STATISTICAL ANALYSIS PLAN

NCT Number: NCT04465396

Study Title: A Randomized, Open-label, Two-treatment, Two-period, Single-dose, Crossover Study to Evaluate the Bioavailability of Teduglutide Administered Subcutaneously by Syringe Injection Versus Pen Injector in Healthy Adult Subjects

Study Number: TAK-633-1001

SAP Version and Date:

Final Version: 26 Mar 2021

[redacted]

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CELERION STUDY NUMBER: CA29179

A Randomized, Open-label, Two-treatment, Two-period, Single-dose, Crossover Study to Evaluate the Bioavailability of Teduglutide Administered Subcutaneously by Syringe Injection Versus Pen Injector in Healthy Adult Subjects

PHASE 1

Version: Final

Date: 26 March 2021

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1.1 Approval Signatures

Electronic signature can be found on the last page of this document.

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Approvals:

01-Apr-2021 | 12:12:49 JST

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2.0 TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

3.0 LIST OF ABBREVIATIONS

AE	adverse event
ANOVA	analysis of variance
AUC_∞	area under the concentration-time curve from time 0 to infinity, calculated using the observed value of the last quantifiable concentration.
[redacted]	[redacted]
AUC_{last}	area under the concentration-time curve from time 0 to time of the last quantifiable concentration
BLQ	below the lower limit of quantitation
BMI	body mass index
CI(s)	confidence interval(s)
CL/F	apparent clearance after extravascular administration, calculated using the observed value of the last quantifiable concentration.
C_{max}	maximum observed concentration
CRF	case report form
CRU	clinical research unit
CV%	arithmetic percent coefficient of variation
DMP	data management plan
ECG	electrocardiogram
Geom CV%	geometric percent coefficient of variation
Geom Mean	geometric mean
GMR(s)	geometric least-squares mean ratio(s)
ICF	informed consent form
kg	kilogram
LSM(s)	least-squares mean(s)
MedDRA®	Medical Dictionary for Regulatory Activities®
mg	milligram
n	number of observations
PK	pharmacokinetic(s)
SAE(s)	serious adverse event(s)
SC	subcutaneous
SD	standard deviation
SEM	standard error of the mean
SOC	system organ class
$t_{1/2z}$	terminal disposition phase half-life
TEAE(s)	treatment-emergent adverse event(s)
TFL(s)	tables, figures, and listings
t_{max}	time of first occurrence of C_{max}
V_z/F	apparent volume of distribution during the terminal disposition phase after extravascular administration, calculated using the observed value of the last quantifiable concentration.
WHO	World Health Organization
λ_z	terminal disposition phase rate constant

Note: The PK parameters presented in the clinical study report (CSR) and in the in-text tables will be subscripted, whereas the PK parameters presented in the end-of-text tables will not be subscripted. In addition, AUC_∞ and λ_z will be presented as AUCinf and Lambdaz in the end-of-text tables, respectively.

4.0 OBJECTIVES

4.1 Primary Objective

To evaluate the bioavailability of teduglutide following the administration of a single subcutaneous (SC) fixed dose of 3 mg or 4 mg teduglutide (depending upon subjects assignment in one of two cohorts as defined by body weight) administered via manual injection or via pen injector in healthy subjects.

4.2 Secondary Objectives

To evaluate the bioavailability of teduglutide, by injection site (ie, thigh, abdomen, and arm), following the administration of a single SC fixed dose of 3 mg or 4 mg teduglutide (depending upon subjects assignment in one of two cohorts as defined by body weight) administered via manual injection or pen injector in healthy subjects.

To evaluate other PK parameters of teduglutide, as appropriate, following the administration of a single dose of teduglutide administered via manual injection or pen injector in healthy subjects.

To assess the safety and tolerability of SC injections of teduglutide in healthy subjects.

To assess the safety and performance of the pen injector for SC drug administration in healthy subjects.

4.3 Study Design

This is a randomized, open-label, two-treatment, two-period, two-sequence, single dose, crossover bioavailability study in healthy adult subjects.

Subjects will undergo screening evaluations to determine eligibility within 28 days prior to first dosing.

