achieve 90% power to confirm superiority in reducing HbA_{1c} of liraglutide vs. placebo. Marginal powers for individual hypotheses are presented in Table 2–2. The planned total sample size in the trial will be 303 subjects.

Table 2–2 Marginal powers for meeting individual hypothesis

Statistical test	HbA_{1c} superiority	Body weight superiority
Power (%)	90%	95%

2.2 Definition of analysis sets

The following analysis sets will be defined:

Full analysis set (FAS): includes all randomised subjects. Subjects in the FAS will contribute to evaluation “as randomised”.

Safety analysis set (SAS): includes all subjects exposed to at least one dose of trial product. Subjects in the SAS will contribute to the evaluation based on the trial product received for the period they were on treatment. This will be referred to as contributing to the evaluation “as treated”.

Exclusion of data from analyses will be used restrictively and normally no data should be excluded from the FAS. The subjects or observations to be excluded, and the reasons for their exclusion must be documented and signed by those responsible before database lock. The subjects and observations excluded from analysis sets, and the reason for this, will be described in the clinical trial report.

Data selections and observation periods

Unless subjects withdraw their informed consent, data collection will continue for the full duration of the trial. The full duration of the trial is defined as up to and including the follow-up visit (visit 12).

Subjects and data to be used in an analysis will be selected in a two-step manner.

- Firstly, subjects will be selected based on the specified analysis set
- Secondly, data points on the selected subjects from first step will be selected based on the specified observation period

Definition of the observation periods:

In-trial: This observation period represents the time period where subjects are considered to be in the trial, regardless of discontinuation of trial product or initiation of rescue medication. The in-trial observation period starts at randomisation (as registered in the IWRS) and ends at the date of:

- the last direct subject-site contact, which is scheduled to take place 7 days after planned last dose of trial product at the follow-up visit (visit 12) for subjects completing the trial
- withdrawal for subjects who withdraw their informed consent
- the last subject-investigator contact as defined by the investigator for subjects who are lost to follow-up
- death for subjects who die before any of the above

On-treatment: This observation period represents the time period where subjects are considered treated with the trial product. The observation period is a subset of the in-trial observation period. It starts at the date of first dose of trial product. Three slightly different end dates will be needed to cover all assessments appropriately:

For AEs, the observation period ends at the first date of:

- the follow-up visit (visit 12)
- the last date on trial product + 1 day (hypoglycaemic episodes only)
- the last date on trial product + 7 days (all AEs excluding hypoglycaemic episodes). The follow-up visit is scheduled to take place 7 days after the last date on trial product. the end-date for the in-trial observation period

A different end date is specified for hypoglycaemic episodes to ensure specificity of reversible effects of treatment, as well as to ensure consistency across the liraglutide phase 3b clinical development programme.

For efficacy and other safety assessments (laboratory assessments, physical examination and vital signs) the observation period ends at the last date on trial product + 1 day. This will be used in order to ensure specificity of reversible effects of treatment.

On-treatment without rescue medication: This observation period is a subset of the on-treatment observation period, where subjects are considered treated with trial product, but have not initiated any rescue medications. Specifically it starts at date of first dose of trial product and the observation period ends at the first date of:

- the last dose of trial product + 1 day
- initiation of rescue medication

The in-trial observation period will be the primary observation period when estimating the primary estimand. The on-treatment without rescue observation period will be the primary observation period when estimating the secondary estimand. The on-treatment observation period will be considered supportive for evaluating efficacy. Safety will be evaluated based on the in-trial and the on-treatment observation periods. For hypoglycaemic episodes, a sensitivity analysis will also be performed using the on-treatment period specified for all other AEs (last date on trial product + 7 days).

Data points collected outside an observation period will be treated as missing in the analysis. Baseline data will always be included in an observation period.

