Title: Phase 1, Randomized, Double-blind, Placebo-Controlled, Single Rising Dose Study to Evaluate Pharmacokinetics, Safety, and Tolerability of TAK-788 Followed by Open-Label, Crossover Evaluation of the Effects of a Low-Fat Meal on TAK-788 Pharmacokinetics and Evaluation of Relative Bioavailability of TAK-788 Capsules in Healthy Subjects

NCT Number: NCT03482453

SAP Approve Date: 27 March 2019

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STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-788-1001

Phase 1, Open-Label, Single Rising Dose Study to Evaluate PK, Safety, and Tolerability of TAK-788 Followed by Crossover Evaluation the Effects of a Low-Fat Meal on TAK-788 PK in Healthy Subjects

PHASE 1

Version: 1.0

Date: 27 March 2019

Prepared by:

PPD

Based on:

Protocol Version: Amendment 03

Protocol Date: 13 November 2018

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3.0 LIST OF ABBREVIATIONS

AE	adverse event
ANOVA	analysis of variance
AUC	area under the plasma concentration-time curve
AUC_{extrap}%	area under the curve from the last quantifiable concentration to infinity calculated using the observed value of the last quantifiable concentration, expressed as a percentage of AUC_{∞}
AUC_t	area under the concentration-time curve from time 0 to time t
AUC_{∞}	area under the concentration-time curve from time 0 to infinity, calculated using the observed value of the last quantifiable concentration
C_{av}	average plasma concentration
C_{max}	maximum observed plasma concentration
CT	computed tomography
C_{trough}	observed plasma concentration at the end of a dosing interval
CV	coefficient of variation
DiC	drug-in-capsule (formulation)
DLco	diffusion capacity
DLT	dose-limiting toxicity
ECG	electrocardiogram
eCRF	electronic case report form
EGFR	epidermal growth factor receptor
GI	gastrointestinal
ln	log-transformed
LSM	least-squares mean
MedDRA	Medical Dictionary for Regulatory Activities
PFT	pulmonary function test
PK	pharmacokinetic(s)
SAE	serious adverse event
SOP	standard operating procedure
$t_{1/2z}$	terminal disposition phase half-life
TEAE	treatment-emergent adverse event
t_{max}	time to first occurrence of C_{max}
WHO	World Health Organization

4.0 OBJECTIVES

4.1 Primary Objectives

The primary objectives are:

Part 1: to assess safety and tolerability of TAK-788 and to identify a tolerable single oral dose of TAK-788 administered as a DiC formulation in healthy subjects.

Part 2: to characterize the effects of a low-fat meal on the PK of TAK-788 and its active metabolites, AP32960 and AP32914, administered as a DiC formulation in healthy subjects.

Part 3: To evaluate the bioavailability of a test (Process B) DiC of TAK-788 relative to a reference (Process A) DiC of TAK-788 in healthy subjects.

4.2 Secondary Objectives

The secondary objectives are:

Part 1: to characterize the PK of TAK-788 and its active metabolites, AP32960 and AP32914, administered as a DiC formulation in healthy subjects.

Part 2/ Part 3: To assess the safety of TAK-788 following a single dose of TAK-788 in healthy subjects.

4.3 Exploratory Objectives

The exploratory objective is:

CCI [redacted]

4.4 Study Design

This is a randomized, double-blind, placebo-controlled single rising dose study, followed by an open-label, crossover evaluation of the effects of a low-fat meal on the PK of TAK-788 and its 2 active metabolites in healthy subjects, and a crossover evaluation of the relative bioavailability of TAK-788 Process B DiC (test) versus Process A DiC (reference) in healthy subjects under fasting conditions. Following the completion of Part 1 (dose escalation phase) where a safe and tolerable dose in healthy subjects will be identified, Part 2 (food effect phase) and Part 3 (relative bioavailability of TAK-788 capsules) will be initiated where the effects of a low-fat meal on TAK-788 and the relative bioavailability of TAK-788 in test versus reference will be studied.

