Title: A Phase 1, Open-Label, Randomized, Two-Way Crossover Study to Evaluate the Effect of Single-Dose Intravenous Rifampin as a Prototypic Inhibitor of OATP1B1 and OATP1B3 on the Single-Dose Pharmacokinetics of Oral TAK-906 in Healthy Adult Subjects

NCT Number: NCT04121078

SAP Approve Date: 02 December 2019

Certain information within this Statistical Analysis Plan has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable (PPD) information or company confidential information (CCI).

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-906-1009
CELERION STUDY NUMBER: CA28400

A Phase 1, Open-Label, Randomized, Two-Way Crossover Study to Evaluate the Effect of Single-Dose Intravenous Rifampin as a Prototypic Inhibitor of OATP1B1 and OATP1B3 on the Single-Dose Pharmacokinetics of Oral TAK-906 in Healthy Adult Subjects

PHASE 1

Version: Amendment 1

Date**:** 02 December 2019

Prepared by:

PPD

Based on:

Protocol Dated: 24 September 2019

1.1 Approval Signatures

Study Title: A Phase 1, Open-Label, Randomized, Two-Way Crossover Study to Evaluate the Effect of Single-Dose Intravenous Rifampin as a Prototypic Inhibitor of OATP1B1 and OATP1B3 on the Single-Dose Pharmacokinetics of Oral TAK-906 in Healthy Adult Subjects

PPD

2.0 TABLE OF CONTENTS

1.0 TITLE PAGE 1
1.1 Approval Signatures 2
2.0 TABLE OF CONTENTS 3
3.0 LIST OF ABBREVIATIONS 5
4.0 OBJECTIVES 7
4.1 Study Primary Objective 7
4.2 Study Secondary Objective 7
4.3 Study Exploratory Objective 7
4.4 Study Design 7
5.0 ANALYSIS ENDPOINTS 9
5.1 Primary Endpoints 9
5.2 Secondary Endpoints 9
5.3 Exploratory Endpoints 9
5.4 Additional Endpoints 10
6.0 DETERMINATION OF SAMPLE SIZE 10
7.0 METHODS OF ANALYSIS AND PRESENTATION 10
7.1 General Principles 10
7.1.1 Study Definitions 12
7.1.2 Definition of Study Days 12
7.2 Analysis Sets 12
7.3 Study Information 13
7.4 Disposition of Subjects 13
7.5 Demographic and Other Baseline Characteristics 13
7.6 Medical History and Concurrent Medical Conditions 13
7.7 Medication History and Concomitant Medications 13
7.8 Study Drug Exposure and Compliance 14
7.9 Efficacy Analysis 14
7.10 Pharmacokinetic Analysis 14
7.10.1 TAK-906 CCI Pharmacokinetic Analysis 14
7.10.2 CCI [redacted] 15
7.11 Other Outcomes 16
7.12 Safety Analysis 16
7.12.1 Adverse Events 16

7.12.2 Clinical Laboratory Evaluations 17
7.12.3 Vital Signs 18
7.12.4 12-Lead ECGs 18
7.12.5 Physical Exams 18
7.12.6 Overdose 18
7.13 Interim Analysis 19
7.14 Preliminary Analysis 19
7.15 Changes in the Statistical Analysis Plan 19
8.0 REFERENCES 20

3.0 LIST OF ABBREVIATIONS

AE	adverse event
ANOVA	analysis of variance
AUC	area under the curve
AUC_{∞} / AUCinf	area under the plasma concentration-time curve from time 0 to infinity
AUC_{last} / 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
CCI	[redacted]
C_{max} / Cmax	maximum observed concentration
CPAP	Clinical Pharmacology Analysis Plan
CCI	[redacted]
CCI	[redacted]
CRF	case report form
CRU	clinical research unit
CS	clinically significant
CSR	clinical study report
CV	coefficient of variation
DDI	drug-drug interaction
DMP	data management plan
ECG	electrocardiogram
Geom CV	geometric coefficient of variation
Geom Mean	geometric mean
GMR	geometric mean ratio
ICF	informed consent form
IV	intravenous
CCI	[redacted]
ln	natural log
LOQ	limit of quantitation
LSM	least-square means
Mean	arithmetic mean
MedDRA	Medical Dictionary for Regulatory Activities

