Cover Page for Statistical Analysis Plan

Sponsor name:	Novo Nordisk A/S
NCT number	NCT02443155
Sponsor trial ID:	NN9828-4150
Official title of study:	A randomised, double-blind, double-dummy, placebo-controlled, parallel-group, multi-centre clinical proof-of-principle trial in adult subjects with newly diagnosed type 1 diabetes mellitus investigating the effect of NNC0114-0006 and liraglutide on preservation of beta-cell function
Document date:	17 September 2019

16.1.9 Documentation of statistical methods

List of contents

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

.

Statistical Analysis Plan

Trial ID: NN9828-4150

A randomised, double-blind, double-dummy, placebo-controlled, parallel-group multi-centre clinical proof-of-principle trial in adult subjects with newly diagnosed type 1 diabetes mellitus investigating the effect of NNC0114-0006 and liraglutide on preservation of beta-cell function

Author
[redacted]
Biostatistics Aalborg 1

Table of contents Page

List of abbreviations

ADA	American Diabetes Association
AE	adverse event
AUC	area under the curve
BG	blood glucose
CI	confidence interval
Cmax	maximum concentration
CPOP	clinical proof of principle
CRF	case report form
CTR	clinical trial report
DBL	Database lock
DKA	diabetic ketoacidosis
DTSQ	Diabetes Treatment Satisfaction Questionnaire
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
FAS	full analysis set
FDA	U.S. Food and Drug Administration
FPG	fasting plasma glucose
GAD	glutamic acid decarboxylase
GLP-1	glucagon-like peptide-1
HbA1c	glycosylated haemoglobin
HLA	human leucocyte antigen
IA2	islet antigen-2
IAA	insulin autoantibodies
i.v.	intravenous(ly)
LOCF	last observation carried forward
LPLT	Last patient last treatment
LSMeans	least square mean
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measurements
MMTT	mixed meal tolerance test
MRT	mean residence time
NK	natural killer
PBMsCs	periphery blood mononuclear cells
PG	plasma glucose
PPG	postprandial glucose
PK	pharmacokinetic

PRO	patient reported outcome
SAE	serious adverse event
SAP	statistical analysis plan
s.c.	subcutaneous(ly)
SD	standard deviation
SE	standard error
SF-36v2	Short Form Health Survey version 2
SLE	systemic lupus erythematosus
SMPG	self-measured plasma glucose
SS	steady state
T1DM	type 1 diabetes mellitus
TSH	Thyroid-stimulating hormone
T-T-T	treat-to-target
ZnT8	zinc-transporter 8

1 Introduction

1.1 Trial information

This section includes the information of objectives, endpoints and type of trial as described in the trial protocol.

1.1.1 Objectives

Primary objective

The primary objective is to evaluate the effect of NNC0114-0006, liraglutide, and the combination of NNC0114-0006 and liraglutide, compared to placebo, on preservation of beta-cell function after 54 weeks of treatment in adult subjects with newly diagnosed type 1 diabetes mellitus (T1DM).

Secondary objectives

Objectives related to treatment period (from baseline (week 0) to week 54):

- To assess safety and tolerability of NNC0114-0006 and liraglutide in combination and alone in subjects with newly diagnosed T1DM
- To assess effect on glycaemic parameters (including insulin usage and insulin regimen) of NNC0114-0006 and liraglutide in combination and alone in subjects with newly diagnosed T1DM
- To assess pharmacokinetic (PK) properties of NNC0114-0006 and liraglutide in combination and alone in subjects with newly diagnosed T1DM
- To explore biomarkers relevant for the effect of NNC0114-0006 and liraglutide in combination and alone in subjects with newly diagnosed T1DM
- To assess disease burden and health status in subjects with newly diagnosed T1DM treated with NNC0114-0006 and liraglutide in combination and alone

Objectives related to the post-treatment observation period (from week 54 to week 80):

- To assess post-treatment safety and tolerability of NNC0114-0006 and liraglutide in combination and alone in subjects with newly diagnosed T1DM
- To assess post-treatment effect on preservation of beta-cell function of NNC0114-0006 and liraglutide in combination and alone in subjects with newly diagnosed T1DM
- To assess post-treatment effect on glycaemic parameters (including insulin usage and insulin regimen) of NNC0114-0006 and liraglutide in combination and alone in subjects with newly diagnosed T1DM
- To explore biomarkers relevant for the post-treatment effect of NNC0114-0006 and liraglutide in combination and alone in subjects with newly diagnosed T1DM

- To assess post-treatment development of disease burden and health status in subjects with newly diagnosed T1DM treated with NNC0114-0006 and liraglutide in combination and alone

1.1.2 Endpoints

1.1.2.1 Primary endpoint

The primary endpoint is $AUC_{0\text{-}4h}$ for a mixed meal tolerance test (MMTT) stimulated C-peptide concentration-time curve at week 54 relative to baseline (defined as the MMTT performed at Visit 2).

- $AUC_{0\text{-}4h,\ C\text{-}peptide,\ 54w}/AUC_{0\text{-}4h,\ C\text{-}peptide,\ baseline}$

1.1.2.2 Supportive secondary endpoints

Supportive secondary efficacy endpoints

- $AUC_{0\text{-}4h}$ for MMTT stimulated C-peptide concentration time curve at week 80 relative to baseline*
- $AUC_{0\text{-}2h}$ for MMTT stimulated C-peptide concentration time curve at week 54 and week 80 relative to baseline*
- Maximum MMTT stimulated C-peptide concentration ($C_{max,\ C\text{-}peptide}$) at week 54 and week 80 relative to baseline*
- $AUC_{0\text{-}4h}$ for MMTT stimulated plasma glucose concentration time curve at week 54 and week 80 relative to baseline
- $AUC_{0\text{-}2h}$ for MMTT stimulated plasma glucose concentration time curve at week 54 and week 80 relative to baseline
- Maximum MMTT stimulated plasma glucose concentration ($C_{max,\ glucose}$) week 54 and week 80 relative to baseline
- Change in total daily insulin dose in units per kg (three day average) from baseline to week 54 and week 80*
- Change in number of insulin injections per day (three day average) from baseline to week 54 and week 80
- Number of weeks off bolus insulin from baseline to week 54 and week 80
- Change in HbA_{1c} from baseline to week 54 and week 80*
- Change in fasting plasma glucose from baseline to week 54 and week 80*
- Change in fasting C-peptide from baseline to week 54 and week 80*
- Change in fasting glucagon from baseline to week 54 and week 80
- 7-point self-measured plasma glucose (SMPG) profiles. The following endpoints will be derived:

  - 7-point profiles at week 54 and week 80
  - Change in postprandial glucose (PPG)/prandial increment (breakfast, lunch, dinner and average over the three meals) from baseline to week 54 and week 80
  - Change in mean of 7-point profiles from baseline to week 54 and week 80
- Before breakfast SMPG at week 54 and week 80
- Change in patient reported outcome (PRO) scores (SF36, Experience of Treatment Benefits and Barriers, Diabetes Treatment Satisfaction Questionnaire (DTSQ)) from baseline to week 54 and week 80

