Cover Page for Statistical Analysis Plan

Sponsor name:	Novo Nordisk A/S
NCT number	NCT02505334
Sponsor trial ID:	NN2211-4174
Official title of study:	A trial comparing the efficacy and safety of liraglutide 1.8 mg/day to liraglutide 0.9 mg/day in Japanese subjects with type 2 diabetes mellitus
Document date:	10 April 2018

16.1.9 Documentation of statistical methods

List of contents

Statistical Analysis Plan
Trial ID: NN2211-4174
UTN: U1111-1164-5462

CONFIDENTIAL

Date: 26 November 2017
Version: 2.0
Status: Final
Page: 1 of 23

Novo Nordisk

Statistical Analysis Plan

Trial ID: NN2211-4174

A trial comparing the efficacy and safety of liraglutide 1.8 mg/day to liraglutide 0.9 mg/day in Japanese subjects with type 2 diabetes

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

.

Author:

Clinical Statistics Group

Table of contents

Page

List of abbreviations

AE	adverse event
ANCOVA	analysis of covariance
BMI	body mass index
CI	confidence interval
CTR	clinical trial report
CV	coefficient of variation
FAS	full analysis set
FPG	fasting plasma glucose
HOMA-IR	homeostasis model assessment as an index of insulin resistance
HOMA-B	homeostasis model assessment of beta-call function
ITT	intention-to-treat
LLOQ	lower limit of quantification
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measurements
SAP	statistical analysis plan
SAS	safety analysis set
SD	standard deviation
SMBG	self-measured blood glucose
T2DM	type 2 diabetes mellitus
TEAE	treatment emergent adverse event
UNR	upper normal range

1   Introduction

1.1   Trial information

This is a 26-week randomised, parallel, two-arm, open-label, multi-centre trial comparing the efficacy and safety of liraglutide 1.8 mg/day to liraglutide 0.9 mg/day in Japanese subjects with T2DM. The liraglutide 1.8 mg/day treatment arm will be continued for a total of 52 weeks after randomisation for monitoring of safety and glycaemic control over 52 weeks. 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 NN2211-4174 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 10 September 2015).

2   Endpoints

2.1   Primary endpoint

Change from baseline in HbA1c after 26 weeks of treatment

2.2   Secondary endpoints

2.2.1   Secondary efficacy endpoints

- Responder for HbA1c after 26 weeks of treatment (Yes/No):

    o   HbA1c < 7.0% (53 mmol/mol)*

    o   HbA1c ≤ 6.5% (48 mmol/mol)*

    o   HbA1c < 7.0% without weight gain*

    o   HbA1c < 7.0% without treatment emergent severe or blood glucose (BG) confirmed symptomatic hypoglycaemic episodes*

- Change from baseline after 26 weeks of treatment in:

    o   Self-Measured Blood Glucose (SMBG) 7-point profile

Statistical Analysis Plan
Trial ID: NN2211-4174
UTN: U1111-1164-5462

CONFIDENTIAL

Date: 26 November 2017
Version: 2.0
Status: Final
Page: 5 of 23

Novo Nordisk

- 7-point profile (individual points in the profile)*

- Mean of 7-point profile*

- Mean of postprandial increments (from before meal to 90 min after for breakfast, lunch and dinner). The mean increment over all meals will be derived as the mean of all available meal increments.*

  o Fasting plasma glucose (FPG)*

  o Waist circumference*

  o Body weight*

  o Body mass index (BMI)*

  o Blood pressure (systolic and diastolic)*

- Fasting C-peptide, fasting insulin, fasting glucagon, proinsulin, proinsulin/insulin, HOMA-B, HOMA-IR after 26 weeks of treatment*

- Fasting lipid profile (total cholesterol, low density lipoprotein cholesterol [LDL cholesterol], high density lipoprotein cholesterol [HDL cholesterol], very low density lipoprotein cholesterol [VLDL cholesterol], triglycerides, and free fatty acids) after 26 weeks of treatment*

2.2.2   Secondary safety endpoints

- Number of treatment emergent adverse events during 26 weeks of treatment*

- Number of treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes during 26 weeks of treatment*

- Number of treatment emergent nocturnal severe or BG confirmed symptomatic hypoglycaemic episodes during 26 weeks of treatment*

- Number of treatment emergent hypoglycaemic episodes according to ADA definition during 26 weeks of treatment*

- Change from baseline after 26 weeks of treatment:

  o Clinical evaluations:

    - Physical examination

- ▪ Eye examination

- ▪ Electrocardiogram (ECG)

- ▪ Pulse*

  o Laboratory assessments:

- ▪ Biochemistry

- ▪ Haematology

- ▪ Calcitonin

The above mentioned primary endpoint, secondary efficacy endpoints and secondary safety endpoints will also be evaluated separately for 52 weeks of treatment.

* Key secondary endpoint prospectively selected for disclosure (e.g. clinicaltrials.gov and EudraCT)

Please note that following endpoints are also selected for disclosure.

