Cover Page for Statistical Analysis Plan

Sponsor name:	Novo Nordisk A/S
NCT number	NCT01923181
Sponsor trial ID:	NN9924-3790
Official title of study:	Multiple dose trial examining dose range, escalation and efficacy of oral semaglutide in subjects with type 2 diabetes
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16.1.9 Documentation of statistical methods

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Statistical Analysis Plan

Trial ID: NN9924-3790

Multiple dose trial examining dose range, escalation and efficacy of oral semaglutide in subjects with type 2 diabetes

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

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List of abbreviations

AE	*Adverse event*
ANCOVA	*Analysis of covariance*
BMI	*Body mass index*
CI	*Confidence interval*
CRF	*Case report form*
CTR	*Clinical trial report*
EoT	*End-of-text*
LOCF	*Last observation carried forward*
LLOQ	*Lower limit of quantification*
MedDRA	*Medical Dictionary for Regulatory Activities*
PD	*Pharmacodynamics*
PK	*Pharmacokinetics*
PP	*Per protocol*
SAE	*Serious adverse event*
SAP	*Statistical analysis plan*
SD	*Standard deviation*
SE	*Standard error*
TEAE	*Treatment emergent adverse event*
MMRM	*Mixed model for repeated measures*

1 Introduction

1.1 Trial information

This is a randomised, partially-blinded, multiple-dose, multicentre trial with a total of nine treatment arms; seven oral semaglutide treatment arms, one oral placebo arm and one open-label subcutaneous (s.c.) semaglutide arm in a parallel design. The trial will include subjects with T2D who have failed on diet and exercise and/or metformin.

The primary objective of the trial is to compare the efficacy on glycaemic control of oral semaglutide in a SNAC formulation against placebo in subjects with T2D.

1.2 Scope of the statistical analysis plan

This statistical analysis plan (SAP) is based on the protocol "3790-consolidated-protocol-file-protocol-version-3 0", that is, the consolidated version 3 which includes protocol amendments one and two.

This SAP contains a more technical and detailed elaboration of the statistical analyses specified in the statistical section of the protocol. .

2 Statistical considerations

Results from the statistical analysis will generally be presented by two-sided confidence intervals with a confidence level of 95% including a p-value for test of no difference between treatments.

The stratification variable referred to in the following is defined as the two level factor of treatment with metformin (yes/no).

The "planned comparisons between treatment arms" referred to in this section covers the following comparisons: a) between each of the oral semaglutide treatment arms and placebo, b) between the s.c. semaglutide arm and placebo, c) between each of the oral semaglutide treatment arms and s.c. semaglutide, and d) between the three oral semaglutide treatment arms with an end dose of 40 mg.

A standard mixed model for repeated measurements (from now on referred to as "the standard MMRM") will be used in the analysis of the primary and continuous secondary endpoints. The model will include treatment, country and the stratification variable as fixed factors, and the corresponding baseline value as covariate. All factors and the covariate will be nested within visit. The model will assume an unstructured covariance matrix within subject.

Unless otherwise stated, the estimated differences with corresponding two sided p-values and 95% confidence intervals at 26 weeks will be presented for the planned comparisons between treatment arms.

The patient years observation time (PYO) used in e.g. the calculation of AE rates will for an observation period be calculated as the difference between start-date and end-date, both inclusive.

Values of laboratory parameters below the blower limit of quantification (LLOQ) will be set to LLOQ/2.

The stratification variable "Treatment with metformin at screening (yes/no)" will based on the actual information on concomitant medication recorded through the eCRF.

2.1 Sample size calculation

Please refer to section 17.1 of the protocol.

2.2 Definition of analysis sets

Full Analysis Set (FAS): includes all randomised subjects who have received at least one dose of randomised semaglutide (oral or s.c.) or semaglutide placebo. Subjects in the FAS will contribute to the evaluation based on their randomised treatment.

Safety Analysis Set (SAS): includes all randomised subjects who have received at least one dose of randomised semaglutide (oral or s.c.) or semaglutide placebo. Subjects in the SAS will contribute to the evaluation based on their actual treatment.

Before data are locked for statistical analysis, a review of all data will take place. Any decision to exclude a subject or single observations from the statistical analysis is the joint responsibility of the members of the study group. 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 (CTR).

2.3 Definition of baseline

For each lab parameter and each vital sign, the baseline assessment is defined as the last valid measurement at or before the randomisation visit (visit 2). This specifically implies that if a visit 2 assessment is missing (whether it's planned or not planned) then the screening assessment (from visit 1) will be used as the baseline assessment, if available.

