Protocol A9001498

A 6-WEEK, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, TWO-ARM, PARALLEL METHODOLOGY STUDY TO ASSESS THE EFFECT OF LIRAGLUTIDE ON FOOD INTAKE IN OBESE SUBJECTS

Statistical Analysis Plan
(SAP)

Version: Final

Date: 16-FEB-2017

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1. VERSION HISTORY

This Statistical Analysis Plan (SAP) for Study A9001498 is based on the protocol dated 21 November 2016.

Table 1. Summary of Major Changes in SAP Amendments

SAP Version	Change	Rationale
1	Not Applicable	Not Applicable

2. INTRODUCTION

Glucagon-like peptide-1 (GLP-1) is a neuroendocrine hormone that is predominantly released from the small intestine in response to food intake. GLP-1 activation of the GLP-1 receptor (GLP-1R) stimulates insulin release, inhibits glucagon secretion in a glucose dependent manner, and delays gastric emptying. In addition, GLP-1 has been shown to increase satiety and suppress food intake, supporting the use of GLP-1R agonists for the treatment of obesity. Several injectable peptidic GLP-1R agonists are approved for the treatment of Type 2 diabetes mellitus. Liraglutide is a peptide GLP-1R agonist that is approved both for the treatment of obesity (known as Saxenda®) and for the treatment of Type 2 diabetes (known as Victoza®).

The primary purpose of this study is to assess the effect of liraglutide on food (energy) intake in non-diabetic, obese subjects, an agent that has been demonstrated to result in decreased food intake. This assessment will aid in determining if food intake is an appropriate decision-making endpoint for CCI [redacted]

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in study A9001498. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

2.1. Study Objectives

Primary Objective(s):	Primary Endpoint(s):
• To assess the effect of liraglutide on food intake during 6 weeks of administration, compared to placebo.	• Mean energy intake (in kcal) during ad libitum lunch meals.
Secondary Objective(s):	**Secondary Endpoint(s):**
• To assess effects on safety measures and tolerability (including spontaneously	• Vital sign measurements, adverse event monitoring, changes in 12-lead ECGs,

reported nausea and vomiting) of liraglutide over 6 weeks of dosing. • To evaluate the effect of liraglutide on additional food intake endpoints during 6 weeks of administration, compared with placebo. • To assess the effect of liraglutide on appetite and satiety during 6 weeks of liraglutide administration, compared to placebo. • To assess the effect of liraglutide on gastric emptying during 6 weeks of liraglutide administration, compared with placebo.	and clinical laboratory testing. • 48-hour energy intake (in kcal). • Appetite and satiety scores, as assessed by Visual Analog scale (VAS) questionnaire. • Plasma area under the curve (AUC) of acetaminophen for 0-60 mins and 0-300 minutes after acetaminophen administration.
CCI [redacted]	

2.2. Study Design

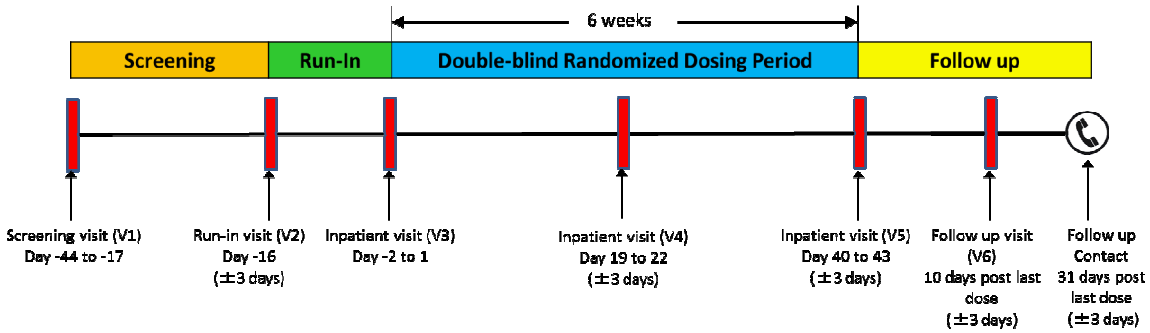
This will be a randomized, double-blind, placebo-controlled, 2-arm, parallel group, methodology study to assess the effect of 6 weeks of liraglutide administration on food intake in obese subjects. Subjects will complete screening procedures to determine eligibility and once confirmed to meet all other criteria, will proceed to a Run in visit (V2) and then to randomization at V3.