- • Change from baseline in HbA1c after 52 weeks of treatment

- • Responder for HbA1c after 52 weeks of treatment (Yes/No):

  o HbA1c < 7.0% (53 mmol/mol)

- • Change from baseline in body weight after 52 weeks of treatment

- • Number of treatment emergent adverse events during 52 weeks of treatment

3 Statistical considerations

Novo Nordisk will analyse and report data from all sites together.

All analyses of efficacy and safety endpoints will be based on the full analysis set (FAS). All efficacy endpoints will be summarised using the FAS and safety endpoints will be summarised using the safety analysis set (SAS).

The impact of protocol deviations and outliers may be investigated further in sensitivity analyses if deemed relevant.

Unless otherwise specified, all continuous measurements will be summarised descriptively at each visit by treatment using all observed data. Descriptive statistics will be presented based both on observed and last observation carried forward (LOCF) imputed data. Endpoints that are analysed untransformed and endpoints that are not formally analysed are summarised by the arithmetic mean, standard deviation (SD), median, and minimum and maximum value. Endpoints that are analysed log-transformed are supplemented with the geometric mean and coefficient of variation (CV). CV is calculated as $\sqrt{exp(s^2) - 1}$ where s^2 is the SD of log-transformed values.

Unless otherwise specified, laboratory values below the lower limit of quantification (LLOQ) will be set to ½ LLOQ.

For measurements over time, mean values will be plotted to explore the trajectory over time. LOCF imputed data will be used as the basis for plotting data, if not otherwise specified. For endpoints that are analysed log-transformed, the geometric mean values will be plotted.

An analysis of covariance (ANCOVA) model will be applied for the primary endpoint and continuous secondary endpoints after 26 weeks of treatment. The model includes treatment as a fixed effect and the corresponding baseline value as a covariate. In the following, this model will be referred to as the standard ANCOVA model.

Presentation of results from a statistical analysis will include the estimated mean treatment effects (Least Square Means [LSMeans]) for absolute values and change from baseline. In addition, estimated mean treatment difference (or ratio) will be presented together with the two-sided 95% confidence interval and corresponding two-sided p-value. The "obsmargins" option will be used in the "LSMEANS TREATMENT".[i]

Handling of missing data

The expected percentage of missing data is around 10%. In accordance with industry guidance[ii] endpoints will be assessed at frequent visits and also on subjects who withdraw prematurely. This will facilitate an analysis in accordance with ITT principles. Also, the combined information on frequent outcomes and information on reason for drop-out is assumed to account for the missing data anticipated.

If not otherwise specified, the value from the randomisation visit (Visit 8) will be used as the baseline value. If the value measured at the randomisation visit is missing and the assessment has also been made at an earlier visit, then the non-missing value obtained at the preceding visit closest to Visit 8 will be used as the baseline value.

Missing values (including intermittent missing values) will be imputed using the LOCF method. Subjects without data after randomisation will be included by carrying forward their baseline value. In this trial, sensitivity analyses will be made to examine the robustness of the LOCF method.

Handling of laboratory measurements

A laboratory measurement in which the central laboratory could not guarantee a reliability of data, e.g. measurements with a comment like "Only for reference because of xxxx", will not be used for the summary and statistical analysis.

For laboratory parameters which is required to be measured in a fasting status (fasting plasma glucose, fasting insulin, fasting C-peptide, fasting glucagon, proinsulin and all lipids), the measurements in a non-fasting status will not be used for the summary and statistical analysis.

Handling of retest data

If more than one measurement exists at a visit after exclusion of non-fasting values for the fasting parameters or non-reliable laboratory data, the first one is chosen.

Visit reallocation

The following basic ideas are followed:

1) Visit reallocation is not applicable for assessments performed before date of first dosing of the randomised treatment.
2) Visit reallocation is only applicable for non-missing assessments. Hence, if an assessment is missing or treated as missing it cannot be reallocated to a different visit.
3) Any scheduled measurement (observed or missing), except the end of trial visit for the premature discontinuation (EOTpd), cannot be relocated to another visit.
4) Observed unscheduled measurements can only substitute preceding and adjacent scheduled assessments if these latter measurements were planned to be sampled in fasting conditions but were in fact sampled in non-fasting conditions.
   Notice that such a non-fasting record which should have been fasting may or may not be actually missing. Regardless, the non-fasting record will be treated as missing.
5) Observed scheduled measurements from EOTpd should replace
   a. the adjacent earlier scheduled assessments from the preceding visit, in case this assessment is missing
   b. the later adjacent scheduled missing assessment from the succeeding visit in case the adjacent earlier scheduled assessment from the preceding visit is not missing.

Statistical Analysis Plan
Trial ID: NN2211-4174
UTN: U1111-1164-5462

CONFIDENTIAL

Date: 26 November 2017
Version: 2.0
Status: Final
Page: 9 of 23

Novo Nordisk

3.1   Sample size calculation

Sample size calculations are described in the protocol section 17.1 and will not further be described here.