2.4 Definition of observation periods

Unless subjects withdraw their informed consent, data collection will continue for the full duration of the trial.

The data for all tables, listings and figures developed for this trial will be selected in a two-step fashion.

In the first step, the population of subjects for the specific analysis is selected based on the specified analysis set (either the full analysis set or the safety analysis set).

In the second step, observations for the subjects in the analysis set are selected according to whether or not they belong to a specified observation period. Observations that do not belong to the specified observation period will be treated as missing for the specific output.

In this trial, three observation periods will be defined, as described below. One observation period will be primary when selecting data related to efficacy and another will be primary when selecting data related to safety. The last observation period is considered supportive. Notice that for adjudicated events, onset date will be the EAC adjudicated onset date.

The three observation periods are:

In-trial observation period

In-trial: This observation period represents the time period in which a subject is considered a participant and where data are collected systematically. This observation period will be used for supportive analyses of both efficacy and safety. The in-trial observation period includes observations recorded at or after randomisation and not after the last subject-investigator contact, which is scheduled to take place 5 weeks after planned last dose of trial treatment at a follow-up visit (visit 12).

For subjects that prematurely discontinue treatment, their in-trial observation period will end with visit 11X if this comes after their follow-up visit.

For subjects that withdraw their informed consent and do not attend visit 11, nor visit 12, their in-trial observation period ends at their date of withdrawal.

If a subject is lost to follow-up, the end of the in-trial observation period is defined as the date of the last subject-investigator contact (site or phone visit).

On-treatment observation period

On-treatment: This observation period is a subset of the in-trial observation period, namely the part where the subject is considered to be exposed to trial treatment.

For adverse events and hypoglycaemic episodes, this period includes those observations from the in-trial observation period that are recorded on or after the date of first dose of trial treatment and not after the end of the 5 week washout period that follows the date of last dose of trial treatment. The follow-up visit is scheduled to take place 5 weeks after the date of last dose of trial product with a visit window of +5 days. For adverse events and hypoglycaemic episodes, the end-date for

the on-treatment observation period is therefore defined as the first date encountered after randomisation of the following dates [date of visit 12, date of last dose + 40 days, end-date for the in-trial observation period], using the convention that a missing date is set to infinity.

For other endpoints than adverse events and hypoglycaemic episodes, including both safety and efficacy, but with the exception of anti-semaglutide antibodies, the end-date for the on-treatment observation period will be defined as [date of visit 12, date of last dose + 7 days, end-date for the in-trial observation period], that is, similarly to above, but adding the s.c. dosing interval of 1 week to the date of last dose instead of 40 days. The on-treatment observation period will not be used to analyse anti-semaglutide antibodies.

The on-treatment observation period is the primary observation period for examination of safety endpoints including adverse events and hypoglycaemic episodes.

The definition of the on-treatment period for adverse events and hypoglycaemic episodes corresponds to the protocol definition of the treatment emergent period.

On-treatment without rescue:

On-treatment without rescue: This observation period is a subset of the on-treatment observation period. To avoid potential confounding of initiation of anti-diabetic rescue therapies on efficacy endpoints, information that is collected after initiation of anti-diabetic rescue therapies are excluded from this observation period. Specifically, it includes observations recorded at or after date of first dose of trial treatment and not after the first occurrence of the following

- the end-date of the on-treatment observation period
- initiation of rescue medication

This observation period is the primary observation period for examination of efficacy endpoints.

We will use the convention that all baseline assessments belong to each of the observation periods.

2.5 Imputation of missing observations

Missing observations for laboratory parameters and vital signs will be imputed with two methods: last observation carried forward (LOCF), where missing observations are imputed as the last post-baseline available value obtained prior to the missing assessment, and by prediction from the standard MMRM for the specific endpoint, where missing observations are imputed as the value that is predicted by the MMRM model. The MMRM imputations will be based on the randomised treatment and carried out for those endpoints where the standard MMRM analysis is part of the examination.

For subjects that have no post-baseline assessment of a given endpoint, no imputation will be done for this endpoint.

Note that the LOCF and MMRM imputations depend on the considered observation period, and separate imputation for the three observation periods will be carried out.

2.6 Primary endpoint

The primary endpoint, change from baseline to end of treatment (i.e., after 26 weeks of treatment) in HbA1c, will be analysed by the standard MMRM.

