Title: A Phase 1 Study of Oral TAK-788 to Evaluate the Drug-Drug Interaction with Itraconazole and Rifampin in Healthy Adult Subjects

NCT Number: NCT03928327

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STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-788-1006
CELERION STUDY NUMBER: CA24219

A Phase 1 Study of Oral TAK-788 to Evaluate the Drug-Drug Interaction with Itraconazole and Rifampin in Healthy Adult Subjects

PHASE 1

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Prepared by:

PPD

[redacted]

Based on:

Protocol Dated: 16 April 2019

1.1 Approval Signatures

Study Title: A Phase 1 Study of Oral TAK-788 to Evaluate the Drug-Drug Interaction with Itraconazole and Rifampin in Healthy Adult Subjects

PPD

Date

2.0 TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

3.0 LIST OF ABBREVIATIONS

AE	adverse event
ANOVA	analysis of variance
AUC	area under the curve
AUC∞	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
AUCt	area under the plasma concentration-time curve from time 0 to a specific time point across all subjects in the same study part
BLQ	below the limit of quantitation
BMI	body mass index
CI	confidence interval
CL/F	apparent clearance after extravascular administration
Cmax	maximum observed plasma concentration
CPAP	Clinical Pharmacology Analysis Plan
CRF	case report form
CRU	clinical research unit
CS	clinically significant
CV	coefficient of variation
CYP	cytochrome P450
DDI	drug-drug interaction
ECG	electrocardiogram
GMR	geometric mean ratio
ICF	informed consent form
ICH	International Conference on Harmonization
Lambda_z	terminal disposition phase rate constant
ln	natural log
LSM	least-squares means
MedDRA	Medical Dictionary for Regulatory Activities
PFT	pulmonary function test
PI	Principal Investigator
PK	pharmacokinetics
PO	orally administered
QD	once daily
SAE	serious adverse event

SD	standard deviation
SOC	system organ class
t½	terminal disposition phase half-life
TBD	to be determined
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 disposition phase after extravascular administration
WHO	World Health Organization

4.0 OBJECTIVES

4.1 Primary Objectives

Part 1

To characterize the effect of itraconazole, a strong cytochrome P450 (CYP) 3A inhibitor, on the single-dose pharmacokinetics (PK) of TAK-788 and its active metabolites (AP32960 and AP32914) in healthy adult subjects.

Part 2

To characterize the effect of rifampin, a strong CYP3A inducer, on the single-dose PK of TAK-788 and its active metabolites (AP32960 and AP32914) in healthy adult subjects.

4.2 Exploratory Objective

Parts 1 and 2

To assess the safety data of TAK-788 following single oral dose with/without strong CYP3A inhibitor or inducer in healthy adult subjects.

4.3 Study Design

This is a 2-part study. Each part will be conducted as an open-label, 2-period, fixed sequence study with TAK-788 designed to characterize TAK-788 drug-drug interaction (DDI) with either a strong CYP3A inhibitor, itraconazole (Part 1) or with a strong CYP3A inducer, rifampin (Part 2) in healthy adult subjects. Subjects participating in Part 1 will be different from those participating in Part 2. Additionally, Part 1 will be a sequential study design; Part 1 Cohort 2 will not start until PK data from Part 1 Cohort 1 (up to Period 2 Day 15) has been evaluated. The study parts may be conducted concurrently.

<u>Part 1: TAK-788 assessment with itraconazole</u>

Part 1 will be conducted in 2 cohorts: Cohort 1 will enroll 4 subjects and will assess whether the 20 mg dose of TAK-788 is an appropriate dose for the TAK-788/itraconazole DDI study; depending on the PK results, Cohort 2 will either continue to enroll 8 more subjects at this same dose level or enroll 12 more subjects at a revised TAK-788 dose level. Other than the dose of TAK-788, the study design will be exactly the same for each cohort.

This study part will comprise of a screening period, 2 treatment periods and a follow-up phone call in up to 16 healthy subjects. Dose administration and PK collection scheme for the treatment period is outlined in the table below.

