Title: A Phase 1, Randomized, 2-Period, 2-Sequence, Crossover Study to Evaluate the Effect of High-Fat Meal on TAK-788 Pharmacokinetics in Healthy Adult Subjects

NCT Number: NCT04441255

SAP Approve Date: 10 August 2020

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

- Named persons or organizations associated with the study.
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STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-788-1005
CELERION STUDY NUMBER: CA24171

A Phase 1, Randomized, 2-Period, 2-Sequence, Crossover Study to Evaluate the Effect of High-Fat Meal on TAK-788 Pharmacokinetics in Healthy Adult Subjects

PHASE 1

Version**:** Final

Date**:** 10 August 2020

Prepared by:

PPD

Based on:

Final Protocol Date: 09 June 2020

1.1 Approval Signatures

Study Title: A Phase 1, Randomized, 2-Period, 2-Sequence, Crossover Study to Evaluate the Effect of High-Fat Meal on TAK-788 Pharmacokinetics in Healthy Adult Subjects

PPD

2.0 TABLE OF CONTENTS

3.0 LIST OF ABBREVIATIONS

AE	adverse event
ANOVA	analysis of variance
AUC	area under the curve
$AUC_{extrap\%}$	percent of AUC_{∞} extrapolated
AUC_{∞}	area under the concentration-time curve from time 0 to infinity
AUC_{last}	area under the concentration-time curve from time 0 to the time of the last quantifiable concentration
BLQ	below the limit of quantitation
BMI	body mass index
CI	confidence interval
CL/F	apparent clearance after extravascular administration
C_{max}	maximum observed concentration
CPAP	clinical pharmacology analysis plan
CRF	case report form
CS	clinically significant
DMP	Data Management Plan
ECG	electrocardiogram
FDA	Food and Drug Administration
FE	food effect
GMR	geometric mean ratio
ICF	informed consent form
IND	Investigational New Drug
λ_z	terminal disposition phase rate constant
LSM	least-squares mean
MedDRA	Medical Dictionary for Regulatory Activities
MPR	metabolite to parent ratio
NDA	New Drug Application
PFT	pulmonary function test
PI	Principal Investigator
PK	pharmacokinetics
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	System Organ Class
$t_{½z}$	terminal disposition phase half-life
TEAE	treatment-emergent adverse event
TFL	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
WHO	World Health Organization

4.0 OBJECTIVES

4.1 Primary Objective

To characterize the effect of a high-fat meal on the pharmacokinetics (PK) of mobocertinib (referred to as TAK-788 in the protocol) administered as a proposed commercial product.

4.2 Secondary Objective

To assess the PK of active metabolites AP32960 and AP32914 of mobocertinib.

4.3 Exploratory Safety Objective

To collect the safety data of mobocertinib following a single oral dose in healthy adult subjects.

4.4 Study Design

This is an open-label, randomized, 2-period, and 2-sequence crossover high-fat meal effect study in healthy adult subjects.

Subjects will undergo screening evaluations to determine eligibility within 21 days prior to dosing. Subjects will be admitted to the clinical facility the day prior to dosing in each period (Day -1). Subjects will be randomized on Day 1 of Period 1 to a crossover sequence in a 1:1 ratio and administered a single oral dose of 160 mg of mobocertinib with or without a high-fat meal on Day 1 of each period (i.e., Period 1 and Period 2). Each dose will be separated by a washout period of 10 days. Blood samples for mobocertinib PK will be collected predose and up to 240 hours following each mobocertinib dose.

Subjects will receive the following treatments on one occasion in a crossover fashion to evaluate the effect of a high-fat meal:

- Treatment A: Administration of a single oral dose of 160 mg mobocertinib (4 x 40 mg capsules) following an overnight fast.
- Treatment B: Administration of a single oral dose of 160 mg mobocertinib (4 x 40 mg capsules) with a high-fat meal.

  * 800-1000 total calories, 500-600 calories, 55-65 g, or 50% from fat

Subjects will remain at the clinical site until the 240-hour study assessments in Period 2 are completed. All doses of mobocertinib will be administered at the clinic during this study. A final safety follow-up phone call will occur 30 ± 2 days after the last mobocertinib dose to determine if any adverse events (AEs) have occurred since the last study visit. Replacement of discontinued or withdrawn subjects due to any reason will be assessed on a case by case basis by the Sponsor and the Principal Investigator (PI) to ensure a minimum of 12 PK-evaluable subjects complete the study.

Any subject who experiences emesis within 8 hours postdose will be excluded in the final PK data analysis and may be replaced with a new subject.

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoints

The following PK parameters will be analyzed for mobocertinib:

- Time of first occurrence of C_{max} (t_{max}).
- Maximum observed concentration (C_{max}).
- Area under the concentration-time curve from time 0 to infinity, calculated using the observed value of the last quantifiable concentration (AUC_{∞}).
- Area under the concentration-time curve from time 0 to the time of the last quantifiable concentration (AUC_{last}).