In order to confirm efficacy of oral semaglutide without risk of inflation of the type 1 error an initial comparison of the primary endpoint will be made between a) the pool of the two treatment arms using standard and fast escalation regimens to an end dose of 40 mg and b) placebo. The comparison will be made by pooling the standard 40 mg arm and the fast 40 mg arm and then estimating the treatment difference between this pooled group and the placebo group by the standard MMRM. The estimated treatment difference with corresponding two sided p-value and 95% confidence interval at 26 weeks will be presented, and efficacy of oral semaglutide will be considered confirmed if the upper limit of the confidence interval is strictly less than zero.

If efficacy of oral semaglutide is confirmed, the planned comparisons between the nine original treatment arms will be evaluated.

Subjects in the FAS and only measurements belonging to the on-treatment without rescue observation period will be included in the analysis.

Due to the uncertainty in relation to if the added variation in the exposure in the oral semaglutide arms compared to s.c. semaglutide will transfer to an added variation in the therapeutic response, a sensitivity analysis allowing the within subject unstructured covariance matrix to be fitted separately for each treatment arm will be conducted.

Furthermore, the following sensitivity analyses will be conducted in order to investigate the sensitivity of the results due to the impact of missing values:

- An MMRM similar to the primary analysis but for the in-trial observation period.
- An analysis of covariance (ANCOVA) model including subjects in the FAS and using imputation of missing values according to the last observation carried forward (LOCF) method. The model will include fixed factors for treatment, country and the stratification variable and the baseline value as covariate and will be based on the on-treatment period.
- A complete case analysis, i.e. an ANCOVA similar to the one above including only data obtained at 26 weeks from subjects who:
    - did not discontinue treatment prematurely

- did not receive rescue therapy
- had a valid HbA1c assessment at baseline and after 26 weeks of treatment

2.7 Supportive secondary endpoints

2.7.1 Efficacy endpoints

The FAS will be used in all analyses of the supportive secondary efficacy endpoints. The on-treatment without rescue observation period will be the primary observation period for examination of efficacy endpoints. The specific outputs developed for efficacy endpoints will be detailed in section 2.7.3.

Subjects who, after 26 weeks of treatment, achieve (yes/no) HbA1c <7% (53 mmol/mol)

The binary endpoint will be analysed by a logistic regression model which will include fixed factors for treatment and the stratification variable and baseline HbA1c as a covariate. Estimated odds ratios with corresponding two sided p-values and 95% confidence intervals at 26 weeks will be presented for the planned comparisons between treatment arms. Missing response data at 26 weeks will be imputed from the MMRM used for the primary analysis of HbA1c.

Change from baseline to week 26 in body weight, waist circumference and fasting plasma glucose

These endpoints will be analysed by the standard MMRM. Both absolute (kg) and relative change from baseline (%) in body weight will be analysed.

Subjects with at least 5 % weight loss after 26 weeks of treatment (yes/no) and subjects with more than 10 % weight loss added after 26 weeks of treatment (yes/no)

These binary endpoints will be analysed by separate logistic regression models which will include fixed factors for treatment and the stratification variable and baseline body weight as a covariate. Estimated odds ratios with corresponding two sided p-values and 95% confidence intervals at 26 weeks will be presented for the planned comparisons between treatment arms. Missing response data at 26 weeks will be imputed from the MMRM used for the analysis of body weight.

Change from baseline to week 26 in C-peptide, fasting insulin, glucagon, HOMA-IR, HOMA-B, total cholesterol, LDL-cholesterol, HDL-cholesterol, VLDL-cholesterol, triglycerides and free fatty acids

For each endpoint, the assessments at every week will be log-transformed and subsequently analysed by the standard MMRM. The estimated differences and corresponding 95% confidence intervals at 26 weeks will be back transformed and presented as ratios together with the two sided

p-values. Standard errors of the back transformed estimated means will be calculated using the Delta-method[i].

The fasting HOMA endpoints (i.e., fasting HOMA-B and HOMA-IR) will be calculated based on fasting insulin and FPG as follows:

1. Fasting HOMA-B (%) = 20 x fasting insulin [μU/ml]/(FPG[mmol/L]-3.5)

2. Fasting HOMA-IR (%) = fasting insulin [μU/ml] x FPG [mmol/L]/22.5

PRO outcomes

The outcomes from the SF-36 questionnaire in terms of total scores overall and within each domain will be calculated. Each of these scores will be analysed by the standard MMRM.