OATP	organic anion transporting polypeptide
PI	Principal Investigator
PK	pharmacokinetics
SAE	serious adverse event
SD	standard deviation
SEM	standard error of the mean
SOC	system organ class
CCI	[redacted]
TEAE	treatment-emergent adverse event
TFL	tables, figures, and listings
CCI	[redacted]
CCI	[redacted]
WHO	World Health Organization

4.0 OBJECTIVES

4.1 Study Primary Objective

To evaluate the effect of single dose intravenous (IV) rifampin on the single-dose pharmacokinetics (PK) of orally administered TAK-906.

4.2 Study Secondary Objective

To evaluate the safety and tolerability of a single oral dose of TAK-906 in the presence and absence of rifampin.

4.3 Study Exploratory Objective

CCI [redacted]

4.4 Study Design

This is a phase 1, open-label, randomized, two-way crossover study to evaluate the effect of single-dose IV rifampin on the single-dose PK of oral TAK-906 in healthy adult subjects.

Subjects will be screened from Day -28 to -2, to determine eligibility before randomization and eligible subjects will return to the clinic at check-in (Day -1, Period 1).

The study will include a screening visit, two treatment periods, and a follow-up visit. Treatment will consist of a single oral dose of 25 mg TAK-906 capsule (Treatment A), and a single oral dose of 25 mg TAK-906 capsule immediately after a single IV dose of 600 mg rifampin (Treatment B). Eligible subjects will be randomly assigned to 1 of 2 treatment sequences (i.e., AB, BA). Randomization sequences are presented in the table below:

Table 4:1 Randomization Sequences

Sequence	Number of Subjects	Study Period 1	Study Period 2
AB	6	TAK-906 oral	Rifampin IV+ TAK-906 oral
BA	6	Rifampin IV + TAK-906 oral	TAK-906 oral

Treatment A = 25 mg TAK-906 capsule

Treatment B = 25 mg TAK-906 capsule given immediately after a single 30-minute IV dose of 600 mg rifampin

Each dose of TAK-906 will be separated by a washout period of at least 7 days from the time of Study Period 1 TAK-906 dose administration.

On Day 1 of Treatment A after an overnight fast of at least 10 hours, a single oral dose of TAK-906 capsule will be administered. On Day 1 of Treatment B after an overnight fast of at

least 10 hours, IV rifampin will be administered over a 30-minute period, and TAK-906 capsule will be given immediately at the end of the infusion.

In each treatment arm, subjects will be confined from the day prior to dosing (Day -1, Check-in), at the time indicated by the clinical research unit (CRU), until after the 48-hour blood draw (Day 3). Blood samples for assessment of TAK-906 concentrations will be measured from predose to 48 hours after each dose of TAK-906. There will be a washout period of at least 7 days between the TAK-906 dosing in each study period.

Safety will be assessed by monitoring for adverse events (AEs), vital signs, electrocardiograms (ECGs), clinical laboratory results, and physical examinations throughout each study period. All subjects who received at least one dose of study drug (including subjects who terminate the study early) will return to the CRU 14 ± 2 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.

A schematic for the study design is included in the figure below:

Figure 4:1 Study Design

<table>
<tr><th>Screening</th><th colspan="3">Treatment Study Periods 1 and 2 [a]</th><th>Follow-up Visit</th></tr>
<tr><td rowspan="4">Day -28 to Day -2</td><td>Day -1</td><td>Day 1</td><td>Days 2 and 3</td><td rowspan="4">14 ± 2 days after last TAK-906 dosing</td></tr>
<tr><td>Check-in</td><td>Dosing at Hour 0 [b]</td><td></td></tr>
<tr><td></td><td colspan="2">PK sampling and safety monitoring up to 48 hours postdose</td></tr>
<tr><td colspan="3">< - - - - - - - - - - - - confinement - - - - - - - - - - - - ></td></tr>
<tr><td colspan="5">[a] Prior to dosing on Day 1 of Period 1, subjects will be randomized in a ratio of 1:1 to one of two treatment sequences. Subjects will receive each treatment on one occasion. Each TAK-906 dosing will be separated by at least 7 days from the time of Study Period 1 dose administration.
[b] TAK-906 administration is defined as Hour 0.</td></tr>
</table>