Confirmatory hypotheses

For the primary HbA_{1c} endpoint and the secondary confirmatory body weight endpoint, the following hypotheses are planned to be tested:

- Superiority in reducing HbA_{1c} of liraglutide 1.8 mg/day vs. placebo after 26 weeks
- Superiority in reducing body weight of liraglutide 1.8 mg/day vs. placebo after 26 weeks

A hierarchical testing procedure is used to control the overall type-1 error at a nominal two-sided 5% level. The primary endpoint and the confirmatory secondary endpoint will be analysed in the following order:

A. Primary endpoint (HbA_{1c})

B. Confirmatory secondary endpoint (Body weight)

In order to be able to conclude significance for the confirmatory secondary endpoint, a significant difference in favour of the liraglutide group must be found both for the primary endpoint and the confirmatory secondary endpoint.

2.3 Primary endpoint

The primary endpoint is change from baseline to week 26 in HbA_{1c}.

2.3.1 Primary analysis for the primary estimand

The primary estimand will be estimated based on the FAS using week 26 measurements from the in-trial observation period. The primary statistical analysis will be a pattern mixture model using multiple imputation to handle missing data assuming that the missing data mechanism is missing at random (MAR) within the groups used for imputation. Imputation of missing data at week 26 for all subjects will be based on patients who discontinue or initiate rescue therapy within each randomised treatment arm, respectively. It is hereby assumed that the values of what the missing data would have been if available are reasonably described by information from subjects on the same treatment arm who at week 26 had discontinued or initiated rescue therapy.

Missing values for each group will be imputed as follows:

- An analysis of covariance (ANCOVA) with country and the stratification factor (metformin use at baseline: yes vs no) as categorical fixed effects and baseline HbA1c measurement as a covariate will be fitted to observed values of the change from baseline at week 26 in HbA1c.
- The estimated parameters for location and dispersion, as well as the variability of these estimates, will be used to impute values for each subject with missing week 26 data based on stratification factor and country and baseline HbA1c. Thus, 1000 complete data sets will be generated including observed and imputed values.

In case there is an insufficient number of patients who discontinue or initiate rescue medication within each levels of country or strata, an analysis of covariance (ANCOVA) with baseline HbA1c measurement as a covariate alone will be fitted to observed values of the change from baseline at week 26 in HbA1c.

Analysis used for confirming superiority versus placebo at week 26:

For each of the 1000 (now complete) imputed data sets the change in HbA_{1c} from baseline to week 26 will be analysed using an ANCOVA with treatment, country and the stratification factor (metformin use at baseline: yes vs. no) as categorical fixed effects and baseline HbA_{1c} as covariate. The results obtained from analysing the datasets will be combined using Rubin's rule[8] to draw inference.

From this analysis the estimated treatment difference between liraglutide and placebo together with two-sided 95% CI and p-value for the test of no difference in effect will be presented.

2.3.2 Primary analysis for the secondary estimand

The secondary estimand will be estimated based on the FAS using post-baseline measurements up to and including week 26 from the on-treatment without rescue observation period. The primary analysis for the secondary estimand will be performed using a Mixed Model for Repeated Measurements (MMRM). A restricted maximum likelihood (REML) will be used in fitting this model. The model will include change from baseline in HbA_{1c} measurements collected at scheduled visits up to and including week 26 as dependent variables. The independent effects included in the model will be treatment, country and the stratification factor (metformin use at baseline: yes vs. no) as categorical fixed effects and baseline HbA_{1c} as a covariate, all nested within visit. An unstructured covariance matrix for HbA_{1c} measurements within the same subject will be employed, assuming measurements from different subjects are independent.

The MMRM is a well-established method that accounts for the uncertainty pertaining to missing data. This analysis assumes that the missing data mechanism is MAR. Under this assumption the statistical behaviour of the missing data (given the observed responses and model fixed effects and covariates) is assumed to be the same as for the observed data.

2.3.3 Sensitivity Analysis

To investigate the sensitivity of the primary analysis results, complementary and separate analyses will be performed for the primary and secondary estimand. In line with the European Medicines Agency (EMA) recommendations[9], and the US National Research Council[10] data.