2.7.2 Safety endpoints

All safety endpoints will be summarised and analysed using the safety analysis set. The on-treatment observation period will be the primary observation period for examination of all safety endpoints.

Adverse events

All AEs will be coded using the most recent version of the Medical Dictionary for regulatory Activities (MedDRA) coding. This is version 17.1. A TEAE is an event that has onset date (or increase in severity) during the on-treatment observation period. On-treatment AEs are summarised descriptively. These are supported by outputs including all in-trial adverse events, i.e. AEs with onset date (or increase in severity) during the in-trial observation period. Adverse events with onset after the end of the in-trial observation period will be reported in a listing.

Most frequent adverse events will be defined as preferred terms that are experienced by at least 5% of the subjects in any of the treatment arms.

Based on MedDRA searches, 19 pre-defined groups of adverse events will be evaluated. These are defined by Global Safety and consist of pre-specified preferred terms. The groups are the following:

- Gastrointestinal adverse events
- Allergic reactions
- Antibody adverse events
- Calcitonin adverse events
- Cardiovascular adverse events
- Gallbladder disease adverse events
- Immune complex adverse events
- Injection site reactions

- Elevated lipase and/or amylase adverse events
- Medication error adverse events
- Neoplasm adverse events
- Overdose adverse events
- Pancreatic carcinoma adverse events
- Pancreatitis adverse events
- Thyroid adverse events
- Transmission adverse events
- Rare adverse events
- Renal failure adverse events
- Malignant tumour adverse events

The definition of rare adverse events is based on a publication by Shakir from 2005 (Pharmacoepidemiology, Fourth Edition), called "Prescription-Event Monitoring". For complete listings of preferred terms included in the pre-defined groups of adverse events see section 4.

Number of confirmed treatment emergent hypoglycaemic episodes

A hypoglycaemic episode will be defined as treatment emergent if the onset of the episode occurs during the on-treatment period. Hypoglycaemic episodes are classified according to the Novo Nordisk classification of confirmed hypoglycaemia and the ADA classification of hypoglycaemia (see Figure 1: ADA classification of hypoglycaemia).

Confirmed hypoglycaemia

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

Confirmed hypoglycaemic episodes are defined as episodes that are:

- severe according to the ADA classification below and/or
- biochemically confirmed by a plasma glucose value of <3.1 mmol/L (56 mg/dL), with or without symptoms consistent with hypoglycaemia

Severe or BG confirmed symptomatic hypoglycaemia

- severe according to the ADA classification below and/or
- biochemically confirmed by a plasma glucose value of <3.1 mmol/L (56 mg/dL), with symptoms consistent with hypoglycaemia

ADA classification[iii] 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 back 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).

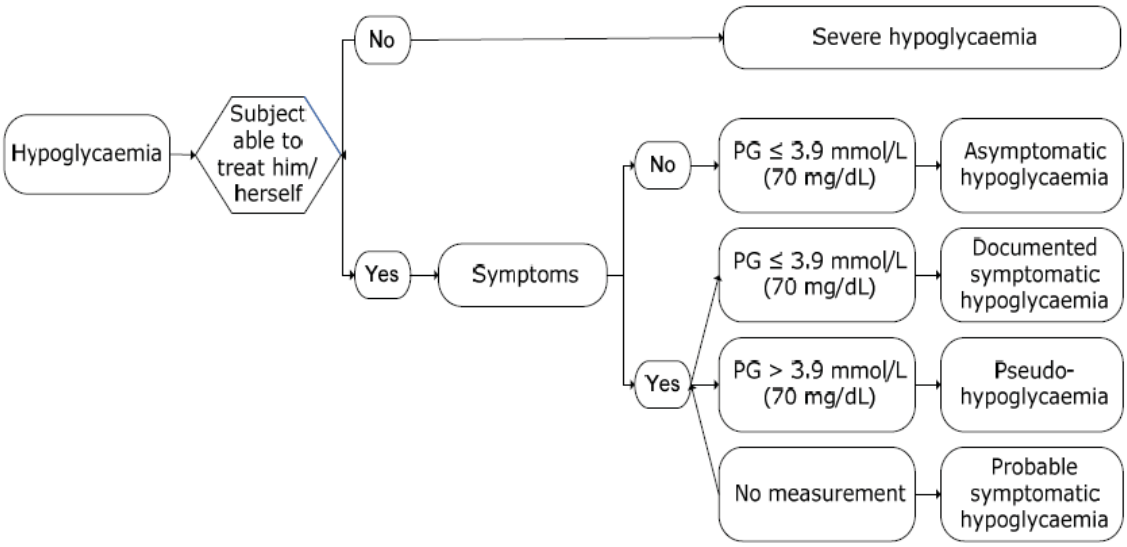

Figure 1: ADA classification of hypoglycaemia

Data on treatment emergent hypoglycaemic episodes will be summarised descriptively using the above definitions.