The treatment description and planned dose levels of TAK-906 and rifampin to be evaluated are outlined in the table below.

Table 4:2 Treatment Descriptions and Planned Dose Levels of TAK-906 and Rifampin

Treatment A	A single oral dose of 25 mg TAK-906 (1 x 25 mg capsule) administered at Hour 0 on Day 1 following an overnight fast.
Treatment B	A single oral dose of 25 mg TAK-906 (1 x 25 mg capsule) immediately after a single 30-minute IV dose of 600 mg rifampin.

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoints

The following plasma PK parameters for TAK-906 on Day 1 following Treatment A and Treatment B:

- C_{max}: maximum observed concentration
- AUC_{∞}: area under the concentration-time curve from time 0 to infinity calculated using the observed value of the last quantifiable concentration
- AUC_{last}: area under the concentration-time curve from time 0 to time of the last quantifiable concentration

5.2 Secondary Endpoints

The secondary endpoints are the following for Treatment A and Treatment B:

- Treatment-emergent adverse event (TEAE) assessments
- Vital signs
- 12-lead ECG
- Clinical laboratory testing (hematology, serum chemistry, and urinalysis)

5.3 Exploratory Endpoints

CCI

[redacted]

5.4 Additional Endpoints

CCI

[redacted]

6.0 DETERMINATION OF SAMPLE SIZE

With a sample size of 12 subjects, there is an 80% probability for the 90% confidence intervals (CIs) to be within 65% and 135% of the point estimate of the geometric mean ratio (GMR) for C_{max} and for AUC of TAK-906 with and without rifampin. Thus, if the observed GMRs of TAK-906 with and without rifampin is 2 for C_{max} and AUC, then the corresponding 90% CIs based on data from 12 subjects will be approximately (1.6, 2.5). This calculation assumes that log(C_{max}) and log(AUC) of TAK-906 are normally distributed with intra-subject coefficients of variation that do not exceed 31%.

Subjects who drop out for non-safety reasons may be replaced at the discretion of the investigator in consultation with the Sponsor. Subjects who drop out for safety reasons will not be replaced.

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 9.4, 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 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 CCI [redacted] hich will be presented with 2 decimal places.

The following summary statistics will be calculated for plasma concentrations and PK parameters: Sample size (n) is presented as an integer (no decimal places), arithmetic mean, median, and geometric mean (Geom Mean) values will be presented to 1 more level of precision than the concentration and PK parameter 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. 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.

Concentration values below the limit of quantitation (BLQ) will be presented as 'BLQ' in the concentration table listings and footnoted accordingly. For TAK-906 and CCI 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. CCI [redacted] The following footnotes will also be added to appropriate concentration versus time figures, as appropriate:

- All values reported as BLQ have been replaced with zero
- All values reported as BLQ have been set to ½ the LOQ

Geometric least-squares means (LSMs) will be reported with 1 more level of precision than the recorded data. 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 C_{max} 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 CPAP for details on the PK parameter calculations and data presentation including specifics on the following:

- Insufficient data to determine a reliable $t_{½z}$ value and other terminal disposition phase rate constant dependent parameters
- PK parameters presented by analyte (if applicable), treatment, including the units, precision, and summary statistics that will be presented in in-text and end-of-text tables

- Concentration data presented by analyte (if applicable), 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
- 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 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.

7.2 Analysis Sets

PK Set:

The PK set will consist of all subjects who received study drug and who have at least 1 measurable plasma PK concentration.

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.