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

Supportive secondary safety endpoints

- Number of treatment emergent adverse events reported
  - from first dose of trial product to week 54
  - from week 54 to week 80
- Number of treatment emergent hyperglycaemic episodes
  - from first dose of trial product to week 54
  - from week 54 to week 80
- Number of treatment emergent episodes of diabetic ketoacidosis (DKA)
  - from first dose of trial product to week 54*
  - from week 54 to week 80
- Number of subjects experiencing treatment emergent injection/infusion site reactions from first dose of trial product and during treatment period (54 weeks) caused by:
  - NNC0114-0006/liraglutide/placebo injection/infusion
- Number of treatment emergent hypoglycaemic episodes according to the American Diabetes Association (ADA) and Novo Nordisk definitions
  - from first dose of trial product to week 54*
  - from week 54 to week 80
- Change in body weight from baseline to week 54 and week 80
- Diabetes complications (retinopathy and estimated glomeruli filtration rate) from baseline to week 54 and week 80
- Change in laboratory safety variables (haematology, biochemistry, coagulation, lipids, IgE, urine dipsticks, cytokine panel, and hormones), vital signs, electrocardiograms (ECGs), eye-examination and outcome of physical examination from baseline to week 54 and week 80
- Change in anti-NNC0114-0006 antibodies from baseline to week 54 and week 80
- Change in anti-liraglutide antibodies from baseline to week 54 and week 80

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

Supportive secondary biomarker endpoints

- Change in biomarker parameters from baseline to week 54 and week 80
  - Immune phenotyping of peripheral blood mononuclear cells (PBMC) (the analyses will include, but are not restricted to, the following populations):
    - NK subpopulations
    - Monocyte subpopulations
    - CD8+ & CD4+ subpopulations (e.g., anergy/exhaustion vs. activation; memory, effector, regulatory cells; follicular helper (Tfh) & regulatory Tfh)
  - Total IL-21
  - Autoantibodies against glutamic acid decarboxylase 65 (GAD), zinc-transporter 8 (ZnT8), islet antigen-2 (IA2), insulin (IAA)
- Change in serum vitamin D (1,25 dehydroxy-calciferol) from baseline to week 54 and week 80

Supportive secondary pharmacokinetic endpoints

NNC0114-0006:

- $AUC_{\tau,\ NNC0114-0006}$, area under the NNC0114-0006 time-concentration curve over a dosing interval at steady state (SS) (defined as after last dose)
- Terminal half-life ($t_{½}$) after last dose of NNC0114-0006
- $V_{ss,\ NNC0114-0006,}$ the apparent volume of distribution of NNC0114-0006 at steady-state
- $CL_{ss,\ NNC0114-0006}$, clearance of NNC0114-0006 at steady state
- $MRT_{,\ NNC0114-0006,}$ the mean residence time of NNC0114-0006
- $R_{A,AUC,\ NNC0114-0006}$, accumulation ratio of NNC114-0006 defined as $AUC_{48-54\ weeks}/AUC_{0-6\ weeks}$
- $C_{trough,\ NNC0114-0006}$, observed NNC0114-0006 concentration prior to dosing of NNC0114-0006 at steady state
- $C_{1h,\ NNC0114-0006}$, observed NNC0114-0006 concentration 1 hour after dosing of NNC0114-0006 at steady state

The following pharmacokinetic endpoints for liraglutide will be derived after the last dose administered at week 54:

- $C_{\ liraglutide}$, liraglutide concentration at steady state

1.1.3 Type of trial

The trial is a randomised, multi-centre, multinational, placebo-controlled, double-dummy, double-blind, efficacy, safety and PK CPOP trial in subjects with newly diagnosed T1DM with residual beta-cell function. The trial includes four parallel treatment groups, one with NNC0114-0006 12 mg/kg i.v. every 6 weeks and liraglutide 1.8 mg s.c. daily, one with NNC0114-0006 12 mg/kg i.v. every 6 week, one with liraglutide 1.8 mg subcutaneously (s.c.) daily and, one placebo arm randomised in an even ratio. The randomisation will take place not more than 4 weeks from start of screening (V1). The exposure period for NNC0114-0006 and liraglutide in combination or alone is

54 weeks. The primary endpoint (C-peptide) is at week 54 as defined per U.S. FDA and EMA requirements[1,2] followed by a 26 weeks observation period. All groups will receive insulin treatment according to a treat-to-target (T-T-T) regimen throughout the entire trial. See Figure 1–1 for the schematic trial design.

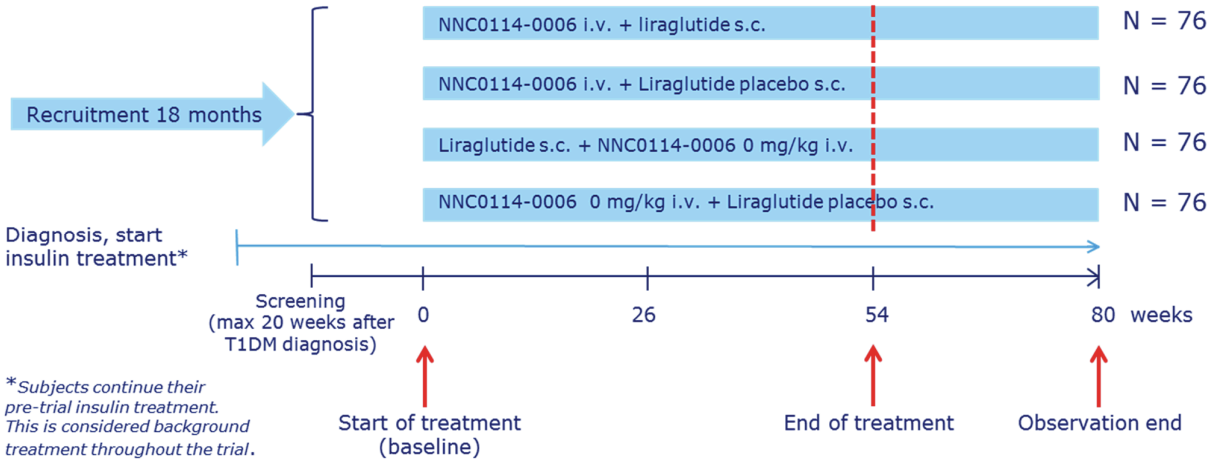


Figure 1–1 Trial design

1.2 Flow-chart

Please refer to the trial protocol, Section 2.

The full PK profile consisting of 25 samples is only applicable for the first minimum 80 subjects. These subjects follows the flowchart listed in the protocol, sub-section 2.1 "Visit procedure for the first 80 randomised subjects only". The remaining subjects will follow a reduced visit schedule. These subjects follows the flowchart listed in the protocol, sub-section 2.2 "Visit procedure for once 80 subjects have been randomised".