The study includes a total of six (6) visits to the site, including 3 outpatient visits (V1, V2 and V6) and 3 inpatient visits (V3, V4 and V5). Subjects will be randomized at V3 to receive 1 of 2 blinded treatment regimens for a duration of 6 weeks: liraglutide (administered subcutaneously via pen injection and titrated per Saxenda® label to maximum dose of 3.0 mg/day) or placebo (0.9% saline, administered subcutaneously via syringe in matching volume). At V3, V4 and V5, subjects will be admitted for an inpatient stay and receive blinded investigation product (IP) from an unblinded administrator. Each inpatient stay consists of 4 days and 3 nights. For the study duration between V3 and V4, and also between V4 and V5, subjects will be administered blinded IP on a daily basis via an unblinded administrator, either at home or at an outpatient visit. The study is double-blind, however the site pharmacist will be unblinded to administer the drug because there is not a perfect match placebo.

Total participation in the study for each subject, including Screening (V1) and investigator site follow-up visits (V6) will be approximately 10 weeks (minimum) to 14 weeks (maximum). In addition, there will be follow up contact with the subject via a phone call, at least 28 after last dose of IP (V5). The overall study scheme is summarized in Figure 1.

Approximately 60 subjects (30 per arm) will be randomized at one or more study sites. A minimum of 50 completed subjects (approximately 25 subjects per arm) are required for the study. The 60 randomized subjects account for a projected approximate premature discontinuation rate of 15% and reflects intent not to replace subjects prematurely discontinued after first dose of IP.

Figure 1. Study Design



3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Efficacy Endpoint(s)

Food intake will be assessed at the times listed in the Schedule of Activities (SoA) in the protocol.

All meals will be prepared at the study site during inpatient visits. For every ad libitum meal, each portion will be weighed and recorded before and after each meal. The following parameters will be measured: total kcal consumed per day, total kcal of each macronutrient (carbohydrate, fat or protein) consumed per day, total kcal consumed per meal and total kcal of each macronutrient consumed per meal. The total daily nutritional composition offered in the inpatient meals will be approximately 50% carbohydrates, 35% fat and 15% protein.

Observed food intake will be measured as the total number of calories consumed during the specified time period, calculated (to the nearest 50 kcal) as the difference of the total number of calories provided minus the total number of calories remaining after meals.

The change from baseline in mean energy intake (in kcal) during ad libitum lunch meals will be the primary endpoint. Baseline is defined as the mean of the measurements at Visit V3 (Day -1 and 0). Change from baseline will be calculated as the measurement at follow-up minus the measurement at Visit V3.

3.2. Secondary Efficacy Endpoint(s)

3.2.1. 48-hour Energy Intake

A secondary efficacy endpoint for food intake is change from baseline in 48-hour energy intake. It will be calculated similar to the primary endpoint. Baseline is defined as the 48-hour period at Visit V3. Change from baseline will be calculated as the measurement at V4 or V5 minus the measurement at Visit V3.

3.2.2. Appetite, Satiety, Fullness, Hunger and Prospective Consumption VAS

An additional secondary endpoint of appetite, satiety, fullness, hunger, and prospective consumption will be measured at the study site using a validated VAS questionnaire. The VAS questionnaire will be completed by the subject at each of 4 time points: immediately prior to administration of the meal, 30, 60 and 120 minutes after start time of the specified meals, per the SoA in the protocol.

The VAS is an assessment in which subjects place a vertical line across a validated 100 millimeter (mm) line to rank their response to various questions. The line is anchored by responses such as “Not At All Full” and “Totally Full” at either end. Scoring will consist of measuring the distance in mm of the vertical line from the response at the left end and will be used to explore the relationships between subjective reports of appetite and other VAS measures immediately prior to and following administration of the meal.

The overall appetite score will be calculated as the average of the four individual scores [satiety+fullness+(100−prospective food consumption)+(100−hunger)] divided by 4. In addition to the overall appetite score the individual scores (for satiety, fullness, nausea, 100−prospective food consumption, 100−hunger) will also be analyzed to estimate the treatment effect. For each of these subscores the parameters to be assessed will be fasting rating (i.e. effect at time point 0 for VAS, i.e. the measure collected prior to administration of the meal), mean rating AUC (30-120) min, maximum rating (maximum for a given meal) and 30 min postprandial rating (i.e. 30 minutes after start time of the specified meals).