3.2   Definition of analysis sets

The following analysis sets are defined in accordance with the ICH-E9 guidance.[iii]

- **Full Analysis Set (FAS):** includes all randomised subjects. The statistical evaluation of the FAS will follow the intention-to-treat (ITT) principle and subjects will contribute to the evaluation "as randomised".

- **Safety Analysis Set (SAS):** includes all subjects receiving at least one dose of liraglutide. Subjects in the safety analysis set will contribute to the evaluation "as treated".

Subjects who are lost to follow up and where no exposure information of liraglutide is available will be handled as unexposed.

3.3   Primary endpoint

The primary endpoint is the change from baseline in HbA1c after 26 weeks of treatment.

The change from baseline in HbA1c after 26 weeks of treatment will be analysed using an analysis of covariance (ANCOVA) model with treatment as a fixed effect and baseline HbA1c as a covariate.

Missing values after 26 weeks of treatment will be imputed applying last observation carried forward (LOCF) using HbA1c values at and after baseline.

Superiority of liraglutide 1.8 mg/day vs. liraglutide 0.9 mg/day will be considered as confirmed if the 95% confidence interval for the treatment difference (liraglutide 1.8 mg/day minus liraglutide 0.9 mg/day) for change from baseline in HbA1c lies entirely below 0.0%; equivalent to a one-sided test with significance level of 2.5%. Conclusion of superiority will be based on FAS.

Additionally, change from baseline in HbA1c after 52 weeks of treatment will be presented descriptively for the liraglutide 1.8 mg/day treatment arm.

Sensitivity analysis

Sensitivity analysis will be performed on FAS using the mixed model for repeated measurements (MMRM) method. All HbA1c values available post baseline at scheduled measurement times will be analysed in a linear mixed normal model using an unstructured residual covariance matrix for HbA1c measurements within the same subject. The model will include treatment and visit as fixed factors and baseline HbA1c as a covariate. Interactions between visit and treatment and between

visit and baseline HbA1c will also be included in the model. The results of sensitivity analyses will be compared to the result of the standard ANCOVA method using LOCF for imputation of missing data.

Further, a pattern mixture model approach using multiple imputation and mimicking an ITT scenario will be applied. Imputation in both arms will be based on liraglutide 0.9 mg/day values. The imputations will be done as follows:

- In the first step, for each subject with a non-monotone missing data pattern, missing values at visits prior to the last non-missing value for that subject are imputed using a Markov Chain Monte Carlo (MCMC) method (with seed of 20170427), in order to obtain a monotone missing data pattern. This imputation is done for each treatment group separately and 1000 copies of the dataset will be generated.
- In the second step, for each of the 1000 copies of the dataset, an analysis of variance model with baseline HbA1c as a covariate is fitted to the change in HbA1c from baseline to 4 weeks (Visit 11) for liraglutide 0.9 mg/day only. The estimated parameter and their variance from this model are used to impute missing values at 4 weeks for subjects in both the liraglutide 0.9 mg/day and liraglutide 1.8 mg/day groups, based on HbA1c at baseline.
- In the third step, for each of the 1000 copies of the dataset, missing HbA1c values at 8 weeks (Visit 12) are imputed in the same way as for 4 weeks. Now the imputations are based on an analysis of variance model with the HbA1c values at baseline and 4 weeks as covariates, fitted to liraglutide 0.9 mg/day group.
- This stepwise procedure is then repeated sequentially over the available planned visits, adding one visit in each step until 26 weeks (Visit 16). In this stepwise procedure, seed of 19671230 will be used.
- For each of the complete data sets, the change from baseline to 26 weeks is analysed using an analysis of covariance model with treatment as a fixed effect and baseline HbA1c value as a covariate.

The estimates and standard deviations for the 1000 data sets are pooled to one estimate and associated standard deviation using Rubin's rule[iv]. From these pooled estimates the confidence interval for the treatment differences and the associated p-value are calculated.

3.4 Secondary endpoints

3.4.1 Efficacy endpoints

Endpoints evaluated after 26 weeks of treatment

In the statistical analysis for the responder endpoints, the endpoint derived from imputed HbA1c and/or body weight by LOCF will be used.

Responder for HbA1c

Two dichotomous endpoints (responder/non-responder) will be defined based on whether a subject has met a specific target level after 26 weeks of treatment:

- HbA1c target < 7.0%[v]

- HbA1c target ≤ 6.5%[vi, vii]

Analysis of each of the two responder endpoints will be based on a logistic regression model with treatment as factor and baseline HbA1c value as a covariate.

HbA1c responder endpoints without weight gain

Responder for HbA1c without weight gain after 26 weeks of treatment will be defined as HbA1c < 7.0% after 26 weeks of treatment and change from baseline in body weight after 26 weeks of treatment below or equal to zero. Analysis will be based on a logistic regression model with treatment as factor and baseline HbA1c and baseline body weight values as covariates.