5.2 Secondary Endpoints

The following PK parameters will be analyzed for active metabolites (AP32960 and AP32914) of mobocertinib:

- Time of first occurrence of C_{max} (t_{max}).
- Maximum observed concentration (C_{max}).
- Area under the concentration-time curve from time 0 to infinity, calculated using the observed value of the last quantifiable concentration (AUC_{∞}).
- Area under the concentration-time curve from time 0 to the time of the last quantifiable concentration (AUC_{last}).

5.3 Exploratory Safety Endpoints

The exploratory endpoint will be assessed through evaluation of the following safety parameters:

- Treatment-emergent adverse events (TEAEs) assessments.
- Clinical laboratory (hematology, serum chemistry, and urinalysis).
- Physical examinations.
- 12-lead electrocardiograms (ECGs).
- Vital signs.

5.4 Additional Endpoints

In addition, the following plasma PK parameters for mobocertinib and its active metabolites (AP32960 and AP32914) will be calculated:

- Terminal disposition phase half-life ($t_{½z}$).
- Terminal disposition phase rate constant (λ_z).
- Percent of AUC_∞ extrapolated
- Apparent clearance after extravascular administration (CL/F) for mobocertinib only.
- Apparent volume of distribution during the terminal disposition phase after extravascular administration (V_z/F) for mobocertinib only.
- The metabolite to parent ratio for molar AUC_∞ (MPR AUC_∞) for AP32960 and AP32914.

6.0 DETERMINATION OF SAMPLE SIZE

The sample size calculation was based on the expected 2-sided 90% confidence interval (CI) for the difference in the paired, log-transformed AUC_{∞} means of mobocertinib in the presence and absence of a high-fat meal. The within-patient coefficient of variation for mobocertinib C_{max} was estimated to be 17.2% on the basis of data from a clinical study conducted in healthy subjects (TAK-788-1001). If the observed geometric mean ratio (GMR) for the mobocertinib AUC_{∞} in the presence and absence of high-fat is 1, with a sample size of 12, the 90% CI for the AUC_{∞} GMR is expected to be 0.881 to 1.13 on the basis of the variance assumptions. Fourteen (14) adult subjects will be enrolled into this high-fat meal effect study to get at least 12 PK-evaluable subjects in each treatment according to the Food and Drug Administration (FDA) guidance Assessing the Effects of Food on Drugs in Investigational New Drugs (INDs) and New Drug Applications (NDAs) – Clinical Pharmacology Considerations Guidance for Industry (FDA food effect [FE] 2019).

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.

The concentration data will be used as reported by the respective bioanalytical groups without rounding for all analyses. 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 [except in cases where more than 2 samples are BLQ between measurable concentrations, BLQ values will be set to 0 instead of missing]), in which case they will be treated as missing. In log-linear plots, these values would not be presented. Missing concentration values will be flagged in the concentration tables and footnoted as missing or not reportable (i.e., for subjects withdrawn or dropped from the study, subjects missing blood draws). Plasma concentration data from subjects excluded from PK parameter analysis will be included in the concentration tables and individual figures, but will be excluded from summary statistics and in the presentation of mean figures.

All concentration and PK parameter values will be presented to 3 significant figures. For concentration and PK parameter tables, all summary statistics will be presented to 3 significant figures. Geometric least-squares means (LSMs) will be presented with 3 significant figures. 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/consumption, 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 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 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
- Any subject, PK concentration, and PK parameter that are excluded in the PK data analyses or summary statistical analyses will be provided in end of text tables.

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 appropriate continuous variables, the number of subjects with non-missing values, mean, standard deviation (SD), minimum, median, and maximum values will be tabulated.

7.1.1 Study Definitions

7.1.1.1 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 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.

For all clinical laboratory evaluations, vital signs, and 12-lead ECGs, baseline is defined as the last assessment including rechecks taken prior to mobocertinib dosing at each period.

7.2 Analysis Sets

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. Any subject who experiences emesis within 8 hours post dosing with mobocertinib will be excluded in the final data analysis.

Safety Set:

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

7.3 Study Information

A study information table will be generated including the following items: date of first subject's signed informed consent form (ICF), 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 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. All medical history will 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 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 MedDRA® Version 23.0, 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 mobocertinib dose along with meal data will be listed by subject.

7.9 Efficacy Analysis

Not applicable.

7.10 Pharmacokinetic/Pharmacodynamic Analysis

7.10.1 Pharmacokinetic Analysis

Blood samples for PK analysis of mobocertinib, AP32960, and AP32914 will be collected as specified in Table 7:1 following administration of mobocertinib under fasted conditions (Treatment A) or with a high-fat meal (Treatment B).

Table 7:1 Collection of Blood Samples for Pharmacokinetic Analysis

Analyte	Matrix	Sampling Day	Period	Scheduled Time (hours)
mobocertinib, AP32960, and AP32914	Plasma	1	1 and 2	Predose and 0.5, 1, 2, 4, 6, 8, 12, 24, 48, 72, 120, 168, and 240 hours postdose (a) (b)

(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 Period 1 Day 11 PK sample will serve as the pre-dose PK sample for Period 2.