1.3 Scope of the statistical analysis plan

This SAP is based on the protocol "A randomised, double-blind, double-dummy, placebo-controlled, parallel-group multi-centre clinical proof-of-principle trial in adult subjects with newly diagnosed type 1 diabetes mellitus investigating the effect of NNC0114-0006 and liraglutide on preservation of beta-cell function" version 8.0, including amendments no. 1, 2, 3, 4, 5, 6 and 7.

2 Statistical considerations

Based on the statistical model, treatment means or geometric means (LSMeans) and treatment comparisons (i.e. treatment differences or treatment ratios) will be presented with 95% confidence intervals (CI) and p-values for the two-sided test of no treatment difference. A significance level of

5% will be used. All pairwise treatment differences (or ratios) will be presented. No adjustment for multiple testing will be performed.

Some endpoints will be summarised for the treatment period, for the observation period and for the entire trial period (i.e. the treatment period together with the observation period)

The treatment period and the observation period will be derived for completed subjects as

- The start of the treatment period will be the date of first trial product administration
- The end of the treatment period will be the date of the visit at week 54 (i.e. the day of visit 63)
- The start of the observation period will be the day after the end of the treatment period
- The end of the observation period will be the date of the last visit

For withdrawn subjects the date of last contact will be the maximum of the date of the last visit and the withdrawal date. The treatment period and the observation period will be derived for withdrawn subjects as

- The start of the treatment period will be defined as described for completed subjects
- The end of the treatment period will be as defined for competed subjects if this date is before or on the date of last contact. Otherwise the end of the treatment period will be the date of last contact
- An observation period will only be defined if the date of last contact is after the end of the treatment period
    - The start of the observation period will be defined as for completed subjects
    - The end of the observation period will be the date of last contact

For endpoints evaluated as change from baseline and/or for baseline adjustment in the statistical analyses, baseline will be defined as the information recorded at the Visit 3 (randomisation). If no measurement is available at Visit 3, then the information recorded at Visit 2 will be used as the baseline. Furthermore, if no measurement is available at Visit 2, then the information recorded at Visit 1 will be used as the baseline.

In case an endpoint is assessed at visits other than baseline, week 6, 12, 18, 24, 30, 36, 42, 48, 54, 65, and 80, values from the other visits will not be included in the mixed model for repeated measurements (MMRM).

As there is no previous experience with NNC0114-0006 in subjects with T1DM, the defined endpoints and analyses may be supplemented with additional endpoints or analyses such that a better evaluation of the effect and safety of NNC0114-0006 can be obtained.

2.1 Sample size calculation

This is a phase 2 trial and the first Novo Nordisk trial of NNC0114-0006 in subjects with newly diagnosed T1DM. Therefore the knowledge on treatment effects and on the standard deviation of the primary endpoint is limited.

The statistical power calculations have been done under the following assumptions

- The primary endpoint is $AUC_{0\text{-}4h}$ for a MMTT stimulated C-peptide concentration-time curve at week 54 relative to baseline, i.e. $AUC_{0\text{-}4h,\ C\text{-}peptide,\ 54w}/AUC_{0\text{-}4h,\ C\text{-}peptide,\ baseline}$. The primary endpoint will be log-transformed in the statistical analysis and this will be denoted $\ln(AUC_{0\text{-}4h,C\text{-}peptide,\Delta 54w})$. Thus, $AUC_{0\text{-}4h,\ C\text{-}peptide,\Delta 54w}$ is the proportion of $AUC_{C\text{-}peptide}$ that is preserved after 54 weeks relative to the level at baseline. E.g. a reduction of $AUC_{C\text{-}peptide}$ of 35% corresponds to a preservation of 65% and value of the $\ln(AUC_{0\text{-}4h,C\ \text{-}peptide,\Delta 54w})$ is $\ln(0.65)=-0.431$.
- The residual standard deviation of $\ln(AUC_{0\text{-}4h,\ C\text{-}peptide,\ \Delta 54w})$ in the model described above may depend on the treatment. Based on the results of Herold et al.[3] the standard deviation is assumed to be 1 in the placebo group and 0.5 in the group treated with NNC0114-0006 in combination with liraglutide.
- The expected preservation in the placebo treated patients is 65%, based on the results of Herold et al.[3] who found a mean of 70% decline in $AUC_{C\text{-}peptide}$ over a 24-months period. Assuming a linear decline, the mean 12-months decline would be 35%, i.e. a preservation of 65%. The statistical power calculations have been done assuming three levels of treatment effects for NNC0114-0006 in combination with liraglutide; a preservation of 85% and 95% and 98%, respectively.

Table 2–1 shows the statistical power for the test of no treatment effect if the true mean preservation is 85%, 95% or 98% in the group treated with NNC0114-0006 in combination with liraglutide and 65% in the placebo group when the numbers of completers are 40, 60 or 80, respectively using a two-sided test and 5% level of significance. The rows corresponding to the chosen number of (completing) subjects are highlighted.

Table 2–1 Power calculations

True treatment effect (preservation)	N (completers per group)	Statistical power
85%	40	0.320
85%	**60**	**0.451**
85%	80	0.566
95%	40	0.561
95%	**60**	**0.740**
95%	80	0.854
98%	40	0.628
98%	**60**	**0.804**
98%	80	0.903

Assuming a preservation of 98% and a SD of 0.5 for NNC0114-0006 in combination with liraglutide and a preservation of 65% and a SD of 1 for placebo, then the power will be 80.4% with 60 subjects completing the trial in each of the two treatment arms.

2.2 Definition of analysis sets

The following analysis sets are defined in accordance with the ICH-E9[4] guidance:

- The full analysis set (FAS) will include all randomised subjects. Only in exceptional cases subjects may be excluded from the FAS. In such cases the reason for exclusion will be justified and documented. The statistical evaluation of the FAS will follow the intention-to-treat (ITT) principle and subjects will contribute to the evaluation 'as randomised'.
- The PK analysis set will include all randomised subjects following the flowchart for the first 80 randomised subjects only, with at least one valid PK measurement. Subjects in the PK analysis set will contribute to the evaluation 'as treated'.
- The safety analysis set will include all subjects receiving at least one dose of randomised treatment. Subjects in the safety analysis set will contribute to the evaluation 'as treated'.

Analyses of efficacy and biomarker endpoints will be based on the FAS. Analyses of the PK endpoints will be based on the PK analysis set. Analyses of safety endpoints will be based on the safety analysis set.

Before the database is locked and ready for statistical analysis a review of all data will take place. Extreme values and outliers will be identified by the study group during programming and data review according to ICH-E9[4] using a fake randomisation. In addition, protocol deviations, which may potentially affect the results, will be identified and it will be evaluated if subjects and/or data should be excluded from analysis.