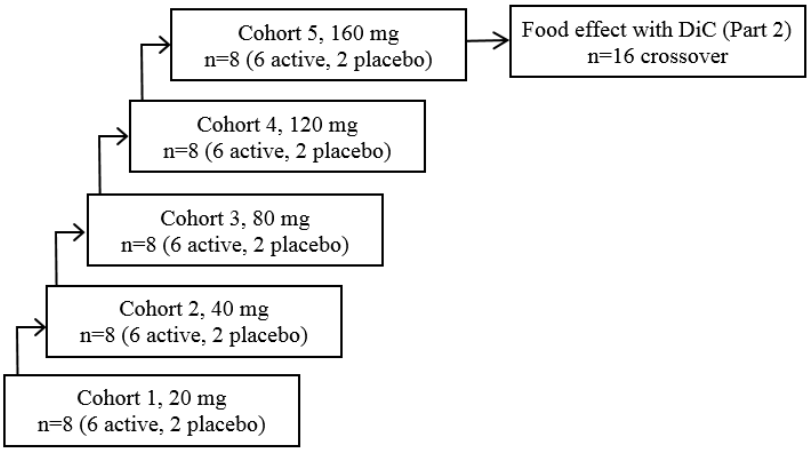
Part 1 – Dose Escalation:

In the double-blind, randomized, placebo-controlled dose escalation phase, cohorts of 8 healthy subjects will be randomized: Under fasting conditions, 6 subjects will receive a single dose of TAK-788 and 2 subjects will receive placebo. The starting dose will be 20 mg, then with each subsequent 8-subject cohort the dose will escalate to a single dose of 40, 80, 120, up to 160 mg. Dose escalation can occur if there are no DLTs following the administration of TAK-788 and all Grade ≥2 treatment-related AEs resolve to Grade ≤1 or return to baseline by Day 5. If all treatment-related Grade ≥2 AEs have not resolved to Grade ≤1 or returned to baseline by Day 5, the assessment will be repeated on Day 8 and Day 15, if necessary, before proceeding to the next planned higher dose. The subjects will remain at the clinical study site for at least 48 hours postdose for close safety monitoring. The subjects will be furloughed from the site 48 hours postdose if there are no Grade ≥2 AEs. Subjects will return to the site for PK sample collection on Days 4, 5, and 8. A final safety phone conference will occur 30 days after the last dose (window of up to 2 days after Day 30).

Additional cohorts may also be enrolled in Part 1 to assess the safety, tolerability, and PK of single-dose TAK-788 DiC containing TAK-788 active pharmaceutical ingredient (API) from a different synthetic process (such as Process A). The dose(s) of TAK-788 in the additional cohort(s) will be determined by the safety, tolerability, and PK exposure data from the completed cohorts in this study and the experience in the ongoing phase 1/2 study in patients with NSCLC (Study AP32788-15-101). The highest dose tested in Part 1 of the study will not exceed the unit dose of the MTD identified in Study AP32788-15-101.

To mitigate the risk of treatment, pulmonary function tests (PFTs: spirometry, lung volumes, and diffusion capacity [DLco]) and chest computed tomography (CT) scan are required to be performed and assessed to be normal (PFTs ≥80% of predicted normal) at screening no more than 7 days before Day 1. At 48 hours postdose before furlough, PFTs will be performed and pulmonary symptoms assessed. If the DLco has decreased by >20% from baseline or the subject reports pulmonary symptoms on Day 3, a chest CT scan will be performed. Any DLco abnormalities or chest CT scan abnormalities will be followed weekly until resolution. An appropriate treatment will be initiated by the investigator or attending pulmonologist in the event of clinically significant pulmonary symptoms, abnormal DLco, or abnormal chest CT scan.

