Title: A Single-Sequence, Open-Label, 2-Period, Crossover Study to Evaluate the Effect of the Proton Pump Inhibitor Esomeprazole on the Single-Dose Pharmacokinetics of Oral TAK-906 in Healthy Adult Subjects

NCT Number: NCT03849690

SAP Approve Date: 22 April 2019

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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-906-1006
CELERION STUDY NUMBER: CA27239

A Single-Sequence, Open-Label, 2-Period, Crossover Study to Evaluate the Effect of the Proton Pump Inhibitor Esomeprazole on the Single-Dose Pharmacokinetics of Oral TAK-906 in Healthy Adult Subjects

PHASE 1

Version: Final

Date: 22 April 2019

Prepared by:

PPD

Based on:

Protocol Dated: 04 February 2019

1.1 Approval Signatures

Study Title: A Single-Sequence, Open-Label, 2-Period, Crossover Study to Evaluate the Effect of the Proton Pump Inhibitor Esomeprazole on the Single-Dose Pharmacokinetics of Oral TAK-906 in Healthy Adult Subjects

PPD

2.0 TABLE OF CONTENTS

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LIST OF IN-TEXT FIGURES

3.0 LIST OF ABBREVIATIONS

AE	adverse event
ANOVA	analysis of variance
AUC	area under the curve
AUCinf	area under the plasma concentration-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
CL/F	apparent total plasma clearance
Cmax	maximum observed plasma concentration
CPAP	Clinical Pharmacology Analysis Plan
CRF	case report form
CRU	clinical research unit
CS	clinically significant
CSR	clinical study report
CV	coefficient of variation
ECG	electrocardiogram
Geom CV	geometric coefficient of variation
Geom Mean	geometric mean
GMR	geometric mean ratio
ICF	informed consent form
ICH	International Conference on Harmonization
ln	natural log
LSM	least-square means
Mean	arithmetic mean
MedDRA	Medical Dictionary for Regulatory Activities
PI	Principal Investigator
PK	pharmacokinetics
PO	orally administered
PPI	proton pump inhibitor
QD	once daily
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
Vz/F	apparent volume of distribution during the terminal elimination phase
WHO	World Health Organization

4.0 OBJECTIVES

4.1 Primary Objectives

To evaluate the effect of the proton pump inhibitor (PPI), esomeprazole, on the single-dose pharmacokinetics (PK) of orally administered (PO) TAK-906.

4.2 Secondary Objective

To evaluate the safety and tolerability of a single PO dose of TAK-906 in the presence and absence of the PPI, esomeprazole.

4.3 Study Design

This is a single-sequence, open-label, 2-period crossover study in 12 healthy adult subjects. The study is designed to investigate the effect of a PPI, esomeprazole, on the PK of TAK-906. The study will include a screening visit, a study Period 1 (Days 1 to 3), followed by at least a 4-day washout from the time of TAK-906 dose, a study Period 2 (Days 1 to 6), and a follow-up visit. Screening of subjects will occur within 28 days prior to the first dosing

In study Period 1, subjects will be confined from the day prior to dosing (Day -1), at the time indicated by the clinical research unit (CRU), until after the 48-hour blood draw (Day 3). In study Period 2, subjects will come to the CRU on the mornings of Day 1 to Day 2, at the time indicated by the CRU, for dosing and/or study procedures as appropriate. Subjects will be confined from morning of Day 3, at the time indicated by the CRU, until after the 48-hour blood draw on Day 6. At any time, a subject may be required to remain at the CRU for longer at the discretion of the Principal Investigator (PI).

On Day 1 of study Period 1, subjects will receive a single oral dose of TAK-906. On Days 1 through 5 of Study Period 2, subjects will receive esomeprazole (Nexium®) dose once daily (QD). On Day 4 of study Period 2, a single oral dose of TAK-906 will be administered 1 hour following the esomeprazole dose. Serial blood samples will be collected predose and for 48 hours after each TAK-906 dose to determine the PK of TAK-906.

All subjects who received at least one dose of study drug (including subjects who terminate the study early) will return to the CRU approximately 10-14 days after the last dose of TAK-906 for follow-up procedures, and to determine if any adverse event (AE) has occurred since the last study visit.

The planned dose levels of TAK-906 and esomeprazole to be used are outlined in Table 4.a.