Subjects will be enrolled into 1 of 2 cohorts based on their weight (≥40.0 kg to ≤75.0 kg [Cohort 1] and >75.0 kg to ≤120.0 kg [Cohort 2]). In each cohort, subjects will be admitted to the clinical facility the day prior to each dosing and will be confined at least 24 hours; subjects will be released following completion of the 24-hour study procedures in each period. On Day 1 of Period 1, subjects in each cohort will be randomized to 1 of 2 treatment sequences as indicated in Table 4:1 below. Fixed teduglutide doses (delivered by pen injector or from approved single-use vials) is 3 mg for subjects in Cohort 1 and 4 mg for subjects in Cohort 2. Each dose will be separated by a washout period of 7 days. Blood samples for teduglutide PK will be collected predose and for 24 hours following each teduglutide dose.

Table 4:1 Treatment Scheme for Each Cohort

Weightband	Cohort / Dose level	No. of Subjects	Sequence*	Treatment Period 1 (Day 1)	Washout Period (7 days)	Treatment Period 2 Day 1)
≥40.0 kg - ≤75.0 kg	Cohort 1 / 3mg	n=16	AB	Reference (fixed dose by vial and syringe)**	→	Test (fixed dose by pen injector)**
>75.0 kg - ≤120.0 kg	Cohort 2 / 4mg	n=16				
≥40.0 kg - ≤75.0 kg	Cohort 1 / 3mg	n=16	BA	Test (fixed dose by pen injector)**	→	Reference (fixed dose by vial and syringe)**
>75.0 kg - ≤120.0 kg	Cohort 2 / 4mg	n=16				

* To ensure adequate distribution across 3 injection sites (ie, thigh, abdomen, and arm), randomization will be stratified by injection site within each cohort.

**Fixed teduglutide doses (delivered by pen injector or from approved single-use vials) is 3 mg for subjects in Cohort 1 (≥40.0 kg - ≤75.0 kg) and 4mg for subjects in Cohort 2 (>75.0 kg - ≤120.0 kg).

Treatment A: Teduglutide administered by syringe injection

Treatment B: Teduglutide administered by pen injector

Safety and tolerability will be assessed by treatment-emergent adverse events (TEAEs), including injection site reaction and injection site injury assessments, clinical laboratory evaluations, physical examinations, and vital signs.

All subjects who received at least one dose of study drug (including subjects who terminate the study early) will be contacted by the clinical research unit (CRU) 7 (±2) days after the last study drug administration to determine if any AE has occurred since the last study visit.

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoints

- PK parameters: AUC_{last}, C_{max}, and AUC_{∞}

5.2 Secondary Endpoints

- PK parameters: AUC_{last}, C_{max}, and AUC_{∞} by injection site (ie, thigh, abdomen, and arm)
- PK parameters: t_{max}, λ_z, $t_{1/2z}$, CL/F, and V_z/F
- Occurrence of TEAEs, including injection site reactions and injection site injury assessments.
- Routine clinical safety monitoring that includes: vital signs, clinical laboratory test results (hematology, serum chemistry, coagulation (as appropriate), and urinalysis) and physical examinations.
- Occurrence of device malfunctions.

5.3 Additional Endpoints

- [redacted]

6.0 DETERMINATION OF SAMPLE SIZE

The overall power for the endpoints (AUC_{last}, AUC_{∞}, and C_{max}) with a total sample size of 64 subjects (32 subjects per cohort) will be 92.6% power based on a 5% type 1 error and a Coefficient of Variation of 21%, assuming a true ratio of test/reference of 1.0 in their relative bioavailabilities based on the acceptance interval of 80.00 to 125.00%, for this statistical comparison of each cohort. The sample size of 28 subjects within each cohort (14 each sequence) was accounted for approximately 10% potential drop-outs and/or non-evaluable concentration time-profiles to yield 32 subjects per cohort (16 subjects per sequence within each cohort). This sample size was calculated with SAS® v9.4.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

All PK analyses will be conducted using Phoenix® WinNonLin® Version 8.1, or higher. All statistical analyses will be conducted using SAS® Version 9.4, or higher. All data recorded on the case report form (CRF) will be listed by subject. All tables, figures, and listings (TFLs) shells and numbering list will be included and specified in the TFL Shells document.

The number of observations (n) will be presented as an integer (no decimal places), arithmetic mean (mean), median, and geometric mean (Geom Mean) values will be presented to 1 more level of precision than the individual values. Standard deviation (SD), 25th and 75th quantiles, and standard error of the mean (SEM) will be presented to 2 more levels of precision than the individual values. Minimum and maximum values will be presented to the same precision as the individual values. Arithmetic percent coefficient of variation (CV%) and geometric percent coefficient of variation (Geom CV%) will be presented to 1 decimal place.