Obviously erroneous data points may be excluded from the analyses or re-analysed (in case of e.g. serum concentrations). The decision to re-analyse or exclude data points from the statistical analysis is the joint responsibility of the study group. Furthermore, the individual profiles for C-peptide and plasma glucose from the MMTT in the treatment phase will be examined prior to interim database lock to establish whether it is possible to calculate all endpoints. If samples that are important for the derivation of certain endpoints are missing, these endpoints will not be calculated and they will be excluded from the analysis. In these cases, the subjects, observations or endpoints to be excluded and the reason for their exclusion will be documented prior to interim database lock. Data that are not in scope for the interim database lock, including individual PK profiles, biomarkers, antibodies, and all data from the observation period may be examined after the interim database lock but before the full database lock. In cases where observations or endpoints are excluded from these data, it will be documented prior to the full database lock, and clearly stated if a decision was taken after randomisation code break. The subjects and observations excluded from analysis and the reason for exclusion will also be described in the clinical trial report.

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

2.3 Primary endpoint

The primary endpoint is $AUC_{0\text{-}4h}$ for a MMTT stimulated C-peptide concentration-time curve at week 54 relative to baseline: $AUC_{0\text{-}4h,\ C\text{-}peptide,\ 54w}/AUC_{0\text{-}4h,\ C\text{-}peptide,\ baseline}$.

The AUC0-4h for MMTT stimulated C-peptide is derived at baseline and at 12, 24, 36, and 54 weeks and is denoted AUC0-4h, C-peptide, t, where t is the time of the assessment. Thus, t=54 weeks corresponds to the primary endpoint.

More specifically, $AUC_{0\text{-}4h,\ C\text{-}peptide,\ t}$ at time 't' will be determined as the area from 0 to 4 hours under the C-peptide concentration profile after a MMTT using the trapezoidal method based on observed concentration values and actual measurement times. If the MMTT is stopped before 4 hours due to hyperglycaemia or hypoglycaemia, the last measured C-peptide concentration will be carried forward for calculation of the primary endpoint. If the MMTT is stopped before 4 hours it will most likely be due to hyperglycaemia as hypoglycaemia is not expected when a high amount of carbohydrates are ingested. Using last observation carried forward (LOCF) will result in an overestimated AUC since the C-peptide response is expected to be at the maximum level during hyperglycaemia. Furthermore, the risk of hyperglycaemia during MMTT will be higher in the placebo group if the active treatments have an effect on beta-cell preservation. Thus, LOCF is considered as a conservative approach. In case the MMTT is stopped before 4 hours for reasons that are not due to hyperglycaemia or hypoglycaemia, the remaining C-peptide concentrations will be set to lloq/2.

Let y_{it} denote the value of $AUC_{0\text{-}4h,\ C\text{-}peptide,\Delta t}$ evaluated relative to baseline at time *t* for subject *i*, i.e.

$y_{it} = AUC_{0\text{-}4h,\ C\text{-}peptide,\Delta t} = AUC_{0\text{-}4h,\ C\text{-}peptide,\ t}/AUC_{0\text{-}4h,\ C\text{-}peptide,\ baseline}$

log of y_{it} will be analysed using an (MMRM) including all available assessments over time with treatment, stratum and sex as factors and $\ln(AUC_{0\text{-}4h,\ C\text{-}peptide,\ baseline})$ and age at baseline as covariates (see Table 2–2). The interaction between all variables and visit (week) will be included in the model as fixed effects.

Table 2–2 Model terms for the statistical model for the primary endpoint

Model term	Description
$\ln(y_{it})$	dependent variable, subject i, time t
$\ln(AUC_{0\text{-}4h,\ C\text{-}peptide,\ baseline})$	fixed effect covariate with a visit dependent coefficient
Visit	fixed effect factor corresponding to time t=12w, 24w, 36w, 54w
Treatment	fixed effect interaction term between treatment and visit (i.e. the treatment effect is not assumed the same for all visits), with treatment as a factor with 4 levels: NNC0114-0006 in combination with liraglutide, NNC0114-0006, liraglutide and placebo
Stratum	fixed effect interaction term between stratum and visit, with stratum as a factor with two levels according to non-fasting max C-peptide measurement during MMTT at Visit 2: 0.2-0.6 nmol/l and >0.6 nmol/l
Age	fixed effect covariate with a visit dependent coefficient
Sex	fixed effect interaction term between sex and visit

The variance-covariance matrix for the repeated measurements for each subject will be unstructured.

From the model, least square means (LSMeans) for each treatment group at selected time points, including week 54 will be estimated, and mean differences between treatment groups in log-transformed $AUC_{0\text{-}4h,\ C\text{-}peptide,\Delta t}$ at these time points will be estimated. These estimates will be back-transformed to the original scale to represent treatment (geometric) means and treatment (geometric mean) ratios with 95% CIs.

The primary endpoint will be summarised using descriptive statistics and presented graphically.

Sensitivity analyses of the primary endpoint

The following sensitivity analyses will be made

- To assess the impact of the endpoints calculated from MMTT that is stopped before 4 hours due to hyperglycaemia or hypoglycaemia, a sensitivity analysis will be performed excluding these endpoints.

- To assess the impact of the endpoints calculated from MMTT profile that includes imputed values, a sensitivity analysis will be performed excluding these endpoints.
- A sensitivity analysis will be performed excluding endpoints calculated from the MMTT, where the date of the MMTT is more than one day after the last liraglutide dosing.
- An analysis using last observation carried forward (LOCF) of the primary endpoint. The analysis will be made using a normal linear regression model for the log-transformed primary endpoint with treatment, stratum and sex as fixed factors and age and baseline value (log-transformed) as covariates.
- An analysis based on the subjects completing the treatment period (i.e. completing the visit at week 54). The analysis will be made using a normal linear regression model for the log-transformed primary endpoint with treatment, stratum and sex as fixed factors and age and baseline value (log-transformed) as covariates
- In case the assumption of equal variance-covariance between the treatments turns out not to be reasonable a sensitivity analysis will be added where the variance-covariance matrix for the repeated measurements for each subject will depend on treatment.

Exploratory analyses

Effect of stratum on the primary endpoint

An exploratory analysis will be made to investigate a potential interaction between treatment and stratum for the primary endpoint. The analysis will be made by adding the interaction between stratum, treatment and visit as a factor in the mixed model for repeated measurements (MMRM) described for the primary endpoint. The treatment means and the treatment ratios at selected time points including week 54 will be presented with 95% CIs for each stratum separately.

Effect of biomarkers on the primary endpoint

The effect of the biomarkers at baseline and high resolution HLA (class I) genotyping on the primary endpoint will be explored one variable at a time.

For continuous variables, the analysis will be made by adding the biomarker at baseline (log-transformed) as a fixed effect covariate with a coefficient that depends on visit and treatment to the MMRM described for the primary endpoint. The estimated effect of the variable at selected time points including week 54 will be presented with a 95% CI for each treatment.

Effect of liraglutide concentration on the primary endpoint

An exploratory analysis will be made to investigate a potential effect of the concentration of liraglutide on the primary endpoint using data from the two groups of subjects treated with liraglutide. This analysis will be made by adding the log-transformed concentration of liraglutide measured on the date corresponding to the last MMTT as a covariate in the analysis using LOCF for the primary endpoint.