HbA1c responder endpoints without treatment emergent severe or blood glucose (BG) confirmed symptomatic hypoglycaemic episodes

Responder for HbA1c without hypoglycaemic episodes after 26 weeks of treatment will be defined as HbA1c < 7.0% after 26 weeks of treatment and without severe or BG confirmed symptomatic episodes during 26 weeks of treatment. Analysis will be based on a logistic regression model with treatment as factor and baseline HbA1c values as a covariate.

Fasting plasma glucose (FPG)

Change from baseline in FPG after 26 weeks of treatment will be analysed using the standard ANCOVA model.

Waist circumference

Change from baseline in waist circumference after 26 weeks of treatment will be analysed using the standard ANCOVA model.

Body weight

Change from baseline in body weight after 26 weeks of treatment will be analysed using the standard ANCOVA model.

Body Mass Index (BMI)

Change from baseline in BMI after 26 weeks of treatment will be analysed using the standard ANCOVA model.

Self measured blood glucose (SMBG) 7-point profile

Three endpoints from the 7 point SMBG profile will be defined:

- 7-point profile (individual points in the profile)
- Mean of the 7-point profile, defined as the area under the profile (calculated using the trapezoidal method) divided by the measurement time. The area under the profile will be calculated for profiles which have at least one valid measurement. If a profile has only one valid measurement (e.g. 170 mg/dL before lunch), the value (i.e. 170 mg/dL) is set to the mean of 7-point profile.
- Mean of postprandial increments (from before meal to 90 min after for breakfast, lunch and dinner). The mean increment over all meals will be derived as the mean of all available meal increments. In case of only one valid increment (eg. 50 mg/dL for breakfast), the increment (i.e. 50 mg/dL) is set to the mean of postprandial increments.

A linear mixed effect model will be fitted to the 7-point SMBG profile data. The model will include treatment, time and interaction between treatment and time as fixed factors and subject as random effect. From the model mean profile by treatment and relevant treatment differences will be estimated and explored.

Change from baseline after 26 weeks of treatment in mean of the 7-point profile and post-prandial increment endpoints will be analysed separately using the standard ANCOVA model.

Blood pressure (systolic and diastolic)

Change from baseline in systolic blood pressure and diastolic blood pressure after 26 weeks of treatment will be analysed separately using the standard ANCOVA model.

Fasting C-peptide, fasting insulin, fasting glucagon, proinsulin, proinsulin/insulin, HOMA-B, HOMA-IR

Statistical Analysis Plan
Trial ID: NN2211-4174
UTN: U1111-1164-5462

CONFIDENTIAL

Date: 26 November 2017
Version: 2.0
Status: Final
Page: 13 of 23

Novo Nordisk

In addition to fasting C-peptide, fasting insulin, fasting glucagon, and proinsulin, three derived parameters will be calculated; proinsulin/insulin ratio, beta-cell function (HOMA-B) and insulin resistance (HOMA-IR).

The calculation of the HOMA endpoints will be done as follows:

- Beta-cell function (%) = 20·fasting insulin[μU/mL]/(FPG[mmol/L]-3.5)
- Insulin resistance (%) = fasting insulin [μU/ml]·FPG [mmol/l]/ 22.5

These endpoints after 26 weeks of treatment will be analysed separately using the standard ANCOVA model. In these statistical analyses the endpoint will be log-transformed and so will the baseline covariate.

Fasting lipid profile

Total cholesterol, low density lipoprotein cholesterol (LDL cholesterol), high density lipoprotein cholesterol (HDL cholesterol), very low density lipoprotein cholesterol (VLDL cholesterol), triglycerides, and free fatty acids after 26 weeks of treatment will be analysed separately by using the standard ANCOVA model. In these statistical analyses the endpoint will be log-transformed and so will the baseline covariate.

Endpoints evaluated after 52 weeks of treatment

All above listed efficacy endpoints will be summarised descriptively for the liraglutide 1.8 mg/day arm after 52 weeks of treatment.

3.4.2   Safety endpoints

Adverse events

AEs will be coded using the most recent version of the Medical Dictionary for Regulatory Activities.

A treatment emergent adverse event (TEAE) is defined as an event that has onset date on or after the first day of IMP administration and no later than seven days after the last day on IMP. If the event has onset date before the first day of IMP administration and increases in severity during the treatment period and until 7 days after the last drug date, then this event should also be considered as a TEAE. Here the first day of IMP administration is defined as the first day of exposure to liraglutide.

AEs will be summarised descriptively for each of the following periods separately:

Statistical Analysis Plan
Trial ID: NN2211-4174
UTN: U1111-1164-5462

CONFIDENTIAL

Date: 26 November 2017
Version: 2.0
Status: Final
Page: 14 of 23

Novo Nordisk

- The run-in period: TEAEs with an onset date on or after the first day of exposure to liraglutide and before the date of randomisation will be reported as part of the run-in period. For the run-in failure subjects, AEs with an onset date on or after the first day of exposure to liraglutide and no later than seven days after the last day of liraglutide treatment will be reported as part of the run-in period.
- The 26 week treatment period: TEAEs with an onset date on or after the date of randomisation and no later than seven days after Visit 16 (EOT26) will be reported as during 26 weeks of treatment. For subjects in the liraglutide 0.9 mg arm as well as for subjects in both arms who withdrew from the trial during 26 weeks of treatment, TEAEs with an onset date on or after the date of randomisation and no later than seven days after the last day of liraglutide treatment will be reported as part of 26 weeks of treatment.
- The 52 week treatment period: For the liraglutide 1.8 mg arm all TEAEs with an onset date on or after the date of randomisation will be reported as during 52 weeks of treatment.