Figure 4.a Study Schema for Single Rising Dose Phase (Part 1)



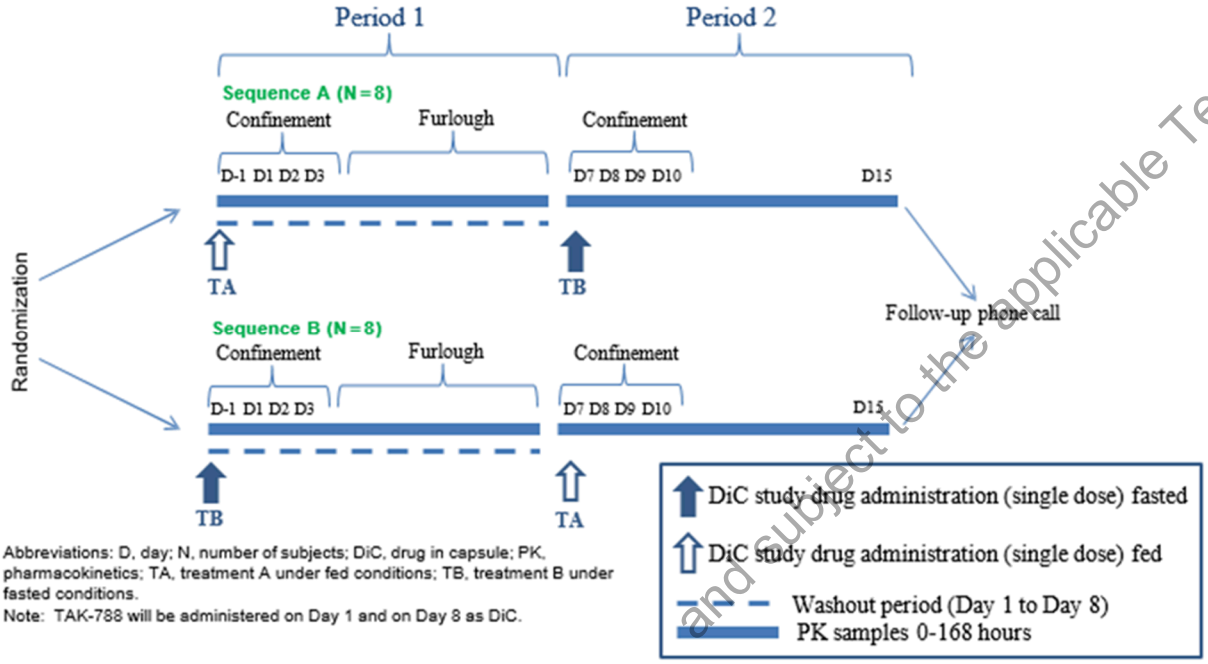
DiC, drug in capsule.

Part 2 – Food Effect:

The purpose of Part 2 is to evaluate the effect of a low-fat meal on TAK-788 PK using a 2-way crossover design. The low-fat meal effect was assessed at 120 mg and 160 mg doses, which are identified as tolerable doses in Part 1.

In the food effects part of the study, subjects will be randomized to a crossover sequence at a 1:1 ratio and administered the tolerable single dose on Day 1 in Period 1 and Day 8 in Period 2 with a low-fat meal (Treatment A) or under fasting conditions (Treatment B) with a planned washout period of at least 7 days which may be updated pending the PK results from Part 1. The content of a low-fat meal is shown in Figure 4.b. The duration of washout will be adjusted to ensure that the C_{trough} (observed plasma trough concentration) of TAK-788 at 168 hours postdose in Part 1 is <5% of the observed C_{max} of TAK-788 at the dose of the food effect evaluation. The planned washout period used in Part 2 is 7 days. PFTs (spirometry, lung volumes, and DLco) and chest CT scan are required to be performed and be assessed as normal at screening. PFTs and chest CT scan will be done on Day 3, Day 10, and/or Early Termination visit in Part 2 only if indicated on the basis of pulmonary symptoms. Other clinical study procedures are the same as those in the dose escalation phase. Subjects will return to the site for the PK sample collection on Days 4, 5, 8, 11, 12, and 15. A final safety phone conference will occur 30 days after the last dose (window of up to 2 days after Day 38).