The actual date and time of sample collection will be recorded on the source document in the CRF.

Concentrations will be listed and summarized descriptively by PK sampling time in mass units for plasma mobocertinib, AP32960, and AP32914. 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 in mass units for each analyte. 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 mobocertinib, AP32960, and AP32914 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 in mass units. The molar AUC_{last}, AUC_{∞}, and C_{max} PK parameters will also be calculated for plasma mobocertinib, AP32960, and AP32914 using the molecular weights of each analyte as outlined in the CPAP. Combined molar AUC_{last}, AUC_{∞}, and C_{max} for plasma mobocertinib, AP32960, and AP32914 will also be presented. 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 will be summarized descriptively by treatment using the summary statistics listed in the CPAP in mass units and molar units. 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.

Food Effect

For evaluation of potential effect of a high-fat meal on mobocertinib PK, a linear mixed-effects model will be used for the analysis on the ln-transformed C_{max}, AUC_{∞}, and AUC_{last} (only if AUC_{∞} is not available for at least 12 subjects) for mobocertinib (mass units) and combined molar C_{max}, AUC_{∞}, and AUC_{last} (only if AUC_{∞} is not available for at least 12 subjects) for mobocertinib, AP3260, and AP32914. 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 LSMs as well as the difference between LSMs.

GMR and 90% CIs, consistent with the two one-sided tests, will be calculated using the exponentiation of the difference between treatment LSMs from the analyses on the ln-transformed C_{max}, AUC_{∞}, and AUC_{last} (only if AUC_{∞} is not available for at least 12 subjects) for mobocertinib, as well as the ln-transformed molar combined C_{max}, AUC_{∞}, and AUC_{last} (only if AUC_{∞} is not available for at least 12 subjects) for mobocertinib, AP32960, and AP32914. The comparison of interest is as follows:

Treatment B (High-Fat Meal) relative to Treatment A (Fasted)

The following SAS code will be used:

```
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;
```

Nonparametric Analysis of t_{max}

A nonparametric analysis for t_{max} will be performed to compare treatment differences using the Wilcoxon Signed Rank test. Median difference (Test-Reference), the Hodges-Lehmann estimator, and estimated confidence interval will be used to examine the location shift in t_{max}. The t_{max} parameter will not be ln-transformed. The median difference, associated 95% CI, and p-value will be presented.

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 (1=Grade 1: Mild, 2=Grade 2: Moderate, 3=Grade 3: Severe or medically significant but not immediately life-threatening, 4=Grade 4: Life-threatening , 5=Grade 5: Death), relationship to study drug (related or not related) and action relative to the study drug mobocertinib. Study procedure taken due to AE will also be listed. All AEs occurring during this study will be coded using the MedDRA® Version 23.0. However, only TEAEs occurring after administration of the first dose of study drug and through the end of the study 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 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 tables, see TFL Shell document.

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 or AEs leading to study drug discontinuation 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 Clinical Study Report (CSR).

7.12.2 Clinical Laboratory Evaluations

Hematology, serum chemistry, and urinalysis will be performed at screening, check-in (Day -1) of each period, Day 4 of each period or prior to early termination from the study, and at the end of Period 2. 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).

For each laboratory test, a shift table will be developed comparing the frequency and percentage of the results at baseline (above normal (H), normal (N), or below normal (L)) with the 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. Additionally, the PI will

provide a 4th flag when the 3rd flag indicates "R" or "^". This 4th flag is intended to capture final CS (+)/NCS (-) when the 3rd flag does not document significance. 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. CS results will also be presented in a table.

7.12.3 Vital Signs

Single measurements of heart rate and blood pressure will be obtained at screening, predose (Day -1), 4 and 12 hours of Day 1, and Day 2 postdose (times relative to mobocertinib dose) in each period or upon early termination, and at the end of Period 2. Respiration rate and temperature will only be collected at screening. 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 (Day -1). 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

12-lead ECGs will be recorded at screening, predose (Day -1), 4 hours of Day 1 postdose (time relative to mobocertinib dose) or upon early termination, and at the end of Period 2. 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 (Day -1). ECG data will also be displayed in a data listing by subject.

7.12.5 Pulmonary Function Test

Pulmonary function tests (PFTs) may be performed in the event of a pulmonary AE and deemed clinically necessary, as determined by the PI. PFT results if present will be presented in a data listing by subject.

7.12.6 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.

7.12.7 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 Interim Analysis

Not applicable.

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 8.1 or higher.

7.15 Changes in the Statistical Analysis Plan

Section 11.1.3.1 of the protocol stated that AUC_{last} will be included in the ANOVA for TAK-788. However, Section 11.1.3.2 of the protocol stated that AUC_{last} will be included in the calculation of GMR and 90% CI only if it is needed. The SAP clarified that AUC_{last} will be included in the ANOVA only if AUC_{∞} is not available for at least 12 subjects.

8.0 REFERENCES

Not applicable.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Biostatistics Approval	20-Aug-2020 20:39 UTC