For each of the above periods, AE data 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 of exposure (R).

Summaries of AEs and of serious AEs will be presented as an overview including all AEs, serious AEs, number of deaths, AEs by severity, AEs by relation to treatment and AEs of special interest including AEs leading to withdrawal for each period.

Furthermore separate summary tables for each period will be presented based on system organ class and preferred terms for:

- All AEs
- Serious AEs
- Possibly or probably related AEs
- Severe, moderate and mild AEs
- AEs reported by safety areas of interest
- AEs with preferred term that are experienced by at least 5% of the subjects in any treatment arm or by at least 5% of all subjects

A listing for non-treatment emergent adverse events with onset date before the first day of exposure to liraglutide will be presented. A listing will also be presented for non-treatment emergent adverse events collected after the treatment emergent period according to the definition of TEAE.

Classification of Hypoglycaemia:

Statistical Analysis Plan
Trial ID: NN2211-4174
UTN: U1111-1164-5462

CONFIDENTIAL

Date: 26 November 2017   **Novo Nordisk**
Version: 2.0
Status: Final
Page: 15 of 23

Treatment emergent: hypoglycaemic episodes will be defined as treatment emergent if the onset of the episode occurs on or after the first day of IMP administration, and no later than 7 days after the last day on IMP. Here the first day of IMP administration is defined as the first day of exposure to liraglutide.

Nocturnal hypoglycaemic episodes: are episodes occurring between 00:01 and 05.59 both inclusive.
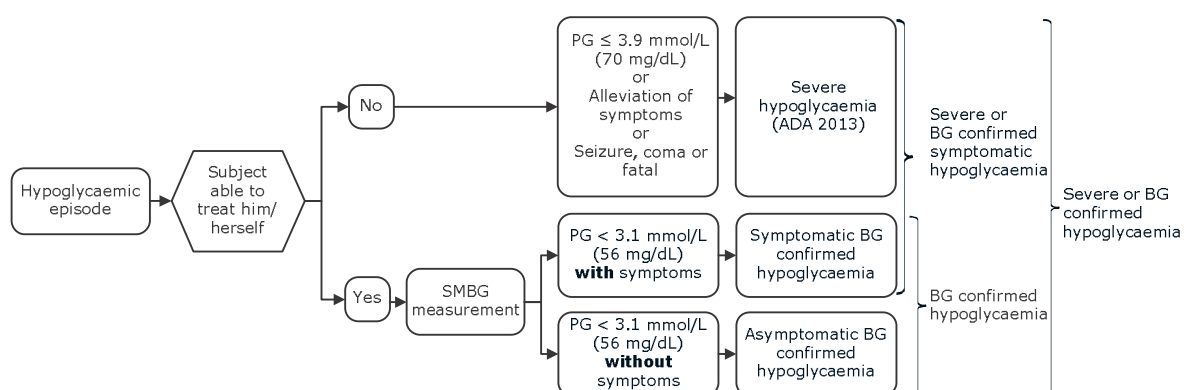
Hypoglycaemic episodes are classified according to the Novo Nordisk classification of hypoglycaemia (see Figure 3-1) and the ADA classification of hypoglycaemia (see Figure 3-2).

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)[viii]. 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 3-1) in addition to the ADA classification:

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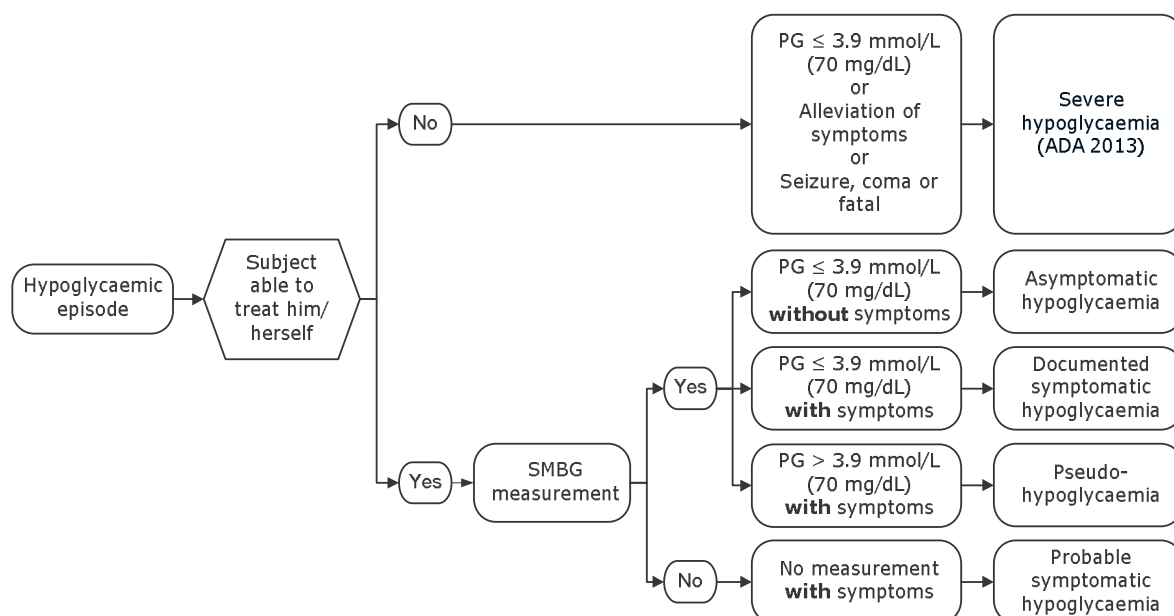

