Title: A Phase 1, Open-Label, Randomized, Single Dose, 5-Period, 5-Treatment, Study to Evaluate the Relative Bioavailability and Effect of Food on TAK-831 Tablet Formulations in Healthy Subjects

NCT Number: NCT03706469

SAP Approve Date: 19 December 2018

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This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-831-1006
CELERION STUDY NUMBER: CA24822

A Phase 1, Open-Label, Randomized, Single Dose, 5-Period, 5-Treatment, Study to Evaluate the Relative Bioavailability and Effect of Food on TAK-831 Tablet Formulations in Healthy Subjects

PHASE 1

Version: Final

Date: 19 December 2018

Prepared by:

PPD

Based on:

Protocol Dated: 26 September 2018

1.1 Approval Signatures

Study Title: A Phase 1, Open-Label, Randomized, Single Dose, 5-Period, 5-Treatment, Study to Evaluate the Relative Bioavailability and Effect of Food on TAK-831 Tablet Formulations in Healthy Subjects

PPD

2.0 TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

3.0 LIST OF ABBREVIATIONS

AE	adverse event
AUC	area under the curve
AUC0-inf	area under the plasmaconcentration-time curve from time 0 to infinity
AUClast	area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration.
BLQ	below the limit of quantitation
BMI	body mass index
CI	confidence interval
Cmax	maximum observed plasma concentration
CPAP	Clinical Pharmacology Analysis Plan
CRF	case report form
CS	clinically significant
CSR	clinical study report
CV	coefficient of variation
ECG	electrocardiogram
eCRF	electronic case report form
Geom CV	geometric coefficient of variation
Geom Mean	geometric mean
ICF	informed consent form
ICH	International Conference on Harmonisation
ln	natural log
LSM	least-square means
Mean	arithmetic mean
MedDRA	Medical Dictionary for Regulatory Activities
PI	Principal Investigator
PK	pharmacokinetics
SAE	serious adverse event
SD	standard deviation
SEM	standard error of the mean
SOC	system organ class
t½	terminal disposition phase half-life
TEAE	treatment-emergent adverse event
TFL	tables, figures and listings

Tmax	time to first occurrence of Cmax
WHO	World Health Organisation

4.0 OBJECTIVES

4.1 Primary Objectives

- To assess the oral bioavailability (BA) of TAK-831 T3 tablet formulation relative to TAK-831 T2 tablet formulation under fasting conditions.
- To assess the effect of food on the pharmacokinetics (PK) of TAK-831 T3 tablet formulation.

4.2 Secondary Objective

To determine the safety and tolerability of single doses of TAK-831 T2 and T3 tablet formulations.

4.3 Study Design

This is an open-label, 5-period, 5-treatment, relative BA and food-effect study in 16 healthy adult subjects. On Day 1 of each treatment period, subjects will receive a single dose of study drug. In Treatment Periods 1 – 4, each subject will receive 2 dose levels of the T2 formulation and 2 doses of the T3 formulation under fasted, per the randomization schedule, to assess the relative BA of the 2 formulations. In Treatment Period 5, all subjects will receive a single oral dose of T3 formulation under fed conditions, in order to assess the food effect. There will be a washout period of at least 7 days between each dose.

A summary of the treatments is presented in Table 4.a.

Table 4.a Summary of Treatments

Treatment	Formulation	TAK-831 Dose	Treatment/meal condition (a)
A	T2	50 (2 x 25 mg tablets)	Fasted (b)
B	T3	50 (2 x 25 mg tablets)	Fasted (b)
C	T2	600 (6 x 100 mg tablets)	Fasted (b)
D	T3	600 (2 x 300 mg tablets)	Fasted (b)
E	T3	600 (2 x 300 mg tablets)	Fed (c)

(a) All study drugs will be administered orally with approximately 240 mL of water. (b) In Treatments A, B, C, and D, subjects will fast overnight for at least 10 hours prior to each study drug administration. (c) In Treatment E, subjects will fast overnight for at least 10 hours until 30 minutes prior to their scheduled morning dose, when they will be given a high-fat breakfast to be entirely consumed within 30 minutes.