Baseline VAS will be the VAS collected at Visit V3 (Day -1 and 0). The baseline value will be the mean of the VAS scores at Day -1 and 0. Moreover the baseline for the fasting rating will be the mean baseline rating at time point 0, baseline for mean rating $AUC_{30\text{-}285}$/255 min will be the mean rating $AUC_{30\text{-}285}$/255 min for Day -1 and 0 (mean of Day -1 and 0), baseline for maximum rating will be mean of maximum rating for Day -1 and maximum rating for Day 0, baseline for 30 min postprandial rating will be mean of 30 min postprandial rating on Day -1 and Day 0.

Change from baseline will be defined as the VAS at the current visit minus VAS at the baseline visit.

3.3. Other Efficacy Endpoints

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3.4. Baseline Variables

The baseline visit will occur at Visit V3. Medical history will be collected at baseline.

3.5. Pharmacokinetic Endpoints

PK samples for acetaminophen will be collected at Visits V3, V4 and V5 at the time points specified in the SoA.

Data permiting the following pharmacokinetic endpoints will be calculated.

Parameter	Definition	Method of Determination
Single Dose		
C_{max}	Maximum plasma concentration	Observed directly from data
T_{max}	Time at which C_{max} occurred	Observed directly from data as time of first occurrence
$AUC_{0\text{-}60\ min}$	Area under the concentration-time profile from time zero to 60 minutes	Linear/Log trapezoidal method
$AUC_{0\text{-}300\ min}$	Area under the concentration-time profile from time zero to 300 minutes	Linear/Log trapezoidal method
Relative acetaminophen exposure (0-1)	Relative acetaminophen exposure during the first postpandrial hour	($AUC_{0\text{-}60\ min}/AUC_{0\text{–}300\ min}$)

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3.6. Safety Endpoints

3.6.1. Adverse Events

An adverse event is considered treatment emergent relative to a given treatment if:

- the event occurs for the first time during the effective duration of treatment and was not seen prior to the start of treatment (for example, during the baseline or run-in period), or
- the event was seen prior to the start of treatment but increased in severity during treatment.

3.6.2. Suicidality Assessment

The C-SSRS is a validated tool to evaluate suicidal ideation and behavior. At Screening Visit, if there is a "yes" to question 1 of the C-SSRS, the subject will not be included in the study. Data relevant to the assessment of suicidality will be mapped to the Columbia-Classification Algorithm of Suicide Assessment (C-CASA) codes (Appendix 4).

3.6.3. Laboratory Data

The following clinical laboratory tests will be performed at times defined in the SoA of this protocol and will be performed by the study site laboratory. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory; or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety concerns.

Table 2. Clinical Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	Blood Urea Nitrogen (BUN) Creatinine Glucose Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Total bilirubin Alkaline phosphatase Albumin Total protein	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Microscopy[a]	Serum β-hCG[b] Lipid panel: total cholesterol, HDL-C, LDL-C, triglycerides Amylase Lipase Calcitonin CCI [redacted] Urine drug screen **At V1, only:** FSH TSH HbA1c Human Immunodeficiency Virus (HIV) Hepatitis Panel: HepBsAg, HepBcAb, HCVAb
	Additional Tests (Needed for Hy's Law)		
	AST, ALT (repeat) Total bilirubin (repeat) Albumin (repeat) Alkaline phosphatase (repeat) Direct bilirubin Indirect bilirubin Creatine kinase GGT PT/INR Total bile acids Acetaminophen drug and/or protein adduct levels		

a. Only if urine dipstick is positive for blood, protein, nitrites or leukocyte esterase.
b. Serum β-hCG for all female subjects at V1. At V2-V6, serum β-hCG for women of childbearing potential ***only***.

The baseline laboratory measurement will be the one taken at Visit V3. Change from baseline will be at V4 or V5 measurement minus baseline.

3.6.4. Vital Signs

BP and PR will be measured at times specified in the SoA of this protocol. Additional collection times, or changes to collection times, of BP and PR will be permitted, as necessary, to ensure appropriate collection of safety data. Baseline will be the measurement taken prior to administration of study treatment at Visit V3 (Day 1). Change from baseline will be the measurement at follow-up minus the measurement at baseline.

3.6.5. ECGs

12-Lead ECGs should be collected at times specified in the SoA.