Geometric least-squares means (LSMs) will be reported with 1 more level of precision than the individual data. Geometric least-squares mean ratios (GMRs) and 90% confidence intervals (CIs) around the ratio will be reported using 2 decimal places.

Concentration values below the lower limit of quantitation (BLQ) will be presented as 'BLQ' in the concentration table listings and footnoted accordingly. BLQ values will be treated as zero for the calculation of summary statistics, the generation of concentration plots, and the calculation of PK parameters, unless they are obvious outliers (eg, BLQ value between measurable values), in which case they will be treated as missing.

A subject's PK parameter data will be included in the listings but excluded from the descriptive and inferential (analysis of variance [ANOVA]) statistics if one or more of the following criteria are met:

- A predose (0 hr) concentration is greater than 5% of that subject's maximum concentration value in that period

- A subject did not meet inclusion/exclusion criteria that may have an effect on the PK (as determined by the Takeda Clinical Pharmacology Lead and Celerion Pharmacokinetic Scientist)
- A subject deviates substantially from the protocol defined study procedures including but not limited to dosing, dose timing, sample collection, meal timing, etc. (as determined by the Takeda Clinical Pharmacology Lead and Celerion Pharmacokinetic Scientist)

The details on PK parameter calculations and TFLs will be outlined in the Clinical Pharmacology Analysis Plan and TFL Shell document including specifics on the following:

- Insufficient data to determine a reliable $t_{1/2z}$ value and other terminal disposition phase rate constant (λ_z)-dependent parameters
- PK parameters presented by cohort and treatment, including the units, precision, and summary statistics that will be presented in in-text and end-of-text tables
- Concentration data presented by cohort and treatment, including the units, precision, and summary statistics that will be presented in end-of-text tables
- Concentration data file used for PK analysis
- PK parameter WinNonlin® output file used to generate the TFLs
- ANOVA results presented in in-text and end-of-text table(s).
- Concentration-time data will be plotted on linear and semi-log scales
- Concentration versus time figures for individual subjects presented in Appendix 16.2.6 of the CSR.

For demographic and safety data where appropriate, variables will be summarized descriptively. For the categorical variables, the count and proportions of each possible value will be tabulated, where applicable. The denominator for the proportion will be based on the number of subjects who provided non missing responses to the categorical variable. For continuous variables, the number of subjects with non-missing values, mean, SD, minimum, median, and maximum values will be tabulated. The level of precision will be presented as follows: minimum/maximum in the same precision as in the database, mean/median in one more precision level than minimum/maximum, SD in one more precision level than mean/median, and n will be presented as an integer. Counts and percentages will be presented as integers.

7.2 Definition of Study Days

Day 1 for each period is defined as the date on which a subject is administered their first dose of the study drug(s) in each period. Other study days are defined relative to Day 1 with Day -1 being the day prior to Day 1 of each period. Study day prior to the first dose of each treatment will be generated as: date of assessment-date of first dose in each period; study day on or after the date of first dose will be generated as: date of assessment-date of first dose in each period +1.

7.3 Analysis Sets

PK Set: All subjects who receive at least one dose of the study drug and have at least 1 quantifiable plasma concentration. All available data will be listed/included in the concentration and PK parameter tables to the extent possible.

PK Evaluable Set: A subset of the PK set; all subjects who comply sufficiently with the protocol and display an evaluable PK profile from which to calculate reliable estimates of the PK parameters (eg., exposure to treatment, availability of measurements in both periods, absence of major protocol violations or events with potential to affect the PK concentrations [eg., emesis], and absence of significant carryover [eg., predose concentration >5% C_{max}). This set will be used for the concentration summaries and mean figures, PK parameter summaries, and statistical analyses on relative bioavailability of treatments. Any subject or data excluded from the analysis will be identified, along with their reason for exclusion, in the CSR.

Safety Set: All subjects who received at least one dose of the study drug will be included in the safety evaluations.

7.4 Treatment Descriptions

Each cohort will receive two treatments.

For Cohort 1, treatments will be:

Treatment A1: a single subcutaneous dose of 3 mg teduglutide administered by syringe injection (Cohort 1)
Treatment B1: a single subcutaneous dose of 3 mg teduglutide administered by pen injector (Cohort 1)

For Cohort 2, treatments will be:

Treatment A2: a single subcutaneous dose of 4 mg teduglutide administered by syringe injection (Cohort 2)
Treatment B2: a single subcutaneous dose of 4 mg teduglutide administered by pen injector (Cohort 2)

Note: Treatments A1, B1, A2, and B2 may be labelled as 3 mg teduglutide (syringe injection), 3 mg teduglutide (pen injector), 4 mg teduglutide (syringe injection), and 4 mg teduglutide (pen injector), respectively, in the TFLs.