Sixteen subjects will be randomized to 1 of 4 treatment sequences in a 1:1:1:1 ratio. The sequences used in the randomization are detailed in Table 4.b below. Subjects will receive each treatment on one occasion.

Table 4.b Treatment Sequences

Sequences	Treatment Period 1	Treatment Period 2	Treatment Period 3	Treatment Period 4	Treatment Period 5
1 (n=4)	A	B	D	C	E
2 (n=4)	B	C	A	D	E
3 (n=4)	C	D	B	A	E
4 (n=4)	D	A	C	B	E

Subjects were screened up to 28 days prior to dosing, to determine eligibility before randomization. Eligible subjects returned to the clinic at Check-in (Day -1).

A schematic of the study design is included as Figure 4.a.

Figure 4.a Schematic of Study Design

Pretreatment Screening	Treatment Periods 1-5				Study Exit (a)	Follow up (b)
	Predose Assessments	Dosing and Study Assessments	Safety and PK Assessments			
Within 28 days prior to first dosing	Day -1	Day 1	Day 1-2	Days 3-4	Day 4 of Treatment Period 5	14 (±2) days after last dose
Outpatient Visit	←- - - - - - - - Confinement (a) (c) - - - - - - →				Outpatient Visits	

(a) At all times, a subject may be required to remain at the clinical research unit for longer at the discretion of the Investigator or designee.

(b) The clinic will contact all subjects (including subjects who terminate the study early) approximately 14 days after the last study drug administration to determine if any adverse events have occurred since the last study visit.

(c) Subjects will start the confinement on Day -1 and be released from confinement after Day 2 study assessments are complete and will return to the study site on Day 3 and Day 4 for subsequent safety and PK assessments.

Subjects for all treatment sequences will be kept in the study unit from Day -1 Check-in until at least 24 hours after dosing (Day 2) for safety and PK assessments before discharge. The minimum confinement will be 2 nights (Days -1 to 2, inclusively). Subjects will return to the study unit on Day 3 and Day 4 for PK and safety assessments. The clinic will contact all subjects (including subjects who terminate the study early) approximately 14 days after the last study drug administration to determine if any adverse events (AEs) have occurred since the last study visit.

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoints

The following plasma PK parameters will be analyzed following a single dose of TAK-831 on Day 1 of each treatment period:

- Area under the plasma concentration-time curve (AUC) from time 0 to time of the last quantifiable concentration (AUClast).
- AUC from time 0 to infinity (AUC0-inf).
- Maximum observed plasma concentration (Cmax).

5.2 Secondary Endpoint

The following safety variable will be used to characterize the safety and tolerability of TAK-831:

- Percentage of subjects who experience at least 1 treatment-emergent adverse event (TEAE).

5.3 Exploratory Endpoints

5.3.1 Safety Endpoints

CCI

[redacted]

5.3.2 PK Endpoints

CCI

[redacted]

6.0 DETERMINATION OF SAMPLE SIZE

A total of 16 subjects was randomized into 4 sequences in a ratio of 1:1:1:1. Assuming there were no more than 1 dropout in each sequence group, this would provide at least 12 observations for each of Treatments A, B, C, and D. Based on the intra-subject variability (CV = 24.49%) of AUC from Study TAK-831-1004, this provided a 2-sided 90% CI of the central value ratios (Treatment B versus Treatment A or Treatment D versus Treatment C) of (0.8484, 1.1787) if the observed central value ratio was 1. If the observed central value ratio was 1.2, the 90% CI would be (1.0180, 1.4144).

The study design provided at least 12 observations for each of Treatments D and E, which would provide a 2-sided 90% CI of the central value ratios (Treatment E versus Treatment D) of (0.8799, 1.1365) if the observed central value ratio was 1. If the observed central value ratio was 1.6, the 2-sided 90% CI would be (1.4078, 1.8184).

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

All PK analyses will be conducted using Phoenix® WinNonlin® Version 7.0, or higher. All statistical analyses will be conducted using SAS® Version 9.3, or higher.