The number of confirmed treatment emergent hypoglycaemic episodes during 26 weeks treatment will be analysed using a negative binomial regression model with a log-link function and the logarithm of the time period in which an occurrence of a hypoglycaemic episode is considered treatment emergent as offset. The model will include treatment, country and stratification variable as fixed factors and baseline HbA1c as covariate. Estimated rate ratios with corresponding two sided p-values and 95% confidence intervals at 26 weeks will be presented for the planned comparisons between treatment arms.

The number of subjects experiencing one or more confirmed treatment emergent hypoglycaemic episode will be analysed using a logistic regression model with fixed factors for treatment and the stratification variable and baseline HbA1c as a covariate. Estimated odds ratios with corresponding two sided p-values and 95% confidence intervals at 26 weeks will be presented for the planned comparisons between treatment arms.

Similar analyses for severe or BG confirmed symptomatic hypoglycaemic episodes will be conducted.

Change in pulse, systolic- and diastolic blood pressure from baseline to after 26 weeks of treatment

These endpoints will be analysed by the standard MMRM.

Change in amylase and lipase from baseline to after 26 weeks of treatment

For each endpoint, the assessments at every week will be log-transformed and subsequently analysed by the standard MMRM. The estimated differences and corresponding 95% confidence intervals at 26 weeks will be back transformed and presented as ratios together with the two sided p-values. Standard errors of the means will be calculated using the Delta-method.

Change from baseline to after 26 weeks of treatment in electrocardiogram (ECG), physical examination, laboratory safety variables (haematology, biochemistry, hormone and urinalysis) other than amylase and lipase

These endpoints will be summarised by descriptive statistics.

Endpoints related to occurrence of anti-semaglutide antibodies during 26 weeks of treatment: Antibody level during 26 weeks of treatment, anti-semaglutide antibodies (positive/negative), antisemaglutide antibodies with in vitro neutralising effect (positive/negative), antisemaglutide antibodies cross reacting with endogenous GLP-1 (positive/negative), cross reacting antibodies with in vitro neutralising effect to endogenous GLP-1 (positive/negative)

These endpoints will be summarised by descriptive statistics and correlated to PK and PD. Categorical summary tables for the occurrence of antibodies by treatment week as well as for occurrence of antibodies versus mean HbA1c and versus mean trough PK value will be produced. In addition, scatter plots of antibody level (%B/T) vs. HbA1c and vs. trough PK value will be developed.

2.7.3 Pharmacokinetics and/or pharmacodynamics modelling

The modelling will be performed by Quantitative Clinical Pharmacology at Novo Nordisk A/S and will be reported separately from the CTR.

2.8 End of text outputs for subject disposition and demographics

To describe the trial population, descriptive tables for the disposition of subjects amongst the two analysis sets and treatment/trial completion statuses will be developed.

The time from randomisation to withdrawal, premature treatment discontinuation and initiation of rescue medication, and the duration of the three observation periods will be examined with descriptive figures.

Baseline characteristics for continuous and categorical variables will be summarised in descriptive tables.

Descriptive tables for general medical history, history of cardiovascular and gall bladder disease and concomitant medication will be developed.

2.9 End of text outputs for efficacy endpoints

As mentioned above, the primary observation period used for examination of efficacy endpoints will be the on-treatment without rescue observation period. For safety endpoints the primary observation period will be the on-treatment observation period. Outputs will be based on data in SI units, and where applicable they will be repeated for conventional units. This will among other endpoints apply to HbA1c, where data is collected in both "%" and "mmol/mol". The analysis of HbA1c in "%" is considered primary.

The specific outputs developed for the different endpoints are detailed here below.