7.5 Study Information

A study information table will be generated including the following items: date of first subject's signed informed consent form, date of first dose, date of last dose, date of last subject's last visit/contact, date of last subject's last procedure for collection of data for primary endpoint, the

version of Medical Dictionary for Regulatory Activities (MedDRA®), the version of World Health Organization (WHO) Dictionary, and SAS version used for creating the datasets.

7.6 Disposition of Subjects

Disposition of subjects (number of subjects dosed, completed the study, discontinued from the study, and reason(s) for discontinuation) will be summarized by randomized treatment sequence and overall for each cohort. Randomized treatment sequence, and disposition information will be listed by subject.

7.7 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by randomized treatment sequence and overall for each cohort. Summary statistics (n, mean, SD, minimum, median, and maximum) will be generated for continuous variables (age [recorded in the CRF], weight, height and body mass index [BMI]) and the number and percentage of subjects within each category will be presented for categorical variables (sex, race, and ethnicity). Height, weight, and BMI recorded at screening will be used in the baseline summaries. Demographics data will also be listed as recorded on the CRF, including the date of informed consent.

7.8 Medical History and Concurrent Medical Conditions

Medical history will be obtained, including any significant conditions or diseases relevant to the disease under study that resolved at or before signing the informed consent form (ICF). Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing the ICF.

Each subject's medical history and concurrent medical conditions will be listed. Any medical condition started after taking the study drug(s) will be classified as an adverse event. All medical history may be coded using the Medical Dictionary for Regulatory Activities (MedDRA®), as described in the Data Management Plan (DMP). The medical history listing will include whether the event was medical or surgical, the body system or organ class involved, coded term, start date (if known) and end date or whether the condition was ongoing, and a description of the condition or event. There will be no analysis of medical history.

7.9 Medication History and Concomitant Medications

Medication history to be obtained includes any medication relevant to eligibility criteria and safety evaluation stopped at or within 28 days prior to signing the ICF. Concomitant medication includes any medication other than study drug taken at any time between time of signing the ICF through the end of the study (including follow-up visit). All medication history and concomitant medications recorded during the study will be coded with the WHO Dictionary, as described in the DMP, and listed. If appropriate, the listing will include the medication name, coded term, dosage, route of administration, start date and time (if known), end date and time, or whether it continued after study completion, and indication for use.

7.10 Study Drug Exposure and Compliance

The date, time, administration site, treatment (pen injector or syringe), and dosage of each teduglutide dose will be listed by subject.

7.11 Efficacy Analysis

Not applicable.

7.12 Pharmacokinetic/Pharmacodynamic Analysis

7.12.1 Pharmacokinetic Analysis

Blood samples for the assessment of plasma teduglutide concentrations will be collected as outlined in Table 7:1

Table 7:1 Collection of Blood Samples for Pharmacokinetic Analysis

Analyte	Matrix	Period	Scheduled Time (Hours)*
Teduglutide	Plasma	1 and 2	Predose, and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, and 24 hours postdose

*The actual date and time of sample collection will be recorded on the source document in the case report form.

Concentration data at each time point will be summarized by cohort and treatment using the following descriptive statistics: n, mean, SD, CV%, SEM, minimum, median, maximum, and 25^{th} and 75^{th} quantiles. Excluded concentrations will be presented and footnoted as such in the concentration table listings, and those values will be excluded from the calculation of descriptive statistics.

Individual concentration-time curves will be presented in linear/linear and log/linear scale. Figures showing the mean (with ±SD as error bars) as well as the median (with 25^{th} and 75^{th} quantile bars) concentration time profiles will be also presented in linear/linear and log/linear scale.

PK parameters will be calculated from evaluable teduglutide concentration-time profiles using non-compartmental methods where all calculations will be based on actual sampling times. PK parameters will be summarized by cohort, treatment, and injection site (ie, thigh, abdomen, and arm), using the following descriptive statistics: n, Mean, SD, CV%, SEM, minimum, median, maximum, Geom Mean, and Geom CV%. Excluded parameters will be presented and footnoted as such in the PK parameter table listings, and those values will be excluded from the calculation of descriptive statistics.