Figure 4.b Study Schema for Food Effect Phase (Part 2)



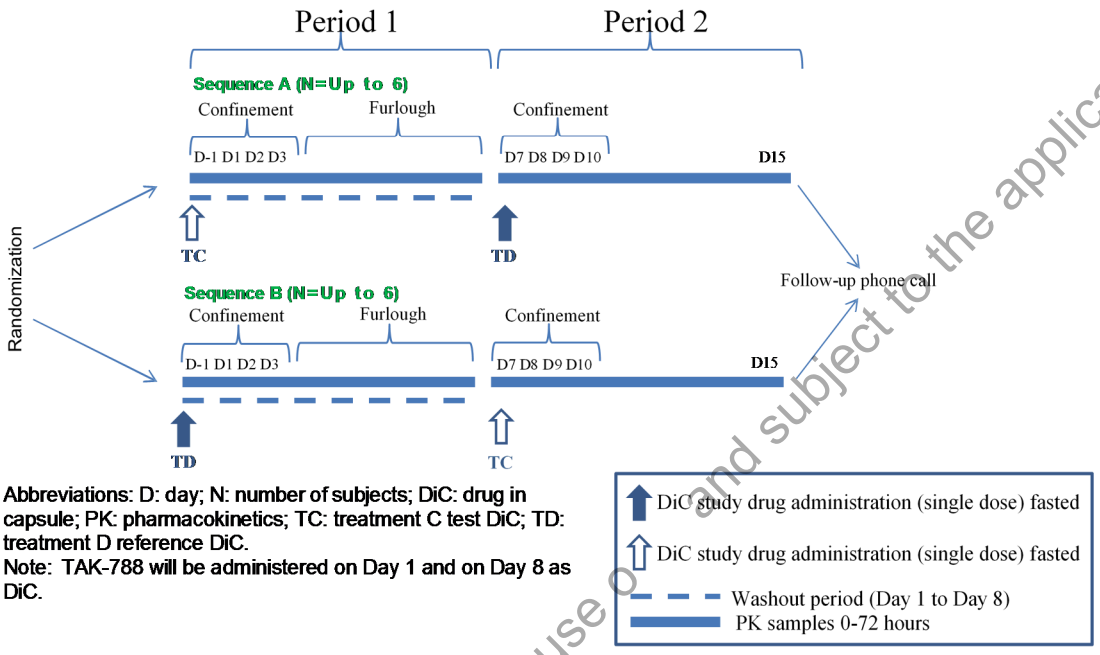
Abbreviations: D, day; N, number of subjects; DiC, drug in capsule; PK, pharmacokinetics; TA, treatment A under fed conditions; TB, treatment B under fasted conditions.
Note: TAK-788 will be administered on Day 1 and on Day 8 as DiC.

Part 3 – Relative Bioavailability:

The purpose of Part 3 is to evaluate the bioavailability of a test DiC of TAK-788 relative to a reference DiC of TAK-788. Part 3 of the study will be open-label.

Subjects will be randomly assigned to a crossover sequence at a 1:1 ratio and administered a single dose of 160 mg TAK-788 capsule A DiC (reference) or 160 mg TAK-788 capsule B DiC (test) on Day 1 in Period 1 and on Day 8 in Period 2 under fasting conditions, with a planned washout period of 7 days. PFTs (spirometry, lung volumes, and DLco) are required to be performed and assessed as normal at screening. PFTs will be performed on Day 3, Day 10, and Early Termination visit in Part 3 only if indicated on the basis of pulmonary symptoms; no chest CT scans will be done. Other clinical study procedures are the same as those in the dose escalation phase. Subjects will have PK collection samples collected during confinement, and the last PK sample will be collected at 72 hours postdose in each period. Subjects will be furloughed after the last PK sample collection in Period 1. Subjects will return to the clinical study site on Day 7 for Period 2 study. Subjects will be released from the clinical study site after the last PK sample collection in Period 2. Safety phone conferences will occur on Day 15 and 30 days after the last dose (window of up to 2 days after Day 38).

Figure 4.c Study Schema for Relative Bioavailability Phase (Part 3)



Abbreviations: D: day; N: number of subjects; DiC: drug in capsule; PK: pharmacokinetics; TC: treatment C test DiC; TD: treatment D reference DiC.
Note: TAK-788 will be administered on Day 1 and on Day 8 as DiC.