The evaluation of the robustness of the primary analysis results will primarily be based on a pattern mixture model approach using multiple imputation. An overview of the sensitivity analyses for each

of the estimands are specified below followed by a more detailed description of the three different pattern mixture models used.

Sensitivity analyses for the primary estimand

The estimation of the primary estimand will be repeated using the following sensitivity analyses:

- A placebo multiple imputation analysis based on FAS using the in-trial observation period.
- A placebo multiple imputation analysis differentiating between reasons for discontinuing treatment prematurely based on FAS using the in-trial observation period.
- A tipping-point multiple imputation analysis based on FAS using the in-trial observation period.
- An MMRM analysis (the primary analysis for the secondary estimand) based on FAS using the in-trial observation period.
- A multiple imputation analysis similar to the primary analysis, but instead using ANCOVA allowing for unequal variances between the two treatment groups based on FAS using the in-trial observation period. This sensitivity analysis aims to evaluate the assumption of equal variances implicit in the ANCOVA model for the primary analysis.

Sensitivity analyses for the secondary estimand

The estimation of the secondary estimand will be repeated using the following sensitivity analyses:

- A placebo multiple imputation analysis based on FAS using the on-treatment without rescue medication observation period.
- A placebo multiple imputation analysis based on FAS using the on-treatment observation period. This sensitivity analysis aims to compare liraglutide versus placebo for subjects who adhere to treatment regardless of whether or not rescue medication has been initiated.
- A placebo multiple imputation analysis differentiating between reasons for discontinuing treatment prematurely based on FAS using the on-treatment without rescue medication observation period.
- A tipping-point multiple imputation analysis based on FAS using the on-treatment without rescue medication observation period.

2.3.3.1 Pattern mixture models

All three pattern mixture model sensitivity analyses aim to stress-test the primary HbA_{1c} results by changing the assumptions for part or all missing data in the liraglutide treatment arm, while maintaining the missing at random data assumption for the placebo arm:

- Placebo multiple imputation analysis: In this sensitivity analysis, missing data at week 26 for subjects in both treatment arms will be imputed to resemble the distribution of the week 26 values observed in the placebo arm. In effect, this imputation approach removes the treatment difference between liraglutide and placebo for subjects randomised to liraglutide with missing data at week 26, given that liraglutide is better in reducing HbA_{1c} than placebo.

- Placebo multiple imputation analysis differentiating between reasons for discontinuing treatment prematurely: In this sensitivity analysis, only missing data at week 26 for subjects who discontinue liraglutide treatment due to treatment related AE(s) will be imputed to resemble the distribution of the week 26 values observed in the placebo arm. For subjects who discontinue liraglutide treatment for reasons other than treatment related AE(s), missing data at week 26 will be imputed to resemble the distribution of the week 26 values observed within each treatment arm. Treatment related AEs are defined as AEs classified as possible or probable related to trial product as reported by the investigator. In effect, this imputation approach removes the treatment difference between liraglutide and placebo for this selected group of subjects randomised to liraglutide. This sensitivity analysis is less conservative as compared to the above sensitivity analysis.

- Tipping-point multiple imputation analysis: In this sensitivity analysis, missing data will first be imputed according to the primary analysis. Second, for the liraglutide arm a penalty will be added to the imputed values at week 26. The approach is to gradually increase this penalty until the confirmed HbA_{1c} conclusion from the primary analysis is reversed. For each hypothesis tested the specific value of the penalty that reverses the conclusion will be used to evaluate the robustness of the primary analysis results.

2.3.3.2 Assessment of sensitivity analyses

The results from the sensitivity analyses will be collectively used to interpret the robustness of the trial results for HbA_{1c}. Due to the inherent conservative nature of the sensitivity analyses, it will not be a requirement that all confirmatory hypotheses are consistently confirmed across the sensitivity analyses. Thus, no absolute success criteria will be pre-defined for each sensitivity analysis. The sensitivity results in totality will be used to substantiate the credibility of the trial results.

2.4 Secondary endpoints

2.4.1 Confirmatory secondary endpoints

Change from baseline to week 26 in body weight will be a confirmatory secondary endpoint.