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) 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 recorded data. Geometric LSMs are least-squares means derived from the analysis of variance (ANOVA) model for the analyses of ln-transformed AUClast, AUC0-inf, and Cmax which have been exponentiated to provide estimates on the original scale. The difference in the LSM on the ln-scale and associated 90% confidence intervals (CIs) will be exponentiated to produce geometric mean ratios of GMRs (presented as a %) and 90% CIs around the ratio and will be reported using 2 decimal places. These ratios will be expressed as a percentage relative to the reference treatment (i.e., Treatments A and C for relative BA assessment, and Treatment D for the food-effect assessment).

Concentration values below the 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 (e.g. BLQ value between 2 measurable values), in which case they will be treated as missing.

For the calculation of PK parameters, if actual times are missing, nominal times will be used instead.

A subject's PK parameter data will be included in the listings but excluded from the descriptive statistics and statistical evaluation if one or more of the following criteria are met:

- A predose (0 hr) concentration is greater than 5% of that subject's Cmax 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).

See Clinical Pharmacology Analysis Plan (CPAP) for details on the PK parameter calculations and data presentation including specifics on the following:

- Insufficient data to determine a reliable t½ value and other terminal elimination rate constant dependent parameters.
- PK parameters presented by treatment, including the units, precision, and summary statistics that will be presented in in-text and end-of-text tables.
- Concentration data presented by 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 tables, figures, and listings (TFLs).
- Dose-normalized PK parameters (DN_AUClast, DN_AUC0-inf, and DN_Cmax) will be determined by dividing each PK parameter with the treatment dose received.
- ANOVA results presented in in-text and end-of-text tables.
- Arithmetic mean concentration-time figures presented as in-text and end-of-text figures.
- Individual concentration-time figures presented in Appendix 16.2.6.

For demographic data where appropriate, variables will be summarized descriptively by treatment sequence and overall. For the categorical variables, the count and proportions of each possible value will be tabulated by treatment sequence, and overall, 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.

7.1.1 Study Definitions

7.1.2 Definition of Study Days

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

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 calculated as: date of assessment/event-date of treatment; study day on or after the date of first dose will be calculated as: date of assessment/event-date of treatment +1.

7.2 Analysis Sets

Safety Set:

All subjects who received at least one dose of the study drug(s) will be included in the safety evaluations. Subjects in this analysis set will be used for demographic, baseline characteristics and safety summaries.

PK Set:

Samples from all subjects will be assayed even if the subjects did not complete the study. All subjects who comply sufficiently with the protocol and display an evaluable PK profile (eg, exposure to treatment, availability of measurements and absence of major protocol violations) will be included in the statistical analyses. In terms of criteria for evaluable subjects, please see CPAP.

7.3 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 for each treatment sequence and overall. Study completion status, including reason for discontinuation, will also be listed by subject.

7.4 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment sequence and overall. Summary statistics (number of subjects [n], mean, SD, minimum, median, and maximum) will be generated for continuous variables (age [calculated from the date of signed Informed Consent Form [ICF], 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). For height the screening measurement will be reported but for weight and BMI the baseline value, which is the last observation prior to dosing, will be reported. The demographics

listing will also include protocol version and date, ICF version and date, the date of each signed the ICF.

7.5 Medical History and Concurrent Medical Conditions

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the disease under study that resolved at or before signing the 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 will be classified as an adverse event. The medical history listing will include whether the event was medical or surgical, the body system or organ class involved, 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 statistical analysis of medical history.

7.6 Medication History and Concomitant Medications

Medication history to be obtained includes any medication relevant to eligibility criteria and efficacy/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 World Health Organization (WHO) Dictionary Version 01-Sep-2018 and listed. The listing will include the medication name, 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.

7.7 Study Drug Exposure and Compliance

Not applicable.

7.8 Efficacy Analysis

Not applicable.

7.9 Pharmacokinetic/Pharmacodynamic Analysis

7.9.1 Pharmacokinetic Analysis

Blood samples (one 4 mL sample per scheduled time) for PK analysis of TAK-831 will be collected as specified in Table 7.a following administration of different formulations and/or different feeding conditions.