Baseline will be the measurement taken prior to administration of study treatment at Visit V3 (Day -1). For change from baseline assessment, it will be the measurement at follow-up minus the measurement at baseline.

4. ANALYSIS SETS

Data for all subjects will be assessed to determine if subjects meet the criteria for inclusion in each analysis population prior to unblinding and releasing the database and classifications will be documented per standard operating procedures.

4.1. Full Analysis Set

All subjects who meet the criteria stated below will be included in the Full analysis set (FAS:

- Completed baseline assessment of food intake;
- Received at least one dose of randomized, blinded IP; AND
- Completed at least one post-baseline measurement (after taking randomized IP).

This also implies that subjects who withdraw prior to tolerating liraglutide 1.8 mg daily will not be included in the efficacy analysis (per protocol Section 9.2). Subjects who only complete V4 (or week 3 visit) will be included in the efficacy analysis.

4.2. Safety Analysis Set

All subjects who receive at least one dose of study medication classified according to the actual study treatment received. The safety analysis set is the primary population for treatment administration/compliance and safety. A randomized but not treated subject will be excluded from the safety analyses. A treated but not randomized subject will be reported under the treatment actually received.

4.3. Other Analysis Sets

The acetaminophen PK analysis set will consist of all subjects who received at least one dose of acetaminophen and has one quantifiable acetaminophen concentration. CCI [redacted]

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

The null hypothesis to be tested is that the difference between liraglutide and placebo is greater than or equal to 0 after 6 weeks of dosing vs. the alternative hypothesis that the difference between liraglutide and placebo is less than 0 after 6 weeks of dosing. Liraglutide will be considered superior to placebo with respect to mean energy intake during ad libitum

lunch meals if the difference is less than 0 and is statistically significant at the one-sided 0.05 level.

6. GENERAL METHODS

6.1. Analyses for Binary Data

Not applicable.

6.2. Analyses for Continuous Data

A linear mixed-effect repeated measures model with fixed effects for treatment, time (visit), a treatment by time interaction, baseline value of energy intake, and a random effect for subject, will be used to analyze the change from baseline in energy intake (this will be denoted as the primary analysis). A sensitivity analysis will conducted that will also include effects for baseline value of energy intake by treatment interaction and baseline body weight and gender in the model. The estimation method used will be restricted maximum likelihood. Due to the unknown nature of the longitudinal data, different covariance structures among repeated measures will be examined based on model diagnostics. Different covariance structures such as unstructured, compound symmetric and AR1, and so on will be tested. The model resulting in the lowest Aikaike Information Criteria (AIC) will be used. Using this model, 95% confidence intervals comparing the mean change from baseline in EI estimates at Week 6 for liraglutide vs. placebo will be computed.

6.3. Analyses for Categorical Data

Not applicable.

6.4. Analyses for Time to Event Data

Not applicable.

6.5. Methods to Manage Missing Data

No adjustments for missing data will be made except for PK data.

In all PK data presentations (except listings), concentrations below the limit of quantification (BLQ) will be set to zero. (In listings BLQ values will be reported as "<LLQ", where LLQ will be replaced with the value for the lower limit of quantification.)

In summary tables and plots of median profiles, statistics will be calculated having set concentrations to missing if 1 of the following cases is true:

A concentration has been collected as ND (ie, not done) or NS (ie, no sample),

A deviation in sampling time is of sufficient concern or a concentration has been flagged anomalous by the pharmacokineticist.

Note that summary statistics will not be presented at a particular time point if more than 50% of the data are missing.

7. ANALYSES AND SUMMARIES

7.1. Primary Endpoint(s)

7.1.1. Mean energy intake (in Kcal) during ad libitum lunch meals

7.1.1.1. Primary Analysis

Endpoints: Change from baseline in energy intake during ad libitum lunches

- Analysis time points**:** Visit V4 and Visit V5 (primary endpoint)
- Analysis population: FAS
- Analysis methodology**:** MMRM model (specified in Section 6.2).

Reporting results:

Raw data: The available sample size (ie, sample size available for this endpoint), mean, standard deviation, median, minimum and maximum at baseline and post-baseline will be presented for each treatment arm.

- Change from baseline: The sample size, mean, standard deviation, median, minimum and maximum will be presented for each treatment arm. The LS means, 95% confidence interval for the LS means, difference between the LS means and the corresponding 95% confidence interval will be presented.