Continuous efficacy endpoints

For continuous efficacy endpoints the end of text outputs will constitute of:

- Tables with descriptive statistics for observed values as well as change from baseline
- Tables with results of statistical analyses including estimated means (LS means) for week 26 values as well as for change from baseline to week 26, and in addition estimated treatment differences/ratios for the planned comparisons of treatment arms
- Panel plots with mean of observed as well as change from baseline values over time grouped by the time of last observation. There will be a panel for each treatment arm in these plots and they serve to illustrate the observed means over time for different time-patterns of missing data.
- Plots with estimated mean values over time. These plots present the estimated means from the statistical analyses.
- Bar plots with estimated means at week 26 from the statistical analyses.

- Forest plots with the estimated treatment differences/ratios from the statistical analyses for the planned comparisons, where deemed relevant

- Cumulative distribution functions presenting the distribution of the endpoints at week 26, including MMRM imputed values

Categorical efficacy endpoints

For HbA1c and body weight, binary responder endpoints have been defined. The outputs for assessment of these include:

- Categorical summary tables with counts and percentages of the response categories.

- Tables with results of statistical analyses including estimated odds at week 26 values as well as odds ratios for the planned comparisons of treatment arms

- Bar plots with observed proportions of subjects achieving the responses

- Forest plots with estimated odds ratios at week 26 based on the statistical analyses

2.10 End of text outputs for safety endpoints

Adverse events

Adverse events will be evaluated with

- Overview tables that summarise the events across treatment arms in relation to seriousness, severity, relationship to trial product, outcome and whether they led to premature treatment discontinuation
    - These will be developed for all adverse events and serious adverse events based on both the on-treatment and the in-trial observation period. For most frequent adverse events, adverse events leading to premature treatment discontinuation and pre-defined MedDRA searches they will be developed for the on-treatment observation period.
- Summary tables describing the distribution of adverse events across treatment arms by system organ classes and preferred terms
    - These will be developed for all adverse events, serious adverse events, adverse events with fatal outcome and pre-defined MedDRA searches based on both the on-treatment and the in-trial observation period. For adverse events leading to premature treatment discontinuation and adverse events by severity they will be developed for the on-treatment observation period alone.
- Figures presenting the time to first event as well as the average number of events over time
    - These will be developed based on the on-treatment observation period for all adverse events, serious adverse events, most frequent adverse events and pre-defined MedDRA searches.
- Plots summarising the incidence by preferred term
    - These will be developed for most frequent adverse events, adverse events leading to premature treatment discontinuation and pre-defined MedDRA searches.
- Plots of the incidence over time by treatment and incidence over time by severity.
    - These will be developed for all gastro-intestinal adverse events, nausea, vomiting and diarrhoea. These plots will both serve for comparison between treatment arms of incidences over time as well as assessment of the distribution over time of the severity of the adverse events.

Number of confirmed treatment emergent hypoglycaemic episodes

Hypoglycaemic episodes will be summarized based on ADA-classification and the combined categories "Confirmed" and "Severe or BG confirmed symptomatic hypoglycaemia".

The number of events and the number subjects experiencing an event will be evaluated for the two combined categories using statistical analyses as described above and using plots for time to first episode and average number of episodes over time.

Continuous safety lab parameters

Safety lab parameters that are treated as continuous variables will be reported in groups defined below. Except for eosinophils and basophils, all examinations of continuous safety lab parameters will be done on logarithmic scale. Where applicable, outputs will be repeated for conventional units.

1. Pancreatic enzymes and hepatic laboratory parameters
    a. Lipase
    b. Amylase
    c. Bilirubin, total
    d. Aspartate aminotransferase (AST)
    e. Alanine aminotransferase (ALT)
    f. Alkaline phosphatase
2. Renal laboratory parameters
    a. Creatinine
    b. Urea
    c. Urinary albumin/creatinine ratio
3. Electrolytes
    a. Potassium
    b. Sodium
    c. Calcium (total)

d. Calcium, albumin corrected (calcium, ionized)

4. Hormones

    a. Calcitonin

5. Other

    a. Creatinine kinase

    b. Albumin

6. Haematology

    a. Haemoglobin

    b. Haematocrit

    c. Erythrocytes

    d. Thrombocytes

    e. Leucocytes

    f. Differential count (eosinophils, neutrophils, basophils, lymphocytes and monocytes)

7. Urinalysis:

    a. Albumin, urine

Descriptive outputs for these will be similar to those produced for continuous efficacy endpoints but based on the on-treatment observation period. The descriptive outputs are:

- Tables with descriptive statistics for observed values as well as change from baseline and ratio to baseline

- Categorical summary tables and shift tables for assessments outside of normal ranges.