2.4 Secondary endpoints

2.4.1 Supportive secondary endpoints

2.4.1.1 Efficacy endpoints

Other endpoints derived from the mixed meal tolerance test

The other endpoints based on the mixed meal tolerance test will be derived from the individual C-peptide concentration-time curves and from the individual plasma glucose concentration-time curves. The AUC endpoints will be derived using the same approach as described for the primary endpoint. The C_{max} endpoints will be derived as the ratio between the C_{max} at the relevant time points.

The endpoints will be analysed using a similar model as applied for the primary endpoint except that the corresponding value at baseline will be included as a covariate.

The endpoints will be summarised using descriptive statistics and presented graphically. The C-peptide concentration-time curves and the plasma glucose concentration-time curves will be presented graphically.

Insulin dose

The total daily insulin dose will be derived as the average of the doses per kg body weight reported on the three days prior to visit 3, 63 and 89.

The endpoints will be analysed using normal linear regression model for the endpoint with treatment, stratum and sex as fixed factors and age and baseline value as covariates. Treatment means (LSMeans) and treatment differences will be presented with 95% CIs. The analysis will not account for missing data.

The endpoints will be summarised using descriptive statistics and presented graphically.

Number of insulin injections

The number of insulin injections will be derived as the average of the reported number on the three days prior to visit 3, 63 and 89. The endpoints will be summarised using descriptive statistics.

Number of weeks off bolus insulin

The number of weeks the subject is off bolus insulin will be derived based on the question in the CRF “Has the subject stopped taking bolus insulin since last visit”. The endpoint will be summarised using descriptive statistics.

HbA_{1c}, FPG, fasting C-peptide and fasting glucagon

The HbA_{1c} and FPG endpoints will be analysed using a similar model as described for the primary endpoint except that the corresponding value at baseline will be included as a covariate and the analysis will be made on the original scale (i.e. without the log-transformation). Consequently, treatment means (LSMeans) and treatment differences will be presented with 95% CIs.

The fasting C-peptide and fasting glucagon endpoints will be analysed using a similar model as described for the primary endpoint except that the corresponding value at baseline will be included as a covariate. The values will be log-transformed prior to analysis, i.e. the change will be calculated for the log-transformed data and the log-transformed value at baseline will be included as a covariate.

In addition to the endpoints listed in Section 1.1.2.1, the following binary endpoints are derived for all subjects at baseline, week 54 and week 80:

- Hba1c < 7.0 %.
- Hba1c <= 6.5 %.

All the endpoints will be summarised using descriptive statistics and presented graphically.

Self-measured plasma glucose profiles

The 7-point SMPG profile will include a pre-meal measurement and a measurements 90 minutes after start of meal for breakfast lunch and dinner as well a measurement at bedtime.

The 4-point SMPG profile will be used for titration of the insulin dose and will include a pre-meal measurement for breakfast, lunch and dinner and a measurement at bedtime.

7-point SMPG profiles at week 54 and week 80

The 7-point SMPG profiles will be summarised using descriptive statistics and presented graphically.

Change in prandial increment and change in mean of 7-point SMPG profile

The prandial increment at a meal will be calculated as the post-meal measurement minus the pre-meal measurement. The prandial increment will be calculated for breakfast, lunch and dinner separately. The average over the three meals will also be calculated. The mean of the 7-point SMPG profile will be calculated as the mean of all 7 points.

The endpoints will be analysed using a similar model as described for the primary endpoint except that the corresponding value at baseline will be included as a covariate and the analysis will be

made on the original scale. Consequently, treatment means (LSMeans) and treatment differences will be presented with 95% CIs.

The endpoints will be summarised using descriptive statistics and presented graphically.

Before breakfast SMPG

The within-subject variability will be evaluated using the before breakfast measurements from 4-point SMPG profiles at week 54 and week 80.

A normal linear mixed effect model will be fitted to the before breakfast SMPG values at week 54. The model will include treatment, sex and stratum as fixed factors, age as a covariate and subject as a random effect. The model will assume independent within- and between-subject error variances depending on treatment. The within-subject variance will be presented for each treatment with the 95% CI. The analysis will not account for missing data.

The same analysis will be made for the before breakfast SMPG values at week 80.

PRO endpoints

Data collected with the PRO questionnaires (SF-36v2, Experience of Treatment Benefits and Barriers, and DTSQ (status)) will be scored according to the instruments' respective scoring algorithms into the following endpoints (domains)

- For Experience of Treatment Benefits and Barriers:
  - 'Perceived benefits'
  - 'Perceived barriers'
- For Diabetes Treatment Satisfaction Questionnaire (status):
  - 'Treatment satisfaction'
  - 'Perceived frequency of hypoglycaemia'
  - 'Perceived frequency of hyperglycaemia'
- For SF-36v2:
  - 'Physical Component Summary' score
  - 'Mental Component Summary' score
  - 'Physical functioning'
  - 'Role-physical'
  - 'Bodily pain'
  - 'General health'
  - 'Vitality'
  - 'Social functioning'
  - 'Role-emotional'
  - 'Mental health'

The PRO endpoints will be summarised using descriptive statistics.

Biomarker endpoints

The biomarker endpoints will be analysed using a similar model as described for the primary endpoint except that the corresponding value at baseline will be included as a covariate and the analysis will be made on the original scale. Consequently, treatment means (LSMeans) and treatment differences will be presented with 95% CIs. If the model assumptions are not fulfilled then transformations of the data will be considered, e.g. the change will be calculated on the log-transformed data and the log-transformed value at baseline will be included as a covariate.

The biomarker endpoints will be summarised using descriptive statistics and presented graphically.

2.4.1.2 Safety endpoints

Adverse events, DKA episodes and infusion/injection site reactions

All adverse events (including DKA episodes and infusion/injection site reactions) will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA). An adverse event will be defined as treatment emergent if the onset of the adverse event occurs on or after the first day of trial product administration.

Treatment emergent adverse events will be summarised by system organ class, preferred term, seriousness, severity and relation to trial product. Separate summaries will be made for treatment emergent DKA episodes and for treatment emergent infusion/injection site reactions. The summaries will be made for the treatment period, for the observation period and for the entire trial period.

Additional information will be recorded on special eCRF pages for selected adverse events. This information will be listed.

All adverse events will be listed and separate listings will be made for DKA episodes and infusion/injection site reactions.

Hyperglycaemic episodes

Hyperglycaemic episodes will be defined as treatment emergent if the onset occurs on or after the first day of trial product administration.

The number of treatment emergent hyperglycaemic episodes will be summarised by treatment. The summaries will be made for the treatment period, for the observation period and for the entire trial period.

Hypoglycaemic episodes

Classification of Hypoglycaemia:

Treatment emergent: hypoglycaemic episodes will be defined as treatment emergent if the onset of the episode occurs on or after the first day of trial product administration, and no later than 1 day after the date of last contact.