Note: Glucose measurements are performed with capillary blood calibrated to plasma equivalent glucose values

Figure 3-1   Novo Nordisk classification of hypoglycaemia

ADA classification[ix] of hypoglycaemia

Statistical Analysis Plan
Trial ID: NN2211-4174
UTN: U1111-1164-5462

~~CONFIDENTIAL~~

Date: 26 November 2017 **Novo Nordisk**
Version: 2.0
Status: Final
Page: 16 of 23

- 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 3-2   ADA classification of hypoglycaemia

Statistical Analysis Plan
Trial ID: NN2211-4174
UTN: U1111-1164-5462

CONFIDENTIAL

Date: 26 November 2017
Version: 2.0
Status: Final
Page: 17 of 23

Novo Nordisk

Hypoglycaemic episodes will be summarised descriptively for each of the following periods separately:

- The run-in period: Treatment emergent hypoglycaemic episodes where the onset date of the episode occurs on or after the first day of exposure to liraglutide and before the date of randomisation will be reported as part of the run-in period. For the run-in failure subjects, hypoglycaemic episodes where the onset date of the episode occurs on or after the first day of exposure to liraglutide and no later than seven days after the last day of liraglutide treatment will be reported as part of the run-in period.
- The 26 week treatment period: Treatment emergent hypoglycaemic episodes where the onset date of the episode occurs on or after the date of randomisation and no later than seven days after Visit 16 (EOT26) will be reported as during 26 weeks of treatment. For subjects in the liraglutide 0.9 mg arm as well as for subjects in both arms who withdrew from the trial during 26 weeks of treatment, treatment emergent hypoglycaemic episodes with an onset date on or after the date of randomisation and no later than seven days after the last day of liraglutide treatment will be reported as part of 26 weeks of treatment.
- The 52 week treatment period: For the liraglutide 1.8 mg arm all treatment emergent hypoglycaemic episodes with an onset date on or after the date of randomisation will be reported as during 52 weeks of treatment.

For each of the periods listed above, data on hypoglycaemic episodes are presented above 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). Separate summaries are made for severe or BG confirmed symptomatic hypoglycaemic episodes, nocturnal severe or BG confirmed symptomatic hypoglycaemic episodes and the ADA classification of hypoglycaemia.

The number of hypoglycaemic episodes during 26 weeks of treatment will be analysed separately for each endpoint listed above using a negative binominal regression model with a log-link function and the logarithm of the time period in which a hypoglycaemic episode is considered to be part of the 26 week treatment period as offset. The model will include treatment as factor. For each endpoint, the analysis will be performed only if the number of episodes observed is adequate for convergence of the model fit.

Pulse

Pulse will be summarized descriptively.

Clinical evaluations (physical examination, eye examination and ECG)

Eye examination (fundoscopy/fundus photography) and ECG findings will be summarised descriptively, including:

- summaries for each visit
- shift table from baseline to after 26 weeks of treatment and after 52 weeks of treatment

Any findings in the physical examination evaluation at screening will be presented as listings. Any clinically significant deterioration of a pre-existing condition after the screening visit, as well as any new clinically significant findings will be recorded as adverse events.

Laboratory assessments

All laboratory parameters will be summarised descriptively.

The following tables will be presented based on both observed and LOCF imputed data:

- Shift tables from baseline to after 26 weeks of treatment and after 52 weeks of treatment
- Proportion of subjects with measurements outside reference range by treatment and week.

Laboratory values will be presented graphically as box plots by treatment and week.

For each laboratory parameter, individual values outside the reference ranges (abnormal values) will be listed.

For lipase and amylase the following rule will apply in the evaluation of the result:

- If the amylase or lipase baseline (at screening) value is > 3xUNR this information is to be recorded as medical history for that subject.

The purpose of the calcitonin analysis is to evaluate longitudinal changes in calcitonin, with main focus on subjects who develop persistently high levels of calcitonin during the trial.