- Tables with descriptive tables of the maximum post-baseline value

- Panel plots with mean of observed as well as change from baseline values over time grouped by the time of last observation. There will be a panel for each treatment arm in these plots and the serve to illustrate the observed means over time for different time-patterns of missing data.

- Cumulative distribution functions presenting the distribution of the maximum value observed post-baseline.

Amylase and lipase will in addition to descriptive examinations also be subject to statistical analyses. These will be done on log-scale and reported with the following statistical outputs:

- Tables with results of statistical analyses including estimated means (LS means) for week 26 values as well as for the ratio to baseline at week 26, and in addition estimated treatment ratios for the planned comparisons of treatment arms

- Plots with estimated mean values over time. These plots present the estimated means from the statistical analyses.

Categorical safety lab parameters

Pregnancy test based on hCG serum assessments and results of the urinalysis will be evaluated as categorical parameters. For pregnancy test, a categorical summary table by treatment week will be produced. The parameters included in the urinalysis are:

a. Blood (erythrocytes)

b. Protein

c. Glucose

d. ketones

e. pH

For these parameters, categorical summary tables and shift tables will be produced.

Vital signs

Pulse, diastolic blood pressure and systolic blood pressure will be evaluated with outputs similar to the continuous safety lab parameters but on observed scale. The evaluation will be based on the on-treatment observation period.

Electrocardiograms (ECGs) will be evaluated based on the on-treatment observation period with categorical summary tables and shift tables by treatment week based on the investigator's assessment.

Physical examination will be evaluated similarly to ECG. For eye examination a categorical summary table of the baseline assessment will be developed.

2.11 Listings

Subject disposition and demographics

Continuous and categorical subject characteristics will be listed. Separate listings for medical history, concomitant illnesses, concomitant medication and diabetes medication will be prepared.

Efficacy endpoints

Listings with individual response data will be produced for HbA1c, body weight, waist circumference, BMI, fasting plasma glucose, Fasting C-peptide, fasting insulin, glucagon and lipids.

In addition, a listing with data points excluded from the efficacy analyses will be prepared.

Safety endpoints

Listings based on the on-treatment period for serious adverse events, adverse events with fatal outcome, adverse events leading to premature treatment discontinuation and adverse events leading to dose reduction.

These will be supplemented by a listing of adverse events occurring before randomisation, a listing of all adverse events during the in-trial observation period as well as a listing for those occurring after the end of the in-trial observation period.

Finally adverse events related to a technical complaint will be listed.

Separate listings for all hypoglycaemic episodes and severe hypoglycaemic episodes will be prepared.

Listings with observations outside the reference ranges will be produced for continuous safety lab parameters.

For amylase, lipase and calcitonin, listings with individual response data will be produced.

Listings for vital signs, overall ECG interpretation and anti-semaglutide antibodies will also be developed.

3 Changes to the statistical analyses planned in the protocol

The definition of the FAS is changed to exclude the requirement that a subject must have post-baseline data. Effectively, the FAS and the SAS will be identical, but subjects will contribute to the evaluations differently (“as randomised” as opposed to “as treated”).

A clear definition of baseline has been added, and imputations of missing data have been clarified.

It has been clarified that the analysis to confirm efficacy of oral semaglutide will be based on a comparison of the pool of two treatment arms (40 mg standard and 40 mg fast) to placebo using the standard MMRM model.

The exploratory analysis to describe the dose-response relation of oral semaglutide and estimate the relative potency vs. s.c. semaglutide with regards to selected key endpoints, will be conducted by Quantitative Clinical Pharmacology.

Statistical analysis of the number of subjects experiencing a confirmed hypoglycaemic episode during the on-treatment observation period is added to the planned analyses. In addition, severe or BG confirmed symptomatic hypoglycaemic episodes will be analysed in the same way as confirmed hypoglycaemic episodes.

Analyses of relative change from baseline in body weight, of subjects with at least 5 % weight loss and of subjects with more than 10 % weight loss added after 26 weeks of treatment added in order to align with other projects.

Evaluations of severe or BG confirmed symptomatic hypoglycaemia have been added to the planned investigations.

Due to sparse data, country will not be included in the negative binomial model for hypoglycaemic episodes.

Treatment emergent adverse events and hypoglycaemic episodes are referred to as on-treatment adverse event / on-treatment hypoglycaemic episodes.

It has been clarified that the stratification variable “Treatment with metformin at screening (yes/no)” will based on the actual information on concomitant medication recorded through the eCRF.