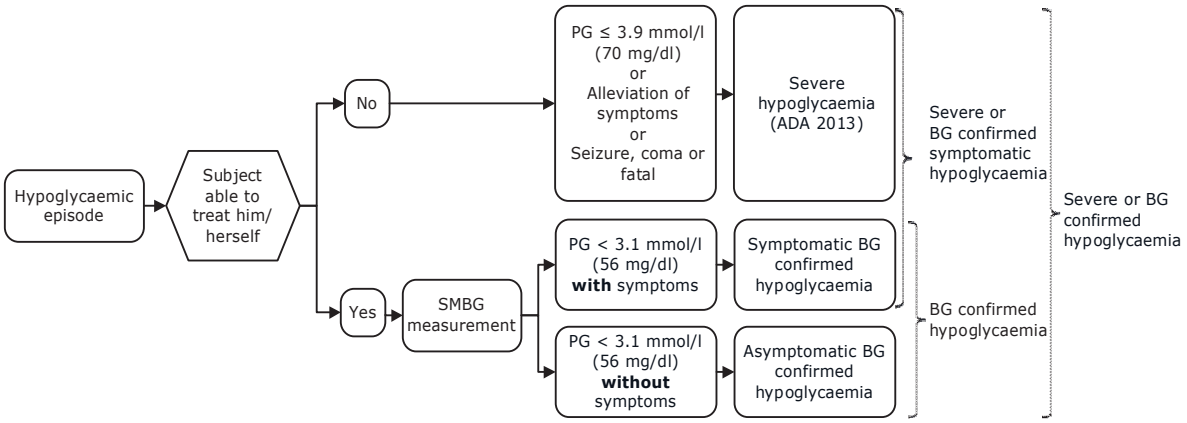
Nocturnal hypoglycaemic episodes: are episodes occurring between 00:01 and 05.59 both inclusive.

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

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)[5].Therefore, Novo Nordisk has included hypoglycaemia with plasma glucose levels below this cut-off point in the definition of blood glucose (BG) confirmed hypoglycaemia.

Novo Nordisk uses the following classification (see Figure 2–1) in addition to the ADA classification:

- Severe hypoglycaemia according to the ADA classification[6]
- Symptomatic BG confirmed hypoglycaemia: An episode that is BG confirmed by plasma glucose value <3.1 mmol/l (56 mg/dl) **with** symptoms consistent with hypoglycaemia.
- Asymptomatic BG confirmed hypoglycaemia: An episode that is BG confirmed by plasma glucose value <3.1 mmol/l (56 mg/dl) **without** symptoms consistent with hypoglycaemia.
- Severe or BG confirmed symptomatic hypoglycaemia: An episode that is severe according to the ADA classification[6] or BG confirmed by a plasma glucose value <3.1 mmol/l (56 mg/dl) **with** symptoms consistent with hypoglycaemia.
- BG confirmed hypoglycaemia: An episode that is BG confirmed by a plasma glucose value <3.1 mmol/l (56 mg/dl) **with** or **without** symptoms consistent with hypoglycaemia.
- Severe or BG confirmed hypoglycaemia: An episode that is severe according to the ADA classification[6] or BG confirmed by a plasma glucose value <3.1 mmol/l (56 mg/dl) **with** or **without** symptoms consistent with hypoglycaemia.

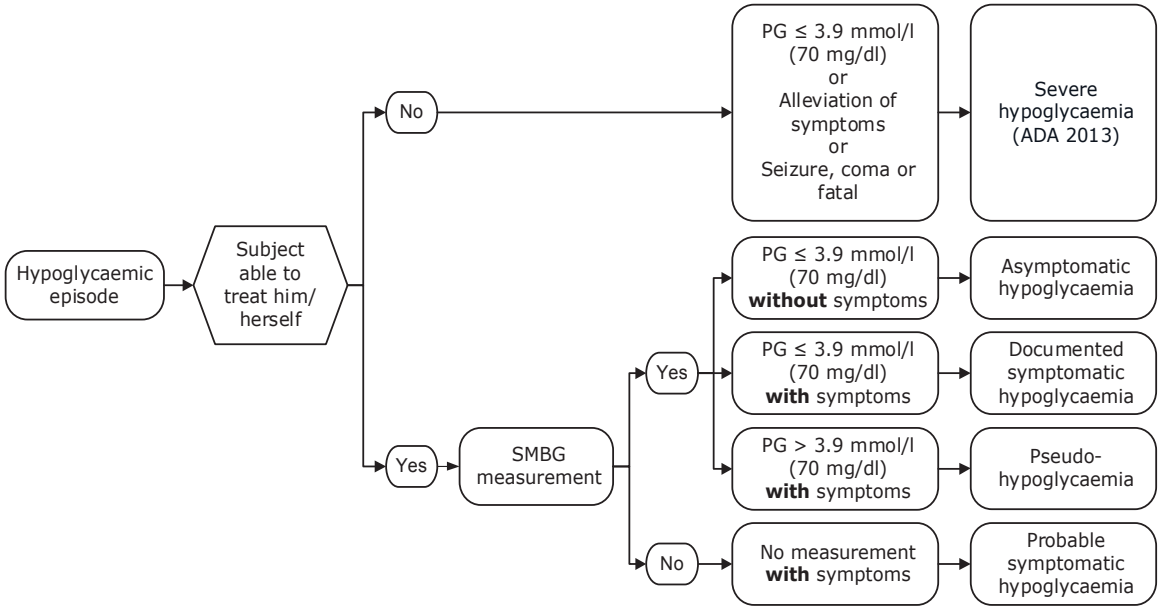


Note: Glucose measurements are performed with capillary blood calibrated to plasma equivalent glucose values

Figure 2–1 Novo Nordisk classification of hypoglycaemia

ADA classification[6] of hypoglycaemia

- Severe hypoglycaemia: An episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.
- Asymptomatic hypoglycaemia: An episode not accompanied by typical symptoms of hypoglycaemia, but with a measured plasma glucose concentration ≤ 3.9 mmol/l (70 mg/dl).
- Documented symptomatic hypoglycaemia: An episode during which typical symptoms of hypoglycaemia are accompanied by a measured plasma glucose concentration ≤ 3.9 mmol/l (70 mg/dl).
- Pseudo-hypoglycaemia: An episode during which the person with diabetes reports any of the typical symptoms of hypoglycaemia with a measured plasma glucose concentration > 3.9 mmol/l (70 mg/dl) but approaching that level.
- Probable symptomatic hypoglycaemia: An episode during which symptoms of hypoglycaemia are not accompanied by a plasma glucose determination but that was presumably caused by a plasma glucose concentration ≤ 3.9 mmol/l (70 mg/dl).



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

Figure 2–2 ADA classification of hypoglycaemia

Analysis of hypoglycaemic episodes

The number of treatment emergent hypoglycaemic episodes will be summarised by treatment. Separate summaries will be made for the Novo Nordisk and for the ADA classifications and for nocturnal episodes. The summaries will be made for the treatment period, for the observation period and for the entire trial period.