Table 4.a Study Drugs Planned Dose Levels

	Dose	Route of Administration
Study Period 1 (Treatment A)	25 mg	Oral capsule
TAK-906		
Study Period 2 (Treatment B)		
TAK-906	25 mg	Oral capsule
Esomeprazole	40 mg	Oral capsule

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

Figure 4.a Schematic of Study Design

<table>
<tr><td>Screening</td><td colspan="3">Study Period 1 (a)</td></tr>
<tr><td rowspan="3">Within Day -28 to -2 for screening; first dosing in Study Period 1</td><td>Day -1</td><td>Day 1</td><td>Days 2 – 3</td></tr>
<tr><td>Check-in</td><td>TAK-906 dosing</td><td></td></tr>
<tr><td></td><td colspan="2">Plasma sampling for TAK-906 PK and safety monitoring for at least 48 hours postdose</td></tr>
<tr><td></td><td colspan="3">< - - - - - - - - - - - - Confinement (b) (c) - - - - - - - - - - - - ></td></tr>
<tr><td colspan="4">(a) There will be a washout of at least 4 days between dosing in Study Period 1 and first dosing in Study Period 2.
(b) A subject may be required to remain at the CRU for longer at the discretion of the PI or designee.
(c) Subjects will start the confinement on Day -1 of Study Period 1 and be released from CRU after Day 3 study assessments are complete.</td></tr>
</table>

<table>
<tr><td colspan="5">Study Period 2 (a)</td><td>Study exit</td><td>Follow-up (b)</td></tr>
<tr><td>Days 1-2</td><td>Day 3</td><td>Day 4</td><td>Day 5</td><td>Day 6</td><td rowspan="6">Day 6 of Treatment Study Period 2</td><td rowspan="6">10-14 days after last dosing</td></tr>
<tr><td></td><td>Check-in</td><td></td><td></td><td></td></tr>
<tr><td>Esomeprazole dosing</td><td>Esomeprazole dosing</td><td>Esomeprazole dosing
TAK-906 dosing</td><td>Esomeprazole dosing</td><td></td></tr>
<tr><td></td><td></td><td colspan="3">Plasma sampling for TAK-906 PK and safety monitoring for at least 48 hours postdose</td></tr>
<tr><td>Outpatient visit</td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td colspan="4">< - - - - - - - - - - - - Confinement (c) (d) - - - - - - - - - - - - ></td></tr>
<tr><td colspan="7">(a) There will be a washout of at least 4 days between dosing in Study Period 1 and first dosing in Study Period 2.
(b) All subjects who received at least one dose of study drug (including subjects who terminate the study early) will return to the CRU approximately 10-14 days after the last dose of TAK-906 for follow-up procedures, and to determine if any AE has occurred since the last study visit
(c) A subject may be required to remain at the CRU for longer at the discretion of the PI or designee.
(d) In Study Period 2, subjects will return to the CRU on the morning of Days 1 and 2 for dosing and/or study procedures as appropriate. Subjects will be confined from morning of Day 3 of Study Period 2, at the time indicated by the CRU, until after 48-hour blood draw on Day 6.</td></tr>
</table>

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoints

The following plasma PK parameters will be calculated for TAK-906 on Day 1 in study Period 1 and on Day 4 in study Period 2:

- Cmax: Maximum observed concentration
- AUClast: Area under the concentration-time curve from time 0 to time of the last quantifiable concentration
- AUCinf: Area under the concentration-time curve from time 0 to infinity

5.2 Secondary Endpoint

The following safety variables will be used to characterize the safety and tolerability of TAK-906:

- Treatment –emergent adverse event (TEAE) assessment
- Vital signs
- 12-lead electrocardiograms (ECG)
- Clinical laboratory testing (hematology, serum chemistry, and urine analysis)

5.3 Exploratory Endpoints

CCI

[redacted]

6.0 DETERMINATION OF SAMPLE SIZE

A total of twelve (12) subjects will be enrolled in this study. This sample size will provide at least 80% power to conclude the Cmax of TAK-906 will not decrease more than 50% in the presence of esomeprazole, assuming that the intra-subject coefficient of variation (CV%) for Cmax of TAK-906 will not exceed 45% and a true ratio of 0.8. Lower intra-subject variability was observed for AUC in previous studies; therefore, the power is expected to be greater for AUC.

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. All data recorded on the CRF will be listed by subject. All tables, figures and listings (TFLs) shells and numbering list specified in the Clinical Pharmacology Analysis Plan (CPAP) will be included.

The concentration data will be used as reported by the respective bioanalytical groups without rounding for all analyses. All PK parameters tables should include three significant figures, except Tmax, and t1/2 which will be presented with 2 decimal places. %CV should have 1 decimal place.

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. In log-linear plots these values would not be presented. In the tables presenting summary statistics of concentration-time series, the total number of values (n) and the number of values that are above the level of quantification (n_ABLQ) will be presented. The following footnote will also be added to appropriate concentration versus time figures: All values reported as BLQ have been replaced with zero.

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

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)
- Analysis of variance (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. 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.

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-date of first dose in Period 1; study day on or after the date of first dose will be calculated as: date of assessment-date of first dose in Period 1 +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-date of first dose in each period; study day on or after the date of first dose will be calculated as: date of assessment-date of first dose in each period +1.