Table 4.a Part 1 TAK-788 Assessment with Itraconazole

	Treatment Period 1								Treatment Period 2														
Study Day	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**8***	**1***	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
TAK-788 PO		X											X										
Itraconazole 200 mg QD PO									X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PK Blood Samples		X	X	X	X	X	X	X*	X*				X	X	X	X	X	X		X	X		X
Overnight in Clinics	X	X	X	X								X	X	X	X								

* Since the washout period is 7 days the timing of the last PK blood draw of Period 1 will occur within 60 minutes prior to the first dose of itraconazole on Period 2 Day 1; only one PK sample will be taken.
Abbreviation: PK=Pharmacokinetics; PO=per oral; QD=once daily

On Period 1 Day 1, subjects will receive a single 20 mg oral dose of TAK-788 or a TAK-788 oral dose to be determined (TBD) (Cohort 2) as capsules (fasting). A standardized meal will be provided at least 4 hours postdose. Subjects will remain in the CRU until the morning of Day 4 after the 72-hour PK sample is collected. Additional PK samples will be taken as an outpatient up to 168 hours postdose (Period 1 Day 8, which is the same as Period 2 Day 1).

In Period 2, subjects will receive 200 mg itraconazole QD alone as an oral solution on an empty stomach (no food from at least 1 hour prior until at least 2 hours after dosing). Subjects will be admitted to the clinical research unit (CRU) on Period 2 Day 4. In the morning of Period 2 Day 5, subjects will receive 200 mg itraconazole together with 20 mg oral TAK-788 or a TBD oral dose of TAK-788 (fasting). A standardized meal will be provided at least 4 hours postdose. Subjects will be furloughed from the CRU after the 72-hour PK sample is collected in the morning of Period 2 Day 8. There will be outpatient visits to the CRU for dosing itraconazole and/or PK sampling from Day 1 to Day 3 and Day 9 to Day 14. A final post-treatment follow-up and last PK sampling will occur at 240 hours post-Day 5 TAK-788 dose (Period 2 Day 15).

All PK data (TAK-788 and its 2 active metabolites, AP32960 and AP32914) collected in Cohort 1 (up to Day 15) will be evaluated to determine the dose of TAK-788 administered to subjects in Cohort 2 of the study. The TAK-788 dose in Cohort 2 may remain at 20 mg or may be modified to an appropriate level to approximate a similar exposure compared to the geometric mean of single-dose exposure previously observed at 160 mg single dose TAK-788 alone in healthy subjects.

Part 2: TAK-788 assessment with rifampin

Part 2 will comprise of a screening period, 2 treatment periods, and a follow-up phone call in 12 subjects. Dose administration and PK collection scheme for the treatment periods are outlined in the table below.

Table 4.b Part 2 TAK-788 Assessment with Rifampin

	Treatment Period 1								Treatment Period 2													
Study Day	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**8***	**1***	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
TAK-788 160 mg PO		X													X							
Rifampin 600 mg QD PO									X	X	X	X	X	X	X	X	X	X	X	X	X	
PK Blood Samples		X	X	X	X	X	X	X*	X*						X	X	X	X	X	X		X
Overnight in Clinics	X	X	X	X										X	X	X	X					

*Since the washout period is 7 days the timing of the last PK blood draw of Period 1 will occur within 60 minutes prior to the first dose of rifampin on Period 2 Day 1; only one PK sample will be taken.
Abbreviation: PK=Pharmacokinetics; PO=per oral; QD=once daily.

On Period 1 Day 1, a different group of subjects from Part 1 will receive a single 160 mg oral dose of TAK-788 as capsules (fasting). A standardized meal will be provided at least 4 hours postdose. Subjects will remain in the CRU until the morning of Day 4 after the 72-hour PK sample is collected. Additional PK samples will be taken as an outpatient up to 168 hours postdose (Period 1 Day 8, which is the same as Period 2 Day 1).

In Period 2, subjects will receive 600 mg rifampin once daily (QD) alone as capsules (fasting). Subjects will be admitted to the CRU on Day 6. In the morning of Day 7, subjects will receive 160 mg oral TAK-788 together with 600 mg rifampin (fasting). A standardized meal will be provided at least 4 hours postdose. Subjects will be furloughed from the CRU after the 72-hour PK sample is collected in the morning of Day 10. There will be outpatient visits to the CRU for dosing rifampin and/or PK sampling from Day 1 to Day 5 and Day 11 to Day 13. A final post-treatment follow-up and last PK sampling will occur at 168 hours post Day 7 dose (Day 14).

Parts 1 and 2:

All of study drugs will be orally administered with approximately 240 mL water or total aqueous volume of approximately 240 mL when dosing with itraconazole oral solution. All doses of TAK-788, itraconazole, and rifampin will be administered at the CRU during this study, either during confinement or on an outpatient basis.