The primary and secondary estimands will be estimated using the same approaches as described for the primary HbA_{1c} endpoint. Baseline body weight will be used as a covariate instead of baseline HbA_{1c} in both the imputation and analysis model. From the analyses, the estimated treatment differences between liraglutide and placebo will be presented together with associated two-sided 95% CIs and p-values for testing no difference from zero. Sensitivity analyses similar to the ones pre-specified for testing superiority for the primary HbA_{1c} endpoint will be made to evaluate the robustness of the body weight results.

2.4.2 Supportive secondary endpoints

The below supportive secondary efficacy endpoints will be evaluated for:

- the primary estimand based on FAS using the in-trial observation period
- the secondary estimand based on FAS using the on-treatment without rescue medication observation period

No sensitivity analyses are planned for these.

2.4.2.1 Efficacy endpoints

Continuous efficacy endpoints

Change from baseline to week 26 in:

- Fasting Plasma Glucose (FPG)
- Self-Measured Plasma Glucose (SMPG): 7-point profile:
  - Mean 7-point profile
  - Mean post prandial increments (over all meals)
- Fasting blood lipids (total cholesterol, LDL cholesterol, VLDL cholesterol, HDL cholesterol, triglycerides and free fatty acids)
- BMI and waist circumference

- Systolic and diastolic blood pressure

BMI will be calculated based on body weight and height based on the formulae:

BMI kg/m2 = body weight (kg)/(height (m) × height (m)) or (kg/m2 = [lb/in2 × 703])

Change from baseline to weeks 14 and 26 in:

- Glucagon, C-peptide and insulin (all fasting)

The above continuous endpoints will be analysed separately using similar modeling approaches as for the primary endpoint with the associated baseline response as a covariate. Fasting lipid profile endpoints as well as fasting glucagon, C-peptide and insulin endpoints will be log-transformed prior to analysis with the associated log-transformed baseline value as a covariate.

Binary efficacy endpoints

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

- HbA_{1c} <7.0% (53 mmol/mol), American Diabetes Association target
- HbA_{1c} ≤6.5% (48 mmol/mol), American Association of Clinical Endocrinologists target
- Weight loss ≥3%
- HbA_{1c} <7.0% (53 mmol/mol) without severe or blood glucose confirmed symptomatic hypoglycaemia episodes and no weight gain
- HbA_{1c} <7.0% (53 mmol/mol) and no weight gain
- HbA_{1c} <7.0% (53 mmol/mol), no weight gain and systolic blood pressure <140 mmHg
- HbA_{1c} reduction ≥1% (11mmol/mol)
- HbA_{1c} reduction ≥1% (11mmol/mol) and no weight gain
- HbA_{1c} reduction ≥1% (11mmol/mol) and weight loss ≥3%

Handling of missing data for the response status of the above binary endpoints will be determined from the imputed continuous responses. A total of 1000 imputed data sets will be created based on the same models as used to analyse HbA_{1c} and body weight. The imputed complete data sets will be analysed using a logistic regression model with treatment, stratification factor and country as categorical fixed effects and baseline response as covariate (i.e. baseline HbA_{1c} for binary HbA_{1c}

endpoints, baseline weight for binary weight endpoints and both baseline HbA_{1c} and body weight for the binary endpoints that combines both parameters). Inference comparing treatments will be drawn using Rubin's rule[8].

For the secondary estimand the binary endpoints will be determined from the continuous responses and response status for missing values at week 26 will be determined from MMRM predicted values. The complete data set will analysed using a logistic regression model with treatment, stratification factor and country as categorical fixed effects and baseline response as covariate.

2.4.2.2 Safety endpoints

The safety endpoints will be evaluated based on SAS using the on-treatment and in-trial observation periods unless otherwise stated. The following endpoints are used to support the safety objective:

Adverse events

- Number of treatment emergent AEs during 26 weeks

All AEs will be coded using version 20.1 of the Medical Dictionary for Regulatory Activities (MedDRA) coding.