Calcitonin will be displayed in terms of the number of subjects (N), the percentage of subjects (%) and the incidence rate per 100 years of exposure (R). The following criteria are defined for tabulations:

Persistent (all post baseline measurements)

- From < UNR to persistently $\geq$ UNR
- From < UNR to persistently $\geq$ 1.5 UNR
- From < UNR to persistently $\geq$ 20 ng/L
- From < UNR to persistently $\geq$ 50 ng/L
- From < 20 ng/L to persistently $\geq$ 20 ng/L
- From < 50 ng/L to persistently $\geq$ 50 ng/L

Statistical Analysis Plan
Trial ID: NN2211-4174
UTN: U1111-1164-5462

CONFIDENTIAL

Date: 26 November 2017
Version: 2.0
Status: Final
Page: 19 of 23

Novo Nordisk

Incidental (at least one post baseline measurements)

- From < UNR to ≥ UNR
- From < UNR to ≥ 1.5 UNR
- From < UNR to ≥ 20 ng/L
- From < UNR to ≥ 50 ng/L
- From < 20 ng/L to ≥ 20 ng/L
- From < 50 ng/L to ≥ 50 ng/L

The distribution of all calcitonin measurements across treatment groups and time will be shown with histograms and corresponding cumulative plots for actual levels of calcitonin and change from baseline. The plots will be presented by treatment group (using EOT measurement - LOCF) and within treatment group by week. Plots will be done by gender.

Summaries tables of calcitonin continuous measurements, will include number and percentage of observations < and ≥ LLOQ, minimum, Q25, median, Q75 and maximum. Summaries will be presented for all subjects and by gender.

Longitudinal changes for subjects with calcitonin levels ≥ 20 ng/L will be plotted (longitudinal plots). The plots will be done by treatment and gender. They will be done for subjects in the persistent and incidental categories, separately.

A listing of subjects with at least one post baseline value ≥ 20 ng/L will be done. The listing will include age, gender, calcitonin measurements over time and AE history (including preferred term, onset and stop dates).

4 Changes to the statistical analyses planned in the protocol

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

Full analysis set

In the protocol, it was stated that "In exceptional cases, subjects may be eliminated from the full analysis set. In such cases the elimination will be justified and documented.". Since it is technically difficult to keep the statisticians and programmers blinded before database lock in this trial design, it is deleted in order to minimise the potential bias by excluding the subjects based on the knowledge of randomised treatment for each subject.

Data handling

The possible data handlings are described in order to minimise the potential bias and the following text in section 17.2 in the protocol section was deleted.

Before data are released for statistical analysis, a review of all data will take place to identify protocol deviations that could potentially affect the results. Any decision to exclude any subject or observation from the statistical analysis is the joint responsibility of the members of the study group. 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.

The following changes from SAP version 1 are implemented in SAP version 2.

Endpoints section is created according to the protocol and endpoints selected for disclosure are updated.

Sensitivity analysis

As a sensitivity analysis for the primary endpoint, a pattern mixture model approach using multiple imputation is added.

Blood pressure (systolic and diastolic)

Statistical analysis is added for change from baseline in systolic blood pressure and diastolic blood pressure after 26 weeks of treatment as well as other efficacy secondary endpoints.

Safety analysis set

In the protocol, it was stated that the Safety Analysis Set "includes all subjects receiving at least one dose of randomised treatment". In order to clarify that all adverse events occurring after initiation of treatment with liraglutide (including during the run-in phase) will be reported appropriately, this has been updated to state "includes all subjects receiving at least one dose of liraglutide". Deletions are ~~strikethrough~~ and new text is in **bold**.

- Safety Analysis Set (SAS): includes all subjects receiving at least one dose of ~~randomised treatment~~**liraglutide**. Subjects in the safety analysis set will contribute to the evaluation "as treated".

~~Randomised s~~**S**ubjects who are lost to follow up and where no exposure information of ~~the investigational product or comparators~~**liraglutide** is available ~~after randomisation~~ will be handled as unexposed.

Adverse events

In order to ensure proper alignment with the updated SAS definition, the definition of treatment emergent and the specification of AEs included in summary tables in each period are updated as follows. Deletions are ~~strikethrough~~ and new text is in **bold**.

A treatment emergent adverse event (TEAE) is defined as an event that has onset date on or after the first day of IMP administration and no later than seven days after the last day on IMP. If the event has onset date before the first day of IMP administration and increases in severity during the treatment period and until 7 days after the last drug date, then this event should also be considered as a TEAE. Here the first day of IMP administration is defined as the first day of exposure to ~~randomised treatment~~**liraglutide**.