7.2 Analysis Sets

Safety Set:

All subjects who received at least one dose of the study drug 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 do 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 Study Information

Study information including date first subject signed informed consent form, date for the first dose, date for the 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 will be listed.

7.4 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. Study completion status, including reason for discontinuation, will also be listed by subject.

7.5 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively. 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.

7.6 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.

7.7 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 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.

7.8 Study Drug Exposure and Compliance

Not applicable.

7.9 Efficacy Analysis

Not applicable.

7.10 Pharmacokinetic/Pharmacodynamic Analysis

7.10.1 Pharmacokinetic Analysis

Blood samples (one 4 mL sample per scheduled time) for PK analysis of TAK-906 will be collected as specified in Table 7:1 following administration of TAK-906 alone (sampling Day 1 – Period 1) or coadministered with esomeprazole (sampling Day 4 – Period 2).

Table 7.a Collection of Blood Samples for Pharmacokinetic Analysis

Analyte	Matrix	Sampling Day	Scheduled Time (hours)
TAK-906	Plasma	1	Predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36 and 48 hours postdose (a) (b).
TAK-906	Plasma	4	Predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36 and 48 hours postdose (a) (b) (c).

(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 PI.
(b) The 16-hour postdose on Day 1 of study Period 1 and Day 4 of study Period 2 will be either on Day 1 or Day 2 of Period 1 and Day 4 or Day 5 of Study Period 2, depending on the time of dosing on Day 1 of study Period 1 and Day 4 of study Period 2, respectively.
(c) The collection times for analysis of TAK-906 PK parameters will be relative to TAK-906 dose on Day 4 for Period 2.

The actual date and time of sample collection will be recorded on the source document in the case report form (CRF). CCI [redacted]

The PK parameters of TAK-906 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.

Drug-Drug Interaction

For evaluation of potential effect of esomeprazole on TAK-906 PK, an ANOVA will be performed on the natural log (ln)-transformed Cmax, AUClast, and AUCinf, which have been exponentiated to provide estimates on the original scale. The ANOVA model will include treatment as fixed effect and subject as a random effect. Each ANOVA will include calculation of least-squares means (LSM) as well as the difference between treatment LSM. The geometric mean of the relative bioavailability of the TAK-906 with esomeprazole relative to the TAK-906 alone and the associated 90% confidence intervals (CIs) will be determined by exponentiation of

the appropriate estimates for the difference between treatments in the log-transformed parameters.

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

7.10.2 Pharmacodynamic Analysis

Not applicable.

7.11 Other Outcomes

Not applicable.

7.12 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.. 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.

7.12.1 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 for both TAK-906 and eomeprazole. Study procedure taken due to AE will also be listed. All AEs occurring during this study will be coded using the 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.

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 non-

serious TEAEs (i.e., those events reported by >5% of all subjects in each treatment group, 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 (TAK-906 and eomeprazole). 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.

For treatment B, the TEAEs will be summarized separately for two segments (Treatment B1 and Treatment B2). Treatment B1 will be esomeprazole which is started from the first esomeprazole dosing and prior to TAK-906 dosing. Treatment B2 will be esomeprazole + TAK-906 which is after the dosing of TAK-906 on Day 4 of Period 2.

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.

7.12.2 Clinical Laboratory Evaluations

Hematology, serum chemistry, and urinalysis will be performed at screening, check-in (Day -1) of Study Period 1, Day 1 predose of Study Period 2, and on Day 6 of Study Period 2 or prior to early termination from the study, and at the follow-up visit. In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the 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 assessment time points. Change from baseline will be summarized. Baseline is defined as the last assessment including rechecks taken prior to dosing in Study Period 1.

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 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.

7.12.3 Vital Signs

Single measurements of heart rate and blood pressure will be obtained at screening, predose, and at 1, 2, 4, 8, and 48 hours postdose (times relative to TAK-906 dose) in each period or upon early termination, and at the follow-up visit. Respiration rate, and temperature, are collected at screening and Day 1 predose of Study Period 1only. 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 TAK-906 dosing in each period. Vital signs will also be displayed in a data listing by subject.

7.12.4 12-Lead ECGs

Standard 12-lead ECGs will be recorded at screening, predose, and at 1, 2, 4, 8, and 48 hours postdose (times relative to TAK-906 dose) or upon early termination, and at the follow-up visit. 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 TAK-906 dosing in each period. ECG data will also be displayed in a data listing by subject.

7.12.5 Physical Exams

A full physical exam will be performed at screening, Day 1 predose of Study Period 1, and at the follow-up visit. 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.

7.12.6 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 Interim Analysis

No interim analysis will be performed.

7.14 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 or higher.

7.15 Changes in the Statistical Analysis Plan

There are no 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	23-Apr-2019 13:50 UTC