Spirometry as the pulmonary function test (PFT) is required to be performed and be assessed as normal at screening. Post-dose spirometry will be performed only if indicated on the basis of pulmonary symptoms, at the discretion of the Investigator or designee.

A final safety follow-up phone call will occur 30 ± 2 days after the last TAK-788 dose to determine if any adverse events (AEs) have occurred since the last study visit.

Any subject who experiences emesis within 8 hours post dosing with TAK-788 will be excluded in the final data analysis. Replacement of discontinued or withdrawn subject due to any reason will be assessed on a case by case basis by the Sponsor and Investigator to ensure a minimum of 10 PK-evaluable subjects complete the study in each part of study.

The treatment description and planned dose levels of TAK-788, itraconazole, and rifampin to be evaluated are outlined in the table below.

Table 4.c Treatment Descriptions and Planned Dose Levels of TAK-788, Itraconazole (Part 1), and Rifampin (Part 2)

Part 1:	
Treatment A	Cohort 1, Period 1: A single oral dose of 20 mg TAK-788 (1 x 20 mg capsule) administered at Hour 0 on Day 1 following an overnight fast.
Treatment B	Cohort 1, Period 2: Multiple oral doses of 200 mg itraconazole oral solution administered every 24 hours for 14 consecutive days (within ±1 hour of Day 1 dosing) with a single oral dose of 20 mg TAK-788 (1 x 20 mg capsule) administered at Hour 0 on Day 5 following an overnight fast.
Treatment A or E *	Cohort 2, Period 1: A single oral dose of TBD mg TAK-788 (1 x TBD mg capsule) administered at Hour 0 on Day 1 following an overnight fast.
Treatment B or F *	Cohort 2, Period 2: Multiple oral doses of 200 mg itraconazole oral solution administered every 24 hours for 14 consecutive days (within ±1 hour of Day 1 dosing) with a single oral dose of TBD mg TAK-788 administered at Hour 0 on Day 5 following an overnight fast.
Part 2:	
Treatment C	Period 1: A single oral dose of 160 mg TAK-788 (4 x 40 mg capsules) administered at Hour 0 on Day 1 following an overnight fast.
Treatment D	Period 2: Multiple oral doses of 600 mg rifampin (2 x 300 mg capsules) administered every 24 hours for 13 consecutive days (within ±1 hour of Day 1 dosing) with a single oral dose of 160 mg TAK-788 (4 x 40 mg capsules) administered at Hour 0 on Day 7 following an overnight fast.

* Note: Interim PK will be provided after completion of Part 1 Cohort 1 to confirm the dose to be used for Part 1 Cohort 2.

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoints

The primary endpoints of the study are:

- 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})
- Time of first occurrence of C_{max} (t_{max})

5.2 Exploratory Endpoints

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

- Treatment–emergent adverse event (TEAE) assessment
- Clinical laboratory testing (hematology, serum chemistry and urinalysis).
- Physical examinations
- 12-lead electrocardiograms (ECGs)
- Vital signs

5.3 Additional Endpoints

In addition, the following plasma PK parameters for TAK-788 and its active metabolites, AP32960 and AP32914 will be calculated:

- Terminal disposition phase half-life ($t_{½}$)
- Terminal disposition phase rate constant (lambda_z),
- Apparent clearance after extravascular administration (CL/F) for TAK-788 only
- Apparent volume of distribution during the terminal disposition phase after extravascular administration (Vz/F) for TAK-788 only

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 TAK-788 in the absence and presence of itraconazole or rifampin. The within-patient coefficient of variation for TAK-788 AUC_∞ was estimated to be 17.2% on the basis of data from a clinical study conducted in healthy subjects (TAK-788-1001). If the AUC_∞ ratio for TAK-788 in the presence versus absence of itraconazole or rifampin is X (an AUC_∞ geometric mean ratio [GMR] to be determined in this study), with a sample size of 10, the 90% CI for the AUC_∞ ratio is expected to be 0.868X to 1.15X on the basis of the variance assumptions.

Up to 28 healthy adult subjects will be enrolled into 2 Parts (up to 16 in Part 1, and 12 in Part 2) to get 10 PK-evaluable subjects for estimation of DDI magnitude in each part of study.