Statistical analysis of PK data will be based on the PK Evaluable Set. PK parameters AUC_{last}, AUC_{∞}, and C_{max}, will be analyzed using an ANOVA model for each cohort separately. PK parameters will be transformed prior to analysis using a logarithmic transformation. The difference in means and the corresponding two-sided 90% CI on the log-transformed scale will be obtained from that model. The difference in means and the corresponding CI will be

back-transformed to obtain the ratio of geometric means and the corresponding two-sided 90% CI for the ratio on the original scale. The terms used in the ANOVA model will be sequence, subject within sequence, period and treatment. According to EMA Guideline on the Investigation of Bioequivalence (EMA Guideline on the Investigation of Bioequivalence, CPMP/EWP/QWP/1401/98 Rev. 1/Corr**, London, 20 January 2010.), subjects who will not provide evaluable data for both periods will be excluded and fixed effects will be used for all terms.

To assess bioavailability between test (pen injector) and reference (syringe injection), the 90% CI for the ratio of geometric means for PK metrics, AUC_{last}, AUC_{∞}, and C_{max} will be derived and compared (and would be contained within the acceptance interval of 80.00 to 125.00% if bioequivalent).

The comparison of interest is as follows:

- Pen injector (Treatment B1) compared to syringe injection (Treatment A1) (Cohort 1)
- Pen injector (Treatment B2) compared to syringe injection (Treatment A2) (Cohort 2)

The following SAS code will be used to run the analysis in each cohort separately:

```
PROC MIXED DATA=XXXX;
CLASS Treatment Subject Period Sequence;
MODEL <PK_Parameter> = Treatment Period Sequence Subject(sequence) / DDFM=KR;
ESTIMATE 'Pen injector vs Syringe' Treatment -1 1 / CL ALPHA = 0.10 E;
LSMEANS Treatment;
Run;
```

7.12.2 Pharmacodynamic Analysis

Not applicable.

7.13 Safety Analysis

For each cohort, safety will be evaluated by the incidence of TEAEs (including injection site reactions and injection site injuries), severity and type of TEAEs, summary of device malfunction (pen injector), changes from baseline in the subjects' clinical laboratory results and vital signs using the Safety Set. All clinical safety data will be listed by subject and assessment time points, including rechecks, unscheduled assessments, and early termination, chronologically.

Where individual data points are missing because of dropouts or other reasons, the data will be summarized based on reduced denominators.

7.13.1 Adverse Events

All AEs captured in the database will be listed in by-subject data listings including verbatim term, coded term, severity (mild, moderate, severe), relationship to study drug (related or not related) and action relative to the study drug as recorded in the CRF. Study procedure taken due to AE will also be listed. All AEs occurring during this study will be coded using the MedDRA®, as described in the DMP. However, only TEAEs occurring after administration of the first dose of study drug and through the end of the study (approximately 7 (± 2) days after the last dose of study drug administration) will be summarized.

A TEAE is defined as an AE that is starting or worsening at the time of or after study drug administration.

For each cohort and treatment, TEAEs (including injection site reactions and injection site injuries recorded as AEs) will be coded using MedDRA® and tabulated by System Organ Class (SOC) and Preferred Term. Summary tables will include number of subjects reporting the AE and as percent of Safety Set by treatment and overall. The most commonly reported non-serious TEAEs (i.e., those events reported by >5% of all subjects in each treatment, excluding serious adverse events [SAEs]) will also be summarized. For the list of all AE summary table see TFL Shells.

In addition, TEAEs will be summarized as number of AEs and percentage of AEs for each treatment for the overview of TEAEs.

Additional TEAE summary tables will be presented by severity and relationship to study drug. If a subject has multiple AEs with different severity levels within the same term, the subject will be counted in the most severe category only. For each relationship to study drug, if a subject has both related and unrelated AEs with the same term, the subject will be counted as having related TEAEs.

Should any SAEs (including all-cause mortalities) occur, they will be summarized the same way as TEAE. All AEs will be displayed in the data listings and TEAEs will be discussed in the text of the CSR.

7.13.2 Injection Site Reaction and Injection Site Injury Assessment

Local tolerability, reactions, and injuries at the injection site will be evaluated by the investigator/designee prior to dosing, 2 minutes after dosing, and 0.5 1, 2, 4, 6, 8, 12, and 24 hours postdose in each period.