  Figures

  Line plot of LS means andplacebo-adjusted LS means and 95% confidence interval at Visit V4 and Visit V5.

7.1.2. Sensitivity/Robustness Analyses

The primary endpoint analysis will be repeated adding a treatment by baseline energy intake interaction, baseline body weight and gender to the model.

7.2. Secondary Endpoint(s)

The secondary endpoints of 48-hour energy intake, appetite and satiety scores, CCI [redacted] will be analyzed using the same methods as the primary endpoint.

7.2.1. 48-hour Energy Intake

Endpoints: Change from baseline in 48-hour energy intake

- Analysis time points**:** Visit V4 and Visit V5
- Analysis population: FAS
- Analysis methodology**:** MMRM model (specified in Section 6.2).

Reporting results:

Raw data: The available sample size, mean, standard deviation, median, minimum and maximum at baseline and post-baseline will be presented for each treatment arm.

- Change from baseline: The sample size, mean, standard deviation, median, minimum and maximum will be presented for each treatment arm. The LS means, 95% confidence interval for the LS means, difference between the LS means and the corresponding 95% confidence interval will be presented.

  Figures

  Line plot of LS means and placebo-adjusted LS means and 95% confidence interval at Visit V4 and Visit V5.

7.2.2. Appetite and Satiety Scores

Endpoints: Change from baseline in appetite and satiety scores

- Analysis time points**:** all post-baseline visits
- Analysis population: FAS
- Analysis methodology**:** MMRM model (specified in Section 6.2).

Reporting results:

Raw data: The available sample size, mean, standard deviation, median, minimum and maximum at baseline and post-baseline will be presented for each treatment arm.

- Change from baseline: The sample size, mean, standard deviation, median, minimum and maximum will be presented for each treatment arm. The LS means, 95% confidence interval for the LS means, difference between the LS means and the corresponding 95% confidence interval will be presented.

  Figures

  Line plot of LS means and placebo-adjusted LS means and 95% confidence interval at Visit V4 and Visit V5.

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7.4. Other Endpoint(s)

7.4.1. Pharmacokinetics

Actual PK sampling times will be used in the derivation of PK parameters.

If a PK parameter cannot be derived from a subject's concentration data, the parameter will be coded as NC (ie not calculated). (Note that NC values will not be generated beyond the day that a subject discontinues.)

In summary tables, statistics will be calculated by setting NC values to missing; and statistics will be presented for a particular dose with ≥3 evaluable measurements.

If an individual subject has a known biased estimate of a PK parameter (due for example to an unexpected event such as vomiting before all the compound is adequately absorbed in the body), this will be footnoted in summary tables and will not be included in the calculation of summary statistics or statistical analyses.

Each acetaminophen PK parameter will be summarized by visit (V3, V4 and V5) and will include the set of summary statistics as specified in the table below:

Single Dose	
$AUC_{0\text{-}60}$, $AUC_{0\text{-}300}$, $AUC_{0\text{-}60}/AUC_{0\text{-}300}$,$C_{max}$,	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.
T_{max}	N, median, minimum, maximum

Presentations for acetaminophen concentrations will include:

- A listing of all concentrations sorted by subject ID, treatment arm (active vs. placebo) and nominal time post acteminophen dose. The concentration listing will also include the actual times. Deviations from the nominal time will be given in a separate listing. The listing will also capture for active arms what liraglutide dose the subject was on when the acetaminophen measurement was taken.

- A summary of concentrations by treatment arm and nominal time post-acetaminophen dose, where the set of statistics will include n, mean, median, standard deviation, coefficient of variation (cv), minimum, maximum and the number of concentrations above the lower limit of quantification.

- Median concentrations time plots (on both linear and semi-log scales) against nominal time post-dose by treatment (active vs. placebo) and visit (all treatments on the same plot per scale, based on the summary of concentrations).

- Mean concentrations time plots (on both linear and semi-log scales) against nominal time post-dose by treatment (active vs. placebo) and visit (all treatments on the same plot per scale, based on the summary of concentrations).

- Individual concentration time plots by treatment and visit (on both linear and semi-log scales) against actual time post-dose.

- Individual concentration time plots by subject (on both linear and semi-log scales) against actual time post-dose.

The length of time used for the x-axes of these plots will be decided on review of the data, and will depend on how long acetaminophen concentration is quantifiable in the matrix.

For summary statistics, median and mean plots by sampling time, the nominal PK sampling time will be used, for individual subject plots by time, the actual PK sampling time will be used.