AEs will be summarised descriptively for each of the following periods separately:
- The run-in period: **TEAEs** with an onset date on or after ~~Visit 2~~**the first day of exposure to liraglutide** and before ~~the first day of exposure to randomised treatment~~**the date of randomisation** will be reported as part of the run-in period. **For the run-in failure subjects, TEAEs with an onset date on or after the first day of exposure to liraglutide and no later than seven days after the last day of liraglutide treatment will be reported as part of the run-in period.**
- The 26 week treatment period: TEAEs with an onset date on or after ~~the first day of exposure to randomised treatment~~**the date of randomisation** and no later than seven days after Visit 16 (EOT26) will be reported as during 26 weeks of treatment. **For subjects in the liraglutide 0.9 mg arm as well as for subjects in both arm who withdrew from the trial during 26 weeks of treatment, TEAEs with an onset date on or after the date of randomisation and no later than seven days after the last day of liraglutide treatment will be reported as part of 26 weeks of treatment.**
- The 52 week treatment period: For the liraglutide 1.8 mg~~/day~~ arm all TEAEs **with an onset date on or after the date of randomisation** will be reported as during 52 weeks of treatment.

A listing for non-treatment emergent adverse events with onset date before ~~Visit2~~**the first day of exposure to liraglutide** will be presented. A listing will also be presented for non-treatment emergent adverse events collected after the treatment emergent period according to the definition of TEAE.

Hypoglycaemic episodes

In order to ensure proper alignment with the updated SAS definition, the definition of treatment emergent and the specification of hypoglycaemic episodes included in summary tables in each period are updated as follows. Deletions are ~~strikethrough~~ and new text is in **bold**.

Statistical Analysis Plan
Trial ID: NN2211-4174
UTN: U1111-1164-5462

CONFIDENTIAL

Date: 26 November 2017 **Novo Nordisk**
Version: 2.0
Status: Final
Page: 22 of 23

<u>Treatment emergent:</u> hypoglycaemic episodes will be defined as treatment emergent if the onset of the episode occurs on or after the first day of IMP administration, and no later than 7 days after the last day on IMP. Here the first day of IMP administration is defined as the first day of exposure to ~~randomised treatment~~**liraglutide**.

Hypoglycaemic episodes will be summarised descriptively for each of the following periods separately:

- The run-in period: **Treatment emergent** hypoglycaemic episodes where the onset date of the episode occurs on or after ~~Visit 2~~**the first day of exposure to liraglutide** and before ~~the first day of exposure to randomised treatment~~**the date of randomisation** will be reported as part of the run-in period. **For the run-in failure subjects, hypoglycaemic episodes where the onset date of the episode occurs on or after the first day of exposure to liraglutide and no later than seven days after the last day of liraglutide treatment will be reported as part of the run-in period.**

- The 26 week treatment period: Treatment emergent hypoglycaemic episodes where the onset date of the episode occurs on or after ~~the first day of exposure to randomised treatment~~**the date of randomisation** and no later than seven days after Visit 16 (EOT26) will be reported as during 26 weeks of treatment. **For subjects in the liraglutide 0.9 mg arm as well as for subjects in both arms who withdrew from the trial during 26 weeks of treatment, treatment emergent hypoglycaemic episodes with an onset date on or after the date of randomisation and no later than seven days after the last day of liraglutide treatment will be reported as part of 26 weeks of treatment.**

- The 52 week treatment period: For the liraglutide 1.8 mg~~/day~~ arm all treatment emergent hypoglycaemic episodes **with an onset date on or after the date of randomisation** will be reported as during 52 weeks of treatment.

For statistical analyses of hypoglycaemic episodes, it is described additionally in text that "For each endpoint, the analysis will be performed only if the number of episodes observed is adequate for convergence of the model fit.".

5 References

i SAS/STAT(R) 9.2 User's Guide, Second Edition

ii Guidance (draft) for Industry Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention. Food and Drug Administration, February 2008.

iii International Conference on Harmonisation. ICH Harmonised Tripartite Guideline. Statistical principles for clinical trials E9. International Conference on Harmonisation E9 Expert Working Group. 5-Feb-1998.

iv Little RJA, Rubin DB. Statistical analysis with missing data: New York: John Wiley & Sons. 1987.

v American Diabetes Association. Classification and Diagnosis of Diabetes. Diabetes Care. 2015;38(Suppl. 1):S8-S16

vi European Commission; The Rules Governing Medicinal Products in the European Union, Volume 4, Annex 13, Investigational Medicinal Products. Brussels, February 2010.

vii Garber AJ, Abrahamson MJ, Barzilay JI, Blonde L, Bloomgarden ZT, Bush MA, et al. AACE comprehensive diabetes management algorithm 2013. Endocrine Practice: Official Journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists. 2013;19(2):327-36

viii Schwartz NS, Clutter WE, Shah SD, Cryer PE. Glycemic thresholds for activation of glucose counterregulatory systems are higher than the threshold for symptoms. J Clin Invest 1987; 79(3):777-781.

ix Seaquist ER, Anderson J, Childs B, Cryer P, Dagogo-Jack S, Fish L et al: Hypoglycemia and Diabetes: A Report of a Workgroup of the American Diabetes Association and The EndocrineSociety. Diabetes Care 2013; 36:1384-1395.