Table 7.a Collection of Blood Samples for Pharmacokinetic Analysis

Analyte	Matrix	Dosing Day	Scheduled Time (hours)
TAK-831	Plasma	1	Predose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, 48, and 72 hours after Day 1 dosing (a).

(a) If a subject experiences a serious adverse event (SAE), a blood sample for PK analysis should also be obtained at the unscheduled visit. PK samples will be collected at Early Termination at the discretion of the investigator.

The actual date and time of sample collection will be recorded on the source document and electronic case report form (eCRF).

The PK parameters of TAK-831 listed in the CPAP for this study will be determined from the concentration-time profiles for subjects in the PK set using a noncompartmental analysis method. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. If actual sample times are missing, nominal times may be used.

Concentrations will be listed and summarized descriptively by PK sampling time. Summary will be done by treatment using the summary statistics listed in the CPAP. Excluded concentrations will be presented and footnoted as such in the concentration table listings, and those values will be excluded from the descriptive summary statistics. Individual subject and arithmetic mean profiles of the concentration-time data will be plotted by treatment on linear (with and without SD) and semi-log scales. For summary statistics and arithmetic 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.

PK parameters will be summarized descriptively by treatment using the summary statistics listed in the CPAP. Excluded parameters will be presented and footnoted as such in the PK parameter table listings, and those values will be excluded from the descriptive summary statistics.

Relative Bioavailability (Treatments A-D)
Natural log (ln)-transformed AUClast, AUC0-inf, and Cmax will be analyzed using an ANOVA model. The model will include sequence, treatment, and treatment period as fixed effects, and subject nested within sequence as a random effect. Each ANOVA will include calculation of least-squares means (LSM) as well as the difference between treatment LSM. Geometric LSM ratios will be calculated using the exponentiation of the difference between treatment LSM from the analyses on the ln-transformed AUClast, AUC0-inf, and Cmax. These ratios will be expressed as a percentage relative to the reference treatments (ie, Treatments A and C for the relative BA assessment). The following SAS® code will be used for the analysis:

```
PROC MIXED DATA=XXXX;
CLASS Sequence Treatment Period Subject;
MODEL <PK_Parameter> = Sequence Treatment Period / DDFM=KR;
RANDOM Subject(Sequence);
ESTIMATE 'Treatment B vs A ' Treatment -1 1 0 0 / CL ALPHA = 0.10 E;
ESTIMATE 'Treatment D vs C ' Treatment 0 0 -1 1 / CL ALPHA = 0.10 E;
LSMEANS Treatment;
Run;
```

Consistent with the two one-sided test, 90% confidence intervals (CIs) for the ratios will be derived by exponentiation of the CIs obtained for the difference between treatment LSM resulting from the analyses on the ln-transformed AUClast, AUC0-inf, and Cmax. The CIs will be expressed as a percentage relative to the reference treatments (ie, Treatments A and C for the relative BA assessment). Bioequivalence (Treatment B versus Treatment A and Treatment D versus Treatment C) will be claimed if the 90% CIs of the ratios of geometric LSMs of PK parameters AUClast, AUC0-inf, and Cmax of TAK-831 fall entirely within 80.00-125.00%.

Food Effect (Treatments D and E)
Ln-transformed AUClast, AUC0-inf, and Cmax will be analyzed using an ANOVA model. The model will have treatment as a fixed-effect and subject as a random-effect to account for the correlation between the repeated measures on each subject. Each ANOVA will include calculation of LSM as well as the difference between treatment LSM. Ratios of geometric LSM will be calculated using the exponentiation of the difference between treatment LSM from the analyses on the ln-transformed AUClast, AUC0-inf, and Cmax. These ratios and associated 90% CI will be expressed as a percentage relative to Treatment D. The following SAS® code will be used for the analysis:

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

7.9.2 Pharmacodynamic Analysis

Not applicable.

7.10 Other Outcomes

Not applicable.

7.11 Safety Analysis

Safety will be evaluated by the incidence of TEAEs, severity and type of TEAEs, changes from baseline in the subjects' clinical laboratory results, vital signs, and ECG's using the safety set. Reasons for discontinuation will be tabulated. All clinical safety data will be listed by subject and assessment time points, including rechecks, unscheduled assessments, and early termination, chronologically.