There will be 1 summary table presenting all acetaminmophenacetaminophen PK parameters. This will include data from both treatment groups and will be paged by visit. The treatment subheading will include the treatment details (active vs. placebo) and visit information.

A listing of the liragultide steady state concentrations may be reported.

Endpoints: Absolute and change from baseline in plasma area under the curve (AUC) of acetaminophen for 0-60 mins and 0-300 minutes after acetaminophen administration

- Analysis time points**:** visits V4 and V5
- Analysis population: FAS
- Analysis methodology**:** MMRM model (specified in Section 6.2).

Reporting results:

Raw data: The sample size, mean, standard deviation, median, minimum and maximum at baseline and post-baseline will be presented for each treatment arm.

- Change from baseline: The sample size, mean, standard deviation, median, minimum and maximum will be presented for each treatment arm. The LS means, 95% confidence interval for the LS means, difference between the LS means and the corresponding 95% confidence interval will be presented.

  Figures

  - Mean concentration curves by treatment group and visit.
  - Line plot of LS means and 95% confidence interval at Visit V4 and Visit V5.
  - Line plot of descriptive means for area under the curve (0-300 mins) and 95% confidence interval at Visit V4 and Visit V5.

Endpoints: T_{max} and C_{max} after acetaminophen administration

- Analysis time points**: V**isits V3, V4 and V5

- Analysis population: FAS
- Analysis methodology: Summary Statistics

Reporting results:

Raw data: The sample size, mean, standard deviation, median, minimum and maximum at baseline and post-baseline will be presented for each treatment arm.

Change from baseline: For C_{max} the sample size, mean, standard deviation, 95% confidence interval median, minimum and maximum will be presented for each treatment arm.

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7.6. Baseline and Other Summaries and Analyses

7.6.1. Baseline Summaries

Demographics and medical history variables will be summarized by treatment group using the FAS.

7.6.2. Study Conduct and Subject Disposition

Subject evaluation groups will show end of study subject disposition and will show which subjects were analyzed in the full analysis set and as well as for safety. Frequency counts will be supplied for subject discontinuations by treatment.

Data will be reported in accordance with reporting standards.

7.6.3. Study Treatment Exposure

A summary of the number of doses received as well as the median total dose by visit and treatment group will be provided.

7.6.4. Concomitant Medications and Non-Drug Treatments

All concomitant medication(s) as well as non-drug treatment(s) will be provided in the listings.

7.7. Safety Summaries and Analyses

7.7.1. Adverse Events

Adverse events will be tabulated and reported by treatment and time, according to sponsor reporting standards.

7.7.2. Suicidality Assessment

Baseline for CSSRS is defined as the measure on Visit V3 (Day -2). Data relevant to the assessment of suicidality will be mapped to the Columbia-Classification Algorithm of Suicide Assessment (C-CASA) codes as given in Appendix 4. Baseline and post-baseline CSSRS data (mapped to C-CASA scores) will be summarized categorically by treatment group at baseline and each post-baseline visit. Categorical summaries of the PHQ-9 will be presented by treatment group at baseline and post-baseline visits.

7.7.3. Laboratory Data

Laboratory data will be listed and summarized by treatment in accordance with the sponsor reporting standards. Baseline is as defined in Section 3.6.2.

7.7.4. Vital Signs

Absolute values and changes from baseline in systolic and diastolic blood pressure, pulse rate will be summarized by treatment and time post-dose, according to sponsor reporting standards. Baseline is as defined in Section 3.6.3.

7.7.5. Electrocardiogram

Categorical summary tables will be summarized by treatment and time post-dose using sponsor reporting standards. Baseline is as defined in Section 3.6.4. Potential effects of Liraglutide on ECG parameters will be assessed using the following:

- Descriptive statistics for PR, QRS, QT, QTcF, QTcB, and HR, and change from baseline in those parameters summarized by treatment and time postdose.

- Categorical comparisons of maximum individual increase from baseline and post-dose QTcF and QTcB intervals by treatment group. The categories are included in Appendix 3. The number and percentage of subjects in each category will be tabulated by treatment group.

Standard algorithms and reporting formats will be applied. A listing of ECG comments on findings and normal/abnormal results will be provided.

7.7.6. Physical Examination

All physical exam data will be provided in the listings.

8. INTERIM ANALYSES

Not applicable.