Additionally, subjects will be instructed to report the development of rash, hives, pruritus, flushing, urticaria, injection site pain, redness, bruising, and/or swelling, etc, that may represent an administration-related reaction or injury to the study medication or administration method. Subjects will be asked to report AEs to the CRU staff immediately as they are experienced.

Appropriate treatment and follow-up will be determined by the investigator. Any injection site reaction or injury will be collected and graded as mild, moderate, or severe.

All injection site reaction and injection injury assessment data recorded in the CRF will be listed by cohort, subject, and treatment. Injection site reactions and injection injuries recorded as AEs will be included in the TEAE summaries.

7.13.3 Clinical Laboratory Evaluations

Serum chemistry, hematology, coagulation (as appropriate) and urinalysis will be performed at screening, check-in (Day -1) of each period, 24 hours postdose of each period or prior to early termination from the study. In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the investigator.

For all laboratory values that are numeric, summary statistics (n, mean, SD, minimum, median, and maximum) will be presented for each laboratory test by cohort, treatment and time point of collection. Change from baseline will be summarized. Baseline is defined as the last assessment including rechecks taken prior to dosing in each period (Day -1 Check-in).

For each laboratory test, a shift table will be developed comparing the frequency of the results at baseline (above normal (H), normal (N), or below normal (L)) with those postdose time points. For urinalysis tests, the categories are normal (N) and abnormal (A). Out-of-range values and corresponding recheck results will be listed.

Out-of-normal range flags will be recorded as follows: high (H) and low (L) for numerical results and did-not-match (*) for categorical results. If a value fails the reference range, it will automatically be compared to a computer clinically significant (CS) range. If the value falls within the computer CS range, it will be noted as “N” for not clinically significant. If the value fails the computer CS range, it will be flagged with a “Y” which prompts the investigator to determine how the out-of-range value should be followed using 4 Investigator flags: "N", not clinically significant, "R", requesting a recheck, "^", checking at the next scheduled visit, or "Y", clinically significant. All clinically significant laboratory tests, as indicated by the investigator, and the corresponding values will be listed by subject. All clinical laboratory data will be presented in by-subject data listings.

7.13.4 Vital Signs

Single measurements of body temperature, respiratory rate, blood pressure (systolic and diastolic), and heart rate, will be obtained at screening, predose, and at 2 and 24 hours postdose in each period or upon early termination. Additional unscheduled vital signs measurements may be taken at other times, if deemed necessary by the investigator.

Summary statistics (n, mean, SD, minimum, median, and maximum) will be reported for vital sign results and change from baseline by cohort, treatment and time point of collection. Baseline is defined as the last assessment, including rechecks, taken prior to dosing (predose) in each treatment. Vital signs will also be displayed in a data listing by subject.

7.13.5 12-Lead ECGs

Single12-lead ECGs will be recorded at screening. Additional unscheduled ECGs may be recorded at other times if deemed necessary by the investigator. All ECG data collected during the study will be displayed in a data listing by subject. No summaries will be provided for ECG data.

7.13.6 Physical Exams

A full physical examination will be performed at screening and prior to discharge in Period 2, or upon early termination. An abbreviated physical examination will be performed at check-in for each period and prior to release at Period 1. Symptom driven physical exams may be performed at other times at the discretion of the investigator. Physical exam findings will be presented in a data listing by subject. Reproductive system findings will also be listed by subject.

7.13.7 Overdose

All cases of overdose will be presented in a data listing by subject. Any AEs associated with overdose will be documented as AEs.

7.13.8 Device Malfunction Assessment

A device malfunction assessment will be performed on the pen injector during preparation, immediately prior, and post teduglutide administration. All device malfunction assessment data, as recorded on the CRF, will be listed by subject and summarized by cohort using the number and percentage of events.

7.13.9 Other Observations Related to Safety

Not applicable.

7.14 Interim Analysis

Not applicable.

7.15 Preliminary Analysis

Analysis will be completed as described in the CPAP and Section 7.12.1 of the SAP, with the following changes: 1) QCed data will be used (not QAed); 2) nominal times will be used for the calculation of PK parameters (not actual sampling times); 3) tables and figures will be created using Phoenix® WinNonlin® Version 8.1 or higher.

7.16 Changes in the Statistical Analysis Plan

The analyses described in this statistical analysis plan do not differ from those specified in the protocol.

8.0 REFERENCES

EMA Guideline on the Investigation of Bioequivalence, CPMP/EWP/QWP/1401/98 Rev. 1/Corr**, London, 20 January 2010.