5.0 ANALYSIS ENDPOINTS

5.1.1 Primary Endpoints

The primary endpoints are:

Part 1: safety profile of orally administered TAK-788.

- number and percentage of subjects with 1 or more AEs.
- number and percentage of subjects with 1 or more SAEs.
- number and percentage of subjects with clinically defined abnormal laboratory values.
- number and percentage of subjects with clinically defined abnormal vital signs.

Part 2: summary statistics of the PK parameters for TAK-788 under fasted conditions or following a low-fat meal.

- C_{max}.
- t_{max}.
- AUC_t (area under the concentration-time curve from time 0 to time t).
- AUC_∞ (area under the first moment concentration-time curve from time 0 to infinity calculated using the last quantifiable concentration.
- $t_{1/2z}$ (terminal disposition phase half-life).

Part 3: summary statistics of the PK parameters for TAK-788 with different DiC under fasted conditions.

- C_{max}.
- t_{max}.
- AUC_t.
- AUC_∞ (if data permitted).
- $t_{1/2z}$.

5.1.2 Secondary Endpoints

The secondary endpoints are:

Part 1: summary statistics of the PK parameters for TAK-788 and its 2 active metabolites, AP32960 and AP32914 under fasted conditions.

- C_{max}.
- t_{max}.
- AUC_t.

- AUC_{∞}.
- $t_{1/2z}$.

Part 2: safety profile of TAK-788 under fasted conditions or following a low-fat meal.

Part 3: safety profile of TAK-788 under fasted conditions.

5.1.3 Exploratory Endpoints

The exploratory endpoint is:

CCI

[redacted]

6.0 DETERMINATION OF SAMPLE SIZE

Part 1: The estimated sample size of approximately 56 subjects is determined on the basis of clinical rather than statistical considerations. The number of subjects in this part of study is consistent with phase 1 dose-finding studies.

Part 2: With a sample size of 14 healthy subjects, the 90% CI for the AUC ratio is expected to be in the range of 84%-119%, using an intrasubject AUC variability of 27% in patients with cancer and assuming a TAK-788 AUC ratio of 1 in the fed versus fasted comparison. After accounting for 2 potential dropouts in Part 2, the final sample size is 16 healthy subjects. Subjects who vomit within 8 hours after dosing will be considered nonevaluable for PK assessments. Subjects who are withdrawn from treatment before completing study-required PK assessments and subjects who are not non–PK-evaluable will not be replaced.

Part 3: With a sample size of 10 healthy subjects, the 90% CI for the C_{max} ratio is expected to be in the range of 87% to 115%, using an intrasubject C_{max} variability of 17% estimated in healthy subjects. After accounting for 2 potential dropouts in Part 3, the final sample size is up to 12 healthy subjects. This sample size assumes no replacement of subjects who may drop out of the study before the completing the PK sample collections in Part 3.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

In general, summary tabulations will include the number of observations, (arithmetic) mean, standard deviation (SD), geometric mean and coefficient of variation (%CV) for PK related parameters, median, minimum, and maximum for continuous variables, and the number and percent (of non-missing) per category for categorical data, unless specified otherwise. Means and medians will be presented to 1 more decimal place than the recorded data. The standard deviations (SDs) will be presented to 2 more decimal places than the recorded data. Confidence intervals (CIs) about a parameter estimate will be presented using the same number of decimal places as the parameter estimate.

The PK parameters will be summarized with a precision of 3 significant digits, while t_{max} is presented with the number of relevant decimal places to specify the sampling time. Percent CV and frequency percentages will be presented as integers.

Summary statistics will be calculated by time point, if applicable.

All confidence intervals, statistical tests, and resulting P-values will be reported as 2-sided and will be assessed at α=0.1 significance level unless otherwise stated. P-values will be rounded to 3 decimal places prior to assessment of statistical significance.

Screen failure subjects will be grouped and listed at the end.

Unless specified otherwise, analyses in Part 2 should be conducted by doses.