A treatment emergent AE is defined as an AE with onset in the on-treatment observation period (see definition of observation periods in Section 2.2).

Treatment emergent AEs will be summarised 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 1000 patient years of observation time (R) for the on-treatment observation period. Supportive summaries of AEs will be made for the in-trial observation period. The development over time in gastrointestinal AEs will be evaluated by the use of graphical methods.

Other safety endpoints

Change from baseline to week 26 in:

- Haematology: haemoglobin, haematocrit, thrombocytes, erythrocytes, leucocytes
- Biochemistry: serum bicarbonate, creatinine, creatine kinase, urea, albumin, bilirubins (total), alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, sodium, potassium, calcium (corrected), calcium (total)
- Pulse
- ECG category

- Physical examination

The above safety endpoints will be evaluated based on SAS using the on-treatment and in-trial observation periods. Continuous endpoints will be summarised descriptively by treatment arm and visit. Categorical safety endpoints will be summarised as counts and relative frequencies.

Ratio to baseline from week 26 in:

Amylase, lipase, estimated glomerular filtration rate, all urinalysis assessments.

Furthermore, these endpoints will be summarised by geometric means instead of arithmetic means, and will be plotted on logarithmic scale.

Hypoglycaemia

- Number of treatment emergent severe or blood glucose confirmed symptomatic hypoglycaemic episodes during 26 weeks*
- Treatment emergent severe or blood glucose confirmed symptomatic hypoglycaemia episodes during 26 weeks (yes/no)

Classification of Hypoglycaemia:

Hypoglycaemic episodes will be summarised for the SAS and the on-treatment observation period only.

Treatment emergent: hypoglycaemic episodes will be defined as treatment emergent if the onset of the episode occurs within the on-treatment observation period (see definition of observation periods in Section 2.2).

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

Hypoglycaemic episodes are classified according to the Novo Nordisk classification of hypoglycaemia and the ADA classification of hypoglycaemia (see Figure 2–1).

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)[11]. 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 in addition to the ADA classification (see Figure 2–1):

- 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.

- Severe or BG confirmed symptomatic hypoglycaemia: An episode that is severe according to the ADA classification[12] or BG confirmed by a plasma glucose value <3.1 mmol/L (56 mg/dL) with symptoms consistent with hypoglycaemia.

- Severe or BG confirmed hypoglycaemia: An episode that is severe according to the ADA classification[13] or BG confirmed by a plasma glucose value <3.1 mmol/L (56 mg/dL) with or without symptoms consistent with hypoglycaemia.

ADA classification[12] of hypoglycaemia

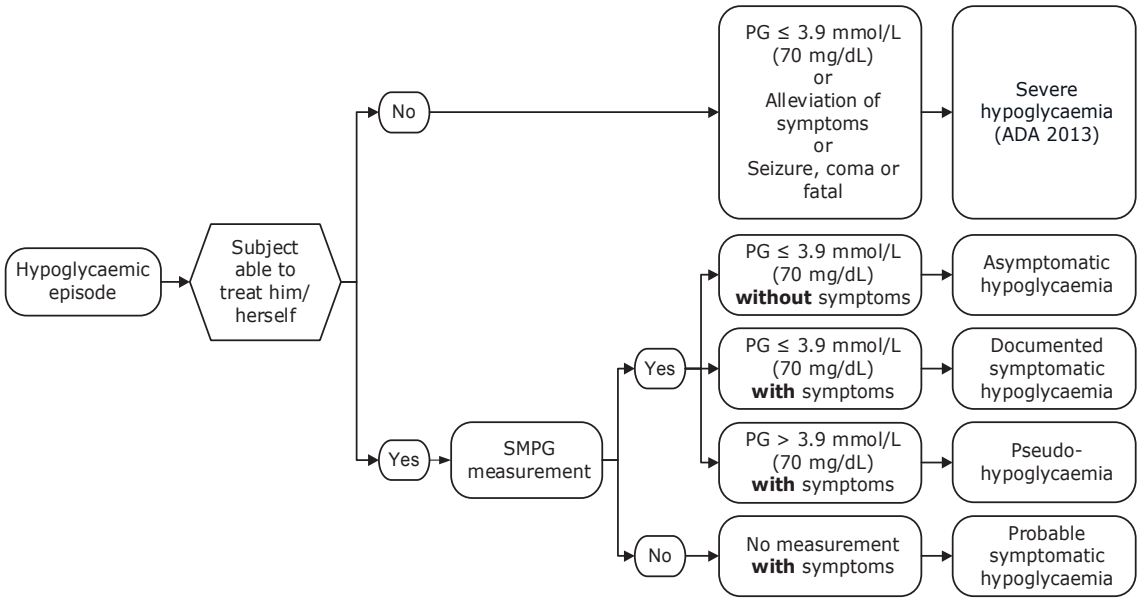
- Severe hypoglycaemia: An episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is 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