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 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. 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. 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 concentrations and PK parameter values will be presented to 3 significant figures Arithmetic mean (mean), median, and geometric mean (Geom Mean) values will be presented to 1 more level of precision than the individual 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 concentration and PK parameter values. Minimum and maximum values will be presented to the same precision as the individual concentration and PK parameter 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. 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
- 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 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

7.1.2 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 (for Parts 1 and 2). 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 (for Parts 1 and 2). 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, for Period 1 of Parts and 2, baseline is defined as the last assessment including rechecks taken at check-in (Day -1) prior to TAK-788 dosing. For Period 2 of Part 1, baseline is defined as the last assessment including rechecks taken prior to TAK-788 dosing at Day 4, and for Period 2 of Part 2, baseline is defined as the last assessment including rechecks taken prior to TAK-788 dosing at Day 6.

For vital signs and 12-lead ECGs, for Period 1 of Parts 1 and 2, baseline is defined as the last assessment including rechecks taken prior to TAK-788 dosing. For Period 2 of Part 1, baseline is defined as the last assessment including rechecks taken prior to TAK-788 dosing at Day 5, and for Period 2 of Part 2, baseline is defined as the last assessment including rechecks taken prior to TAK-788 dosing at Day 7.

7.2 Analysis Sets

Safety Set:

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

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 (e.g., 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 TAK-788 will be excluded in the final data analysis. In terms of criteria for evaluable subjects, please see CPAP.

7.3 Study Information

For each part, 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

For each part, disposition of subjects (number of subjects dosed, completed the study, subjects in the PK-evaluable population who 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. Subjects will be considered to have completed the study if they have completed the protocol-specified assessments within the protocol. Percentages will be based on the number of subjects in the safety set.

7.5 Demographic and Other Baseline Characteristics

For each part, 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

For each part, 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. All medical history of this study will be coded using the MedDRA® Version 22.0. There will be no statistical analysis of medical history.

7.7 Medication History and Concomitant Medications

For each part, 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-Mar-2019_b3 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

For each part, the date, time, and dose of single oral dose of TAK-788 and multiple oral doses of itraconazole and rifampin will be respectively listed by subject.

7.9 Efficacy Analysis

Not applicable.

7.10 Pharmacokinetic/Pharmacodynamic Analysis

7.10.1 Pharmacokinetic Analysis

For Part 1, blood samples (one 3 mL sample per scheduled time) for PK analysis of TAK-788, AP32960, and AP32914 will be collected as specified in Table 7:1 following administration of TAK-788 alone (sampling Day 1 – Period 1) or coadministered with itraconazole (sampling Day 5 – Period 2).

Table 7.a Collection of Blood Samples for Pharmacokinetic Analysis for Part 1

Analytes	Matrix	Sampling Day	Scheduled Time (hours)
TAK-788, AP32960, and AP32914	Plasma	1	Predose, 0.5, 1, 2, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, and 168 hours postdose (a) (b).
TAK-788, AP32960, and AP32914	Plasma	5	Predose, 0.5, 1, 2, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, 168, 192, and 240 hours postdose (a) (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 168-hour postdose blood draw on sampling Day 1 of study Period 1 will be drawn prior to itraconazole dosing of Period 2.
(c) The collection times for analysis of TAK-788 PK parameters will be relative to TAK-788 dose on Day 5 for Period 2.

For Part 2, blood samples (one 4 mL sample per scheduled time) for PK analysis of TAK-788, AP32960, and AP32914 will be collected as specified in Table 7:2 following administration of TAK-788 alone (sampling Day 1 – Period 1) or coadministered with rifampin (sampling Day 7 – Period 2).

Table 7.b Collection of Blood Samples for Pharmacokinetic Analysis for Part 2

Analytes	Matrix	Sampling Day	Scheduled Time (hours)
TAK-788, AP32960, and AP32914	Plasma	1	Predose, 0.5, 1, 2, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, and 168 hours postdose (a) (b).
TAK-788, AP32960, and AP32914	Plasma	7	Predose, 0.5, 1, 2, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, and 168 hours postdose (a) (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 168-hour postdose blood draw on sampling Day 1 of study Period 1 will be drawn prior to rifampin dosing of Period 2.
(c) The collection times for analysis of TAK-788 PK parameters will be relative to TAK-788 dose on Day 7 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 TAK-788, 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 TAK-788, 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 TAK-788, 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 TAK-788, 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.