9. REFERENCES

1. A9001498 Protocol 21st November, 2016.

2. Flint A, Kapitza C, Zdravkovic M. The once-daily human GLP-1 analogue liraglutide impacts appetite and energy intake in patients with type 2 diabetes after short-term treatment. Diabetes Obes Metab. 2013; 15(10):958-62.

3. Van Can J, Sloth B, Jensen CB, et al. Effects of the once-daily GLP-1 analog liraglutide on gastric emptying, glycemic parameters, appetite and energy metabolism in obese, non-diabetic adults. Int J Obes (Lond). 2014; 38(6):784-93.

10. APPENDICES

Appendix 1. Summary of Efficacy Analyses

Endpoint	Analysis Set	Statistical Method	Model	Missing Data	Interpretation
Change from baseline in energy intake during lunch	FAS	MMRM	Treatment, Visit, Treatment by Visit, baseline energy intake	None	Primary
Change from baseline in energy intake during lunch	FAS	MMRM	Treatment, visit, Treatment by Visit, baseline energy intake, treatment by baseline energy intake, baseline weight, gender	None	Sensitivity
Change from baseline in 48-hour intake	FAS	MMRM	Treatment, Visit, Treatment by Visit, baseline energy intake	None	Secondary
CCI [redacted]					
Change from baseline in appetite and satiety scores	FAS	MMRM	Treatment, Visit, Treatment by Visit, baseline energy intake	None	Secondary
CCI [redacted]					

Appendix 2. Example SAS code for primary analysis

```
PROC MIXED data=new covtest;
CLASS subjid treatmnt xvisit;
MODEL FI_CHG=treatmnt xvisit treatmnt*xvisit baseline /alpha=0.05 cl ddfm=kr;
REPEATED xvisit/TYPE=un SUBJECT=subjid;
lsmeans treatmnt*xvisit/cl pdiff alpha=0.05;
run;
```

Appendix 3. Categorical Classes for ECG and Vital Signs

Categories for QTcF

QTcF (ms)	450≤ max. <480	480≤ max.<500	max. ≥500
QTcF (ms) increase from baseline	30≤ max. <60	max. ≥60	

Categories for PR and QRS

PR (ms)	max. ≥300	
PR (ms) increase from baseline	Baseline >200 and max. ≥25% increase	Baseline ≤200 and max. ≥50% increase
QRS (ms)	max. ≥200	
QRS (ms) increase from baseline	Baseline >100 and max. ≥25% increase	Baseline ≤100 and max. ≥50% increase

Categories for Vital Signs

Systolic BP (mm Hg)	min. <90	
Systolic BP (mm Hg) change from baseline	max. decrease ≥30	max. increase ≥30
Diastolic BP (mm Hg)	min. <50	
Diastolic BP (mm Hg) change from baseline	max. decrease ≥20	max. increase ≥20
Supine pulse rate (bpm)	min. <40	max. >120
Standing pulse rate (bpm)	min. <40	max. >120

Appendix 4. C-SSRS Mapped to C-CASA

Table 3. C-CASA Suicidality Events and Codes

Event Code	Event
1	Completed suicide
2	Suicide attempt
3	Preparatory acts towards imminent suicidal behavior
4	Suicidal ideation
5	Self-injurious behavior, intent unknown
6	Not enough information, fatal
7	Self-injurious behavior, no suicidal intent
8	Other, accident, psychiatric; mental
9	Not enough information, non fatal

* Note: Event Codes 5, 6, 8 and 9 are not applicable to prospectively collected data

Table 4. C-SSRS Mapped to C-CASA (Suicidality Events and Codes)

C-CASA Event Code	C-CASA Event	C-SSRS Response
1	Completed suicide	As captured in the safety database
2	Suicide attempt	"Yes" on "Actual Attempt"
3	Preparatory acts towards imminent suicidal behavior	"Yes" on any of the following: "Aborted attempt", or "Interrupted attempt", or "Preparatory Acts or Behavior"
4	Suicidal ideation	"Yes" on any of the following: "Wish to be dead", or "Non-Specific Active Suicidal Thoughts", or "Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act", or "Active Suicidal Ideation with Some Intent to Act, without Specific Plan", or "Active Suicidal Ideation with Specific Plan and Intent"
7	Self-injurious behavior, no suicidal intent	"Yes" on "Has subject engaged in Non-suicidal Self-Injurious Behavior?"