Safety Set:

The safety analysis set will consist of all subjects who are enrolled and received at least 1 dose of study drug.

7.3 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.

7.4 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 by randomized treatment sequence and overall. 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 by randomized treatment sequence and overall. Summary statistics (number of subjects [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.

7.6 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 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). If appropriate, 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 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 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, 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.

7.8 Study Drug Exposure and Compliance

The date, time, and dosage of each TAK-906 and rifampin dose will be listed by subject.

7.9 Efficacy Analysis

Not applicable.

7.10 Pharmacokinetic Analysis

7.10.1 TAK-906 and CCI Pharmacokinetic Analysis

Blood samples (one 4 mL sample per scheduled time) for PK analysis of TAK-906 CCI will be collected as specified in Table 7:1 following administration of TAK-906 alone (Treatment A) or TAK-906 + rifampin (Treatment B).

Table 7:1 Collection of Blood Samples for Pharmacokinetic Analysis

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

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.

The actual date and time of sample collection will be recorded on the source document in the CRF. Plasma CCI concentrations may be measured from the same samples used for TAK-906 plasma concentration assessments.

Concentrations of TAK-906 CCI will be listed and summarized descriptively by analyte and PK sampling time. Summary will be done by treatment using the summary statistics described above. 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. The individual subject profiles of the concentration-time data will be plotted by treatment on linear (without SD) and semi-log scales. The arithmetic mean profiles of the concentration-time data will be plotted by treatment on linear (with and without SD) and semi-log scales. The median profiles of concentration-time data will be plotted on linear (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.

The PK parameters of TAK-906 CCI for this study listed in the CPAP and above in Section 5.0 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. PK parameters of TAK-906 CCI [redacted] will be summarized descriptively by analyte and treatment using the summary statistics described above. 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

An ANOVA will be performed on the natural log (ln)-transformed AUC_{∞}, AUC_{last}, and C_{max}, using a mixed effects model, to assess the potential effect of rifampin on TAK-906 CCI [redacted] PK parameters. The mixed effects models will include sequence, treatment, and period as fixed effects, and subject nested within sequence as a random effect. Each model will include calculation of LSM as well as the difference between treatment LSM. Ratios of LSM will be calculated using the exponentiation of the difference between treatments LSM from the analyses on the ln-transformed AUC_{∞}, AUC_{last}, and C_{max}.

Consistent with the two one-sided test, 90% 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 AUC_{∞}, AUC_{last}, and C_{max}.

The comparison of interest is as follows:

- Treatment B compared with Treatment A

The following SAS code will be used to run the analysis:

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

7.10.2 CCI [redacted]

CCI [redacted]

CCI

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 12-lead 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 (CTCAE Grades 1 through 5), relationship to study drug(s) (related or not related) and action relative to the study drug(s) 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 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® 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, 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(s). 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 study report.

7.12.2 Clinical Laboratory Evaluations

Hematology, serum chemistry, and urinalysis will be performed at screening, check-in (Day -1) of each period, Day 3 of each period 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 treatment and assessment time points. Change from baseline will be summarized. Baseline is defined as the last assessment including rechecks taken prior to the first 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 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 laboratory tests, as indicated by the PI, 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 will only be collected at screening and prior to first dosing in each period. 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. Change from baseline will not be calculated for respiratory rate and temperature. Vital signs will also be displayed in a data listing by subject.

7.12.4 12-Lead ECGs

Triplicate 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.

The average of the triplicates will be calculated for each parameter, reported as an integer, and used in the analysis. 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 average of the last triplicate assessment including rechecks taken prior to 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, prior to dosing in each period, 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 7.10.1 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

The effect of the drug-drug interaction (DDI) for CCI metabolite following TAK-906 + rifampin compared to TAK-906 alone was not outlined in the final protocol (dated 24 September 2019). The concentrations and PK parameters CCI ill be presented and summarized, and the model-based statistical analysis on the DDI effect will be performed CCI data.

8.0 REFERENCES

Not applicable.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Biostatistics Approval	04-Jan-2020 21:40 UTC