Drug-Drug Interaction

For evaluation of potential effect of itraconazole (Part 1) and rifampin (Part 2), a linear mixed-effects model will be used for the analysis on the ln-transformed Cmax and AUC∞ (AUClast or AUCt if AUC∞ is not available) for TAK-788, AP32960, and AP32914 and ln-transformed combined molar Cmax and AUC∞ for TAK-788, AP32960, and AP32914. The model will include treatment as a fixed-effect and subject as a random-effect. Each model will include calculation of LSMs as well as the difference between LSMs.

GMR and 90% confidence intervals, consistent with the two one-sided test, will be calculated using the exponentiation of the difference between treatment LSMs from the analyses on the ln-transformed Cmax and AUC∞ (AUClast or AUCt if AUC∞ is not available) for TAK-788, AP32960, and AP32914 and ln-transformed combined molar Cmax and AUC∞ for TAK-788, AP32960, and AP32914. These ratios will be expressed as a percentage of the following comparisons:

Part 1:

Treatment B (itraconazole + 20 mg TAK-788) relative to Treatment A (20 mg TAK-788)

And if applicable Treatment F (itraconazole + TBD* mg TAK-788) relative to Treatment E (TBD* mg TAK-788)

*Note: The dose of TAK-788 may be modified following results from interim analysis from Cohort 1 (Part 1). Cohorts 1 and 2 of Part 1 will be combined if 20 mg TAK-788 is the dose, and the comparison will be Treatment B versus Treatment A. However, if after interim analysis, a different dose of TAK-788 is used, only the 12 subjects in Cohort 2 receiving the TBD dose of TAK-788 will be used, and the comparison will be Treatment F versus Treatment E. If the dose of TAK-788 in Cohort 2 is different from Cohort 1, the concentrations and PK parameters for subjects receiving the 20 mg TAK-788 dose will be presented in post-text concentration and PK parameter tables only, as outlined in the CPAP. Consequently, no statistical comparisons will be performed for subjects receiving the 20 mg TAK-788 dose level.

Part 2:

Treatment D (rifampin + 160 mg TAK-788) relative to Treatment C (160 mg TAK-788)

The following SAS code will be used respectively for each part:

PROC MIXED DATA=XXXX;

CLASS Treatment Subject;

MODEL ln<PK_Parameter> = Treatment / DDFM=KR;

RANDOM Subject;

ESTIMATE 'Treatment B vs A' Treatment -1 1 / CL ALPHA = 0.10 E; (For Part 1 when the original dose of 20 mg TAK-788 is used.)

ESTIMATE 'Treatment F vs E' Treatment -1 1 / CL ALPHA = 0.10 E; (For Part 1 when after the interim analysis, a different TBD TAK-788 dose is used.)
ESTIMATE 'Treatment D vs C' Treatment -1 1 / CL ALPHA = 0.10 E; (For Part 2)
LSMEANS Treatment;
Run;

Nonparametric Analysis of Tmax

A nonparametric analysis for Tmax 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 Tmax (Hollander and Wolf (1999)). Tmax will not be ln-transformed.

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 consequences, 5=Grade 5: Death related to AE), relationship to study drug (related or not related) and action relative to the study drug for both TAK-788 and itraconazole or rifampin. Study procedure taken due to AE will also be listed. All AEs occurring during this study will be coded using the MedDRA® Version 22.0. However, only TEAEs occurring after administration of the first dose of study drug and through the end of the study (approximately 30 (± 2) days after the last dose of TAK-788 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 of each part, TEAEs will be coded using MedDRA® Version22.0 and tabulated by System Organ Class (SOC) and Preferred Term. For each part, 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-788 and itraconazole or rifampin). 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 itraconazole which is started from the first itraconazole dosing and prior to TAK-788 dosing. Treatment B2 will be itraconazole + TAK-788 which is after the dosing of TAK-788 on Day 5 of Period 2. Note: Treatments E and F (including F1 and F2) will be added, if after interim analysis, 12 subjects in Cohort 2 will be treated with E and F of the TBD dose.

For treatment D, the TEAEs will be summarized separately for two segments (Treatment D1 and Treatment D2). Treatment D1 will be rifampin which is started from the first rifampin dosing and prior to TAK-788 dosing. Treatment D2 will be rifampin + TAK-788 which is after the dosing of TAK-788 on Day 7 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

For Part 1, hematology, serum chemistry, and urinalysis will be performed at screening, check-in (Day -1), and 48 hours (Day 3) postdose of Period 1, Day 1 predose, Day 4 predose, 48 hours (Day 7), and 240 hours (Day 15) postdose of Period 2 (times relative to TAK-788 dose) or upon early termination. For Part 2, hematology, serum chemistry, and urinalysis will be performed at screening, check-in (Day -1), and 48 hours (Day 3) postdose of Period 1, Day 1 predose, Day 6 predose, 48 hours (Day 9), and 168 hours (Day 14) postdose of Period 2 (times relative to TAK-788 dose) or upon early termination. 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.