Continuous variables will be summarized using n, mean, SD, minimum, median, and maximum. Frequency counts and percentages will be reported for categorical data when appropriate. Where individual data points are missing because of dropouts or other reasons, the data will be summarized based on reduced denominators.

7.11.1 Adverse Events

All AEs captured in the database will be listed in by-subject data listings including verbatim term, coded term, severity (mild, moderate or severe), relationship to study drug (related or not related) and action relative to the study drug. All AEs occurring during this study will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®), Version 21.1. However, only TEAEs occurring after administration of the first dose of study drug and through the end of the study (approximately 14 (± 2) days after the last dose of investigational product 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. If an AE increases in severity, that AE will be given a resolution date and time, and a new AE will be entered with the new severity. If the severity of an AE remains the same or decreases, the AE will be kept open through to resolution.

For each treatment, TEAEs will be coded using MedDRA® Version 21.1 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. The most commonly reported TEAEs (i.e., those events reported by >5% of all subjects in each treatment group or at least 2 subjects, excluding SAEs) will also be summarized. For the list of all AE summary table see CPAP.

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. 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 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 study report.

7.11.2 Clinical Laboratory Evaluations

Hematology, serum chemistry, and urinalysis will be performed at screening, check-in (Day -1) and Day 4 (hour 72) postdose in each period, or upon early termination. In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the Principal Investigator (PI).

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

For each laboratory test, a shift table will be developed comparing the frequency of the results at treatment baseline (above normal (H), normal (N), or below normal (L)) with those postdose time points for each regimen. 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 clinically significant (CS) range. If the value falls within the CS range, it will be noted as "N" for not clinical significant. If the value fails the CS range, it will be flagged with a "Y" which prompts the PI 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 lab tests and the corresponding values will be listed by subject. All clinical laboratory data will be presented in by-subject data listings.

7.11.3 Vital Signs

Single measurements of heart rate and blood pressure will be obtained at screening, check-in (Day -1), Day 1 predose, Day 1 Hour 1, Days 2, and Day 4 in each period, or upon early termination. Respiration rate, temperature, and orthostatic vital signs are collected at screening only. Additional unscheduled vital signs measurements may be taken at other times, if deemed necessary by the PI.

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

7.11.4 12-Lead ECGs

Standard 12-lead ECGs will be recorded at screening, check-in (Day -1), Day 1 predose; postdose at Hours 1 and 4, and Day 4 (Hour 72) in each period or upon early termination. Additional unscheduled ECGs may be recorded at other times if deemed necessary by the PI.

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

7.11.5 Physical Exams

A full physical exam will be performed at screening. Symptom driven physical exams may be performed at other times at the discretion of the PI. Physical exam findings will be presented in a data listing by subject. Reproductive system findings will also be listed by subject.

7.11.6 Columbia Suicidality Symptoms Rating Scale (C-SSRS)

The C-SSRS questionnaire will be administered at screening, check-in, and Day 4 (hour 72) in each period or upon early termination. At screening the C-SSRS Baseline/Screening version will be administered; at all other time points, the Since Last Visit version will be administered. C-SSRS findings will be presented in the data listings by subject.

7.11.7 Overdose

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

7.12 Interim Analysis

No interim analysis was performed.

7.13 Preliminary Analysis

Analysis will be completed as described in the CPAP and Section 7.9.1 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 7.0.

7.14 Changes in the Statistical Analysis Plan

Although not outlined in the protocol, dose-normalized PK parameters will also be determined by dividing the PK parameters AUClast, AUC0-inf, and Cmax by the treatment dose received, and descriptive statistics for each PK parameter will be summarized.

In the analysis of food effects a sequence fixed-effects was added to the statistical model to account for period-to-period variation.

There are no other changes in the statistical analysis plan.

8.0 REFERENCES

Not applicable.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Biostatistics Approval	20-Dec-2018 19:55 UTC
	Biostatistics Approval	20-Dec-2018 19:58 UTC
	Clinical Pharmacology Approval	20-Dec-2018 20:05 UTC
	Clinical Science Approval	21-Dec-2018 17:30 UTC