The total number of treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes will be analysed using a negative binominal regression model with a log link function, and the logarithm of the exposure time as an offset. The model will include treatment, stratum and sex as factors and age as a covariate. The treatment ratio will be estimated and the corresponding two-sided 95% CI will be calculated. The analysis will be made for the treatment period, for the observation period and for the entire trial period.

The total number of treatment emergent nocturnal severe or BG confirmed symptomatic hypoglycaemic episodes will be analysed using the same model as above. The analysis will be made for the treatment period, for the observation period and for the entire trial period.

To the extent that data allows, additional analyses may be performed for the other classes of hypoglycaemic episodes using the same model as described above.

Sensitivity analyses will be made (for each analysed class of hypoglycaemia) comparing number and individual rates of hypoglycaemic episodes, respectively, using the Wilcoxon-Mann-Whitney method. This will be made for all different pairs of treatments.

Body weight

The body weight endpoints will be analysed using a similar model as described for the primary endpoint except that the body weight at baseline will be included as a covariate and the analysis will be made on the original scale. Consequently, treatment means (LSMeans) and treatment differences will be presented with 95% CIs.

Body weight endpoints will be summarised using descriptive statistics and presented graphically.

Diabetes complications, eye examination and physical examination

The eGFR endpoint will be log-transformed and analysed using normal linear regression model with treatment, stratum and sex as fixed factors and age and baseline value as covariates. Treatment means (LSMeans) and treatment ratio for the back-transformed results will be presented with 95% CIs. The analysis will not account for missing data.

All endpoints will be summarised. The endpoints for eGFR will be presented graphically.

Laboratory safety variables (haematology, biochemistry, coagulation, lipids, IgE, urine dipsticks, cytokine panel and hormones)

The laboratory safety variables will be flagged if outside the reference range and abnormal values will be listed.

All endpoints for the laboratory safety variables will be summarised and the numerical variables will be presented graphically.

The endpoints for amylase and lipase will be analysed using a similar model as described for the primary endpoint except that the corresponding value at baseline will be included as a covariate. The individual values will be log-transformed prior to analysis, i.e. the change will be calculated on the log-transformed data and the log-transformed value at baseline will be included as a covariate.

The endpoints for TSH, IgE and cytokine panel will be analysed using a similar model as described for the primary endpoint except that the corresponding value at baseline will be included as a covariate and the analysis will be made on the original scale. Consequently, treatment means (LSMeans) and treatment differences will be presented with 95% CIs. If the model assumptions are not fulfilled then transformations of the data will be considered, e.g. the change will be calculated on the log-transformed data and the log-transformed value at baseline will be included as a covariate.

Vital signs and ECG

The systolic blood pressure, diastolic blood pressure and pulse endpoints will be analysed using a similar model as described for the primary endpoint except that the corresponding value at baseline will be included as a covariate and the analysis will be made on the original scale. Consequently, treatment means (LSMeans) and treatment differences will be presented with 95% CIs.

All endpoints will be summarised. The numerical endpoints will be presented graphically.

Anti-NNC0114-0006 antibodies and anti-liraglutide antibodies

All endpoints will be summarised and presented graphically.

2.4.1.3 Pharmacokinetic endpoints

The PK endpoints described in Table 2–3 will be derived from the individual NNC0114-0006 concentration-time curves after the first dose and after the last dose of NNC0114-0006. Furthermore, the trough concentration prior to dosing and the concentration 1 hour after dosing will be determined for NNC0114-0006 and the liraglutide concentration will be determined for liraglutide at the visits specified in the protocol, Section 2.

Table 2–3 Definition and calculation of PK endpoints

Endpoint	Description	Calculation
$AUC_{\tau,\ NNC0114-0006}$	Area under the NNC0114-0006 concentration-time curve over a dosing interval at steady state (SS) (defined as after last dose)	$AUC_{\tau,\ NNC0114-0006}$ will be derived as the area under the concentration-time curve using the linear trapezoidal technique based on observed values and actual measurement times between 0 and 6 weeks (after the last dose). Missing values will be imputed using linear interpolation, possibly using measurements after 6 weeks. If the end time of the interval (i.e. 6 weeks) is after the time of the last quantifiable concentration, t_z, and the terminal rate constant, λ_z, can be determined then $AUC_{\tau,\ NNC0114-0006}$ will be derived as the sum of $AUC_{0-tz,\ NNC0114-0006}$ and $AUC_{tz-6\ weeks,\ NNC0114-0006,}$ where $AUC_{tz-6\ weeks,NNC0114-0006}$ will be approximated using estimated values from the linear regression model applied for estimation of λ_z. If λ_z cannot be determined, then $AUC_{0-tz,\ NNC0114-0006}$ will be used instead of $AUC_{\tau,\ NNC0114-0006}$.

Endpoint	Description	Calculation
λ_z	Terminal rate constant for NNC0114-0006 (this is not an endpoint but it is used for calculation of some endpoints)	The terminal rate constant λ_z will be determined through linear regression with the logarithm to concentration as the response variable and actual measurement time as the explanatory variable. Valid observations from the terminal part of the curve, which is approximately linear, will be used for the determination.
$t_{½}$	Terminal serum half-life after last dose of NNC0114-0006	Calculated as $\log(2)/\lambda_z$
$V_{ss,\ NNC0114-0006}$	The apparent volume of distribution of NNC0114-0006 at steady-state	Calculated as $MRT_{NNC0114-0006} * CL_{SS,\ NNC0114-0006}$
$CL_{ss,\ NNC0114-0006}$	Clearance of NNC0114-0006 at steady state	Calculated as dose/$AUC_{\tau,\ NNC0114-0006}$
$MRT_{NNC0114-0006}$	The mean residence time of NNC0114-0006	Calculated as $$MRT = \frac{AUMC_\tau + \tau * AUC_{\tau-\infty}}{AUC_\tau}$$ where $$AUC_{\tau-\infty} = AUC_{0-tz} + AUC_{tz-\infty} - AUC_{0-\tau}$$ and $$AUMC_{0-\tau} = \sum_{i=2}^{n}(t_i - t_{i-1})(t_i C_i + t_{i-1} C_{i-1})$$
$R_{A,AUC,\ NNC0114-0006}$	Accumulation ratio of NNC114-0006 defined as $AUC_{48-54\ weeks}/AUC_{0-6\ weeks}$	$AUC_{48-56\ weeks}$ will be calculated as described for $AUC_{\tau,\ NNC0114-0006}$. $AUC_{0-6\ weeks}$ will be calculated using a similar approach except that extrapolation using λ_z will not be made

The PK endpoints will be summarised using descriptive statistics. The PK data will be presented graphically.

2.4.2 Interim analysis

No formal interim analysis has been planned. However, an internal Novo Nordisk analysis is to be conducted after global last patient last treatment (LPLT) (visit 63) to inform on future clinical trials. An additional database lock (DBL) will be performed, when all patients have completed the main phase of the trial, i.e. after LPLT at visit 63. After the additional DBL, Novo Nordisk will become unblinded, while the trial investigators and patients will remain blinded throughout the entire trial.