PG: plasma glucose SMPG: Self-measured plasma glucose

Figure 2–1 ADA classification of hypoglycaemia

Data on treatment emergent hypoglycaemic episodes will be presented in terms of the number of subjects with at least one episode, the percentage of subjects with at least one episode (%), the total number of episodes and the episode rate per 100 patient years of observation time.

Analysis of severe or BG confirmed symptomatic hypoglycaemic endpoints

Because the number of hypoglycaemic episodes are expected to be very low in this trial, statistical analyses of severe or BG-confirmed symptomatic hypoglycaemia will not be performed.

3 Changes to the statistical analyses planned in the protocol

The following changes from the protocol are implemented in this SAP.

On-treatment observation period

The on-treatment period is changed from treatment start date to treatment end date + 3 days to treatment start date to treatment end date + 1 day for efficacy laboratory parameters and from treatment start date to treatment end date + 10 days to treatment start date to treatment end date + 7

days. The on-treatment period is consistent with the PSPS ensuring consistency across the liraglutide phase 3b clinical development programme.

Pattern mixture model with multiple imputation

The strategy for the multiple imputation is specified in case only few subjects discontinue trial product or initiate rescue medication. If there is an insufficient number of patients who discontinue or initiate rescue medication for any level of country and strata, an analysis of covariance (ANCOVA) with baseline HbA1c measurement as a covariate will be fitted to observed values of the change from baseline at week 26 in HbA1c. For the placebo multiple imputation differentiating between reasons for discontinuing treatment prematurely, it has been further clarified that for subjects with reasons other than treatment related AE(s), missing data at week 26 will be imputed to resemble the distribution of the week 26 values observed within each treatment arm.

Responder analyses for the secondary estimand

For the responder analyses for the secondary estimand, binary endpoints will be determined from the continuous responses. For missing values at week 26 the binary endpoints will be determined from MMRM predicted values.

MedDRA version

It has been clarified that MedDRA version 20.1 is used for this trial.

Log-transformation

Further description is added on which assessments are treated as lognormally distributed. Fasting lipid profile endpoints, fasting glucagon, C-peptide and insulin will be analysed on the logarithmic scale. Amylase, lipase, estimated glomerular filtration rate and urinalysis assessments will be presented in ratio to baseline from week 26 and summarised by geometric means instead of arithmetic means.

Analyses of hypoglycaemic episodes

The pre-specified analyses of severe or BG-confirmed symptomatic hypoglycaemic episodes will not be performed due to sparse data. Following text was removed from the statistical considerations section:

The number of treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes will be analysed for the on-treatment period using a negative binomial regression model with a log-link function and the logarithm of the duration of the subject's on-treatment observation period as

offset. The model will include factors for treatment, stratification factor and country as fixed factors and baseline HbA_{1c} as covariate.

The binary endpoint showing whether a subject has at least one treatment emergent severe or BG confirmed symptomatic hypoglycaemic episode will be analysed using a logistic regression model with treatment, stratification factor and country as fixed factors and baseline HbA_{1c} as covariate.

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