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 post-baseline 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

For Part 1, single measurements of heart rate and blood pressure will be obtained at screening, Day 1 predose and at 4, 12 (Day 1), and 24 hours (Day 2) postdose of Period 1, and Day 1 predose, Day 5 predose and at 4 hours (Day 5), 12 hours (Day 5), 24 hours (Day 6), and 240 hours (Day 15) postdose of Period 2 (times relative to TAK-788 dose) or upon early termination. For Part 2, single measurements of heart rate and blood pressure will be recorded at screening, Day 1 predose and at 4 hours (Day 1), 12 hours (Day 1), and 24 hours (Day 2) postdose of Period 1, and Day 1 predose, Day 7 predose and at 4 hours (Day 7), 12 hours (Day 7), 24 hours (Day 8), and 168 hours (Day 14) postdose of Period 2 (times relative to TAK-788 dose) or upon early termination. For Parts 1 and 2, respiration rate and temperature are collected at screening, 240 hours (Day 15) postdose at Period 2 for Part 1, 168 hours (Day 14) postdose at Period 2 for Part 2 or upon early termination. Additional unscheduled vital signs measurements may be taken at other times, if deemed necessary by the PI.

For each part, summary statistics (n, mean, SD, minimum, median, and maximum) will be reported for vital sign results and change from baseline (heart rate and blood pressure only) by

treatment and time point of collection. Vital signs will also be displayed in a data listing by subject.

7.12.4 12-Lead ECGs

For Part 1, standard 12-lead ECGs will be recorded at screening, Day 1 predose and at 4 hours (Day 1) and 24 hours (Day 2) postdose of Period 1, and Day 1 predose, Day 5 predose and at 4 hours (Day 5), 24 hours (Day 6), and 240 hours (Day 15) postdose of Period 2 (times relative to TAK-788 dose) or upon early termination. For Part 2, standard 12-lead ECGs will be recorded at screening, Day 1 predose and at 4 (Day 1) and 24 hours (Day 2) postdose of Period 1, and Day 1 predose, Day 7 predose and at 4 hours (Day 7), 24 hours (Day 8), and 168 hours (Day 14) postdose of Period 2 (times relative to TAK-788 dose) or upon early termination. Additional unscheduled ECGs may be recorded at other times, if deemed necessary by the PI.

For each part, 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. ECG data will also be displayed in a data listing by subject. ECG overall interpretation will indicate if the results are normal, abnormal NCS (not clinically significant) or abnormal CS (clinically significant).

7.12.5 Pulmonary Function Test (PFT)

For Parts 1 and 2, spirometry measures will be taken at screening (within 7 days prior to first dosing) using a standard calibrated spirometer to determine the parameters: FEV_1 (forced expiratory volume), FVC (forced vital capacity), and FEV_1/FVC. Spirometry may be repeated during the study in response to pulmonary symptoms at the discretion of the Investigator or designee. PFT results will be presented in a data listing by subject. Results will be interpreted by the PI and recorded in the comment column.

7.12.6 Physical Exams

For Parts 1 and 2, a full physical exam will be performed at screening. Symptom driven physical exams may be performed at other times, if deemed necessary by the PI. Physical exam findings will be presented in a data listing by subject. Reproductive system findings will also be listed by subject. For "Abnormal" result, a flag "*" will be added as "Abnormal*".

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

Interim PK analysis will be conducted after completion of Part 1 Cohort 1 to determine the dose to be used for Part 1 Cohort 2.

7.14 Preliminary Analysis

QCed plasma concentration data will be plotted using nominal times to aid in the determination of samples for repeat bioanalysis. If requested, a preliminary PK 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

Two (2) protocol clarification letters were issued for this study. The first clarification letter issued on 24 April 2019 was written to correct an error in the number and strength of rifampin capsules. The second clarification letter issued on 25 April 2019 was written to correct an inconsistency in the contraceptive wording in Appendix D (Pregnancy and Contraception) of the protocol.

During generation of the SAP, it was determined to include a nonparametric analysis of Tmax in the study to address the Tmax primary endpoint.

8.0 REFERENCES

Not applicable.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	[illegible]	[illegible]