It has been clarified that values of laboratory parameters below the blower limit of quantification (LLOQ) will be set to LLOQ/2.

The evaluations of the pre-defined groups of adverse events have been added to the overview of planned investigations.

4 Pre-defined groups of adverse events

4.1 Gastrointestinal adverse events

Preferred term	High level term	High level group term	System organ class
Abdominal adhesions	Peritoneal and retroperitoneal fibrosis and adhesions	Peritoneal and retroperitoneal conditions	Gastrointestinal disorders
Abdominal discomfort	Gastrointestinal signs and symptoms NEC	Gastrointestinal signs and symptoms	Gastrointestinal disorders
Abdominal distension	Flatulence, bloating and distension	Gastrointestinal signs and symptoms	Gastrointestinal disorders
Abdominal mass	Abdominal findings abnormal	Gastrointestinal signs and symptoms	Gastrointestinal disorders
Abdominal pain	Gastrointestinal and abdominal pains (excl oral and throat)	Gastrointestinal signs and symptoms	Gastrointestinal disorders
Abdominal pain lower	Gastrointestinal and abdominal pains (excl oral and throat)	Gastrointestinal signs and symptoms	Gastrointestinal disorders
Abdominal pain upper	Gastrointestinal and abdominal pains (excl oral and throat)	Gastrointestinal signs and symptoms	Gastrointestinal disorders
Abdominal rigidity	Gastrointestinal and abdominal pains (excl oral and throat)	Gastrointestinal signs and symptoms	Gastrointestinal disorders
Abdominal tenderness	Gastrointestinal and abdominal pains (excl oral and throat)	Gastrointestinal signs and symptoms	Gastrointestinal disorders
Abnormal faeces	Faecal abnormalities NEC	Gastrointestinal signs and symptoms	Gastrointestinal disorders
Achlorhydria	Gastrointestinal mucosal dystrophies and secretion disorders	Gastrointestinal conditions NEC	Gastrointestinal disorders
Acute abdomen	Gastrointestinal signs and symptoms NEC	Gastrointestinal signs and symptoms	Gastrointestinal disorders
Amalgam tattoo	Gingival disorders NEC	Dental and gingival conditions	Gastrointestinal disorders
Anal dilatation	Anal and rectal disorders NEC	Anal and rectal conditions NEC	Gastrointestinal disorders
Anal fissure	Anal and rectal disorders NEC	Anal and rectal conditions NEC	Gastrointestinal disorders
Anal fistula	Gastrointestinal fistulae	Gastrointestinal conditions NEC	Gastrointestinal disorders
Anal leukoplakia	Anal and rectal disorders NEC	Anal and rectal conditions NEC	Gastrointestinal disorders

Trial: NN9924-3790

Statistical methods, Version 1.0 dated 01 July 2015

Overview of deleted pages

Pages	Section	Title
25-550	4	Pre-defined groups of adverse events

5 References

[i] Casella, G. and Berger, R. L. (2002), Statistical Inference, 2nd ed.

[ii] 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.

[iii] 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 Endocrine Society. Diabetes Care 2013; 36(5):1384-1395.

Memo

~~CONFIDENTIAL~~

To:
DBL Team

Copy:

From: [redacted]

23 January 2015
Ref.: [redacted]

NN9924-3790: Statistical memo for the pre-DBL meeting

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Stratification variable

The stratification variable "Treatment with metformin at screening (yes/no)" was reconciled with concomitant medication data. For 7 subjects, discrepancies were identified and queried were issued. The stratification variable included in statistical analyses was defined to reflect the concomitant medication data, and this resulted in the following changes in the stratification variable for these subjects:

Subject	Change in stratification variable
[redacted]	"No" -> "Yes"
	"No" -> "Yes"
	"Yes" -> "No"
	"Yes" -> "No"
	"Yes" -> "No"
	"Yes" -> "No"
	"Yes" -> "No"

Reporting of pregnancy tests

Results of pregnancy tests (based on human chorionic gonadotropin samples) for male subjects will not be summarised.

Subjects lost to follow-up

1. Lost to follow-up (Yes/No) will be defined based on comments to reasons for premature treatment discontinuation given on the end-of-trial electronic case report form. For the following subjects status is thus "Yes" for lost to follow-up:

   [redacted]

   For these subjects, the on-treatment and the on-treatment without rescue observation periods will use the date of last drug from the IVRS system as end-date.