3 Changes to the statistical analyses planned in the protocol

The below changes are made prior to the randomisation code break at the interim database lock:

- Various minor changes in wording done for clarification.
- The end of the treatment period is changed from the day before the visit at week 54 to the date of the visit at week 54, to ensure that the observations at end of treatment (Visit 63) gets assigned to the treatment period.
- Due to the change in assessments between the two flowcharts, it has been added that in case an endpoint is assessed at visits other than baseline, week 6, 12, 18, 24, 30, 36, 42, 48, 54, 65, and 80, values from the other visits will not be included in the MMRM.
- Subjects in the full analysis set will contribute 'as randomised' and not 'as treated' as per the ITT principle.
- The definition of the PK analysis set has been updated to include randomised subjects following the flowchart for the first 80 randomised subjects only.
- The following paragraph has been re-written to specify that decisions on data that are not in scope for the interim database lock can be taken after randomisation code break.
    - Furthermore, the individual profiles for C-peptide and plasma glucose from the MMTT in the treatment phase will be examined prior to interim database lock to establish whether it is possible to calculate all endpoints. If samples that are important for the derivation of certain endpoints are missing, these endpoints will not be calculated and they will be excluded from the analysis. In these cases, the subjects, observations or endpoints to be excluded and the reason for their exclusion will be documented prior to interim database lock. Data that are not in scope for the interim database lock, including individual PK profiles, biomarkers, antibodies and all data from the observation period may be examined after the interim database lock but before the full database lock. In cases where observations or endpoints are excluded from these data, it will be documented prior to the full database lock, and clearly stated if a decision was taken after randomisation code break.
- Specification on how to derive the primary endpoint in case the MMTT is stopped before 4 hours for reasons that are not due to hyperglycaemia or hypoglycaemia has been added:
    - In case the MMTT is stopped before 4 hours for reasons that are not due to hyperglycaemia or hypoglycaemia, the remaining C-peptide concentrations will be set to lloq/2.
- The description of the stratification variable has been updated from non-fasting C-peptide measurement at screening to non-fasting peak C-peptide measurement during MMTT at Visit 2 in alignment with protocol amendment 2.
- In the analysis of the primary endpoint, it has been deleted, that the variance-covariance matrix may depend on treatment, if an assumption of equal variance-covariance matrix between treatments turns out not to be reasonable. Instead it has been included that a sensitivity analysis where the variance-covariance matrix depends on treatment will be added if an assumption of equal variance-covariance matrix between treatments turns out not to be reasonable.

- Update of the first sensitivity analysis to specify that it is the endpoints calculated from MMTT stopped before 4 hours due to hyperglycaemia or hypoglycaemia that are excluded from the analysis, and not all the data for that subject.
- Sensitivity analysis added where endpoints calculated from MMTT profile that includes imputed values is excluded.
- Sensitivity analysis added where endpoints calculated from the MMTT, where the date of the MMTT is more than one day after the last liraglutide dosing is excluded.
- In the analysis exploring the effect of the different biomarkers on primary endpoint, the description of the analysis for categorical biomarkers has been deleted, as all biomarkers are continuous.
- In the exploratory analysis that investigates a potential effect of the concentration of liraglutide on the primary endpoint, it has been specified that the liraglutide concentration should be measured at the date corresponding to the MMTT, and not just the visit corresponding to the MMTT. The specification is done as the MMTT can be re-scheduled within 1-10 days.
- In alignment with the endpoint description in Section 1.1.2.2, it is specified that the endpoint for total daily insulin dose is derived per kg body weight.
- As only the insulin doses prior to visit 3, 63 and 89 will be transferred from the eDiary (as per the trial data handling plan), the description of the endpoints has been updated, and the statistical analysis has been changed from a MMRM to a normal regression model:
    - The total daily insulin dose will be derived as the average of the doses reported on the three days prior to visit 3, 63 and 89.
    - The endpoints will be analysed using normal linear regression model for the endpoint with treatment, stratum and sex as fixed factors and age and baseline value as covariates. Treatment means (LSMeans) and treatment differences will be presented with 95% CIs. The analysis will not account for missing data.
      The number of insulin injections will be derived as the average of the reported number on the three days prior to visit 3, 63 and 89.
- As only the insulin doses prior to visit 3, 63 and 89 will be transferred from the eDiary, the calculation of the endpoint "The number of weeks the subject is off bolus insulin" is not derived based on the dose information in the eDiary as originally planned, but based on the question in the CRF "Has the subject stopped taking bolus insulin since last visit".
- The following analysis has been deleted in alignment with standard in GLP-1 trials:
    - A normal linear mixed effect model will be fitted to the 7-point SMPG profile data at week 54. The model will include treatment, time-point, the interaction between treatment and time-point, sex and stratum as fixed factors, age as a covariate and subject as a random effect. The variance-covariance matrix will be unstructured and may depend on treatment if an assumption of equal variance-covariance matrix between treatments turn out not to be reasonable. From this model the treatment

differences at each time-point will be estimated and explored. The same analysis will be made using the 7-point SMPG profile data at week 80

- For the analysis of within-subject variability of the before breakfast SMPG, it has been deleted that the 95% CI will be calculated using the delta method. Furthermore it has been clarified that the analysis will not account for missing data.
- As eGFR is only assessed at visit 1, 63 and 89, the statistical analysis has been changed from a MMRM to a normal regression model. Furthermore, it has been specified that the analysis will be done for the log-transformed endpoint:
    - The eGFR endpoint will be log-transformed and analysed using normal linear regression model with treatment, stratum and sex as fixed factors and age and baseline value as covariates. Treatment means (LSMeans) and treatment ratio for the back-transformed results will be presented with 95% CIs. The analysis will not account for missing data.
- Added:
    - In addition to the endpoints listed in Section 1.1.2.1, the following binary endpoints are derived for all subjects at baseline, week 54 and week 80:
        - $HbA_{1c} < 7.0$ %.
        - $HbA_{1c} <= 6.5$ %.

4 References

1. FDA Guidance for Industry Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention, Draft Guidance. 13 Feb 2008.
2. EMA/CPMP/EWP/1080/00 Rev.1 Guideline on clinical investigation of medicinal products in the treatment of diabetes mellitus. 15 Nov 2012.
3. Herold KC, Gitelman SE, Ehlers MR, Gottlieb PA, Greenbaum CJ, Hagopian W et al. Teplizumab (anti-CD3 mAb) treatment preserves C-peptide responses in patients with new-onset type 1 diabetes in a randomized controlled trial: metabolic and immunologic features at baseline identify a subgroup of responders. Diabetes 2013; 62(11):3766-3774.
4. ICH E9 guidelines: Statistical principles for clinical trials, step 4 version, 1998, CPMP/ICH/363/96. 1-35. 5 Feb 1998.
5. 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.
6. 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.