7.1.1 Study Definitions

A Subject is considered to be enrolled when the first dose of study drug has been administered. Study start date is defined as the date of first dose of study drug.

7.1.2 Definition of Study Days

Study Day 1 is defined as the date on which a subject is administered their first dose of the study drug. Other study days are defined relative to the Study Day 1 with Day 1 being Study Day 1 and Day -1 being the day prior to Study Day 1.

7.1.3 Definition of Baseline Values

Unless otherwise specified, the baseline value is defined as the value collected at the time closest to, but prior to, the start of study drug administration.

7.1.4 Windowing of Visits

All data will be categorized based on the scheduled visit at which they were collected. The analysis of PK data and determination of PK parameters will be based on the actual elapsed time post dose relative to the first dosing.

7.1.5 Withdrawals, Dropouts, Loss to Follow-up

Any subject who voluntarily withdraws consent or is discontinued (eg, because of an AE) from the study before completion will be considered withdrawn from the study. Treatment with study drug may also be discontinued for any of the following reasons:

- AE.
- Pregnancy.
- Withdrawal by subject.
- Lost to follow-up.
- Protocol violation.
- Termination of the study.
- Other.

When an event such as a family emergency, a transient intercurrent illness (such as a cold) unrelated to study drug, or a remediable act of non-compliance prevents a subject from participating in a scheduled visit but the subject wishes to continue in the study, with the agreement of the investigator, the research site staff may attempt to reschedule the visit and retain the subject in the study.

If a subject is prematurely discontinued from participation in the study for any reason after drug administration, the investigator or designee must make every effort to perform the assessments scheduled for the follow-up visit. The reason for withdrawal will be recorded in the eCRF and the subject's source medical record.

Subjects in Part 2 and 3 who discontinue their participation in the study before receiving the Day 8 dose will undergo the safety follow-up as specified in the Schedules of Events.

Replacement of subjects is not planned but may occur under special circumstances at the sponsor's discretion, in agreement with the investigator.

7.1.6 Imputations for Missing Dates

7.1.6.1 Analysis of Missing Adverse Event Dates

- If the start date has month and year but day is missing, the event will be considered.
  - treatment emergent if both the month and year of the start date of the event are on or after the month and year of the date of the first dose of study drug, and on or before the month and year of the date of the last dose of study.
- If the start date has year, but day and month are missing, the event will be considered.
  - treatment emergent if the year of the start date of the event is on or after the year of the date of the first dose of study drug, and on or before the year of the date of the last dose of study drug plus 30 days.

- If the start date of an event is completely missing, the event will be considered treatment emergent.

7.2 Randomization and Stratification

Subjects in Part 1 will receive a single dose of TAK-788 or placebo under fasted conditions.

In Part 2, subjects will receive TAK-788 under fed or fasted conditions then crossover to receive TAK-788 under the alternate condition (fed versus fasted) after a washout of at least 7 days between doses of TAK-788.

In Part 3, subjects will receive TAK-788 Process B DiC (test) or Process A DiC (reference), then crossover to receive the alternate TAK-788 (test or reference) formulation after a washout of at least 7 days between doses of TAK-788.

Before dosing on Day 1, subjects will be assigned a randomization number in accordance with the randomization code generated by the sponsor, the sponsor's designee, or the clinical site. The randomization code will be maintained in a room with access restricted to pharmacy personnel only.

Once a randomization number has been allocated to one subject, it may not be assigned to another subject. Subjects withdrawn prematurely from the study will not be replaced.

7.3 Unblinding

Part 1 of this study will be performed in a double-blind manner.

Because TAK-788 and the placebo formulations may be different in appearance, all subjects will be blindfolded during dosing. An unblinded site pharmacist will dispense study drugs. These personnel will not be involved in any other study procedures (data collection, assessments, or documentation activities).

One person in the bioanalytical laboratory will be unblinded to exclude the PK samples collected from subjects who were dosed with placebo from the bioanalysis.

If needed, 1 or 2 PK scientists may also be unblinded to conduct the preliminary PK data analysis during the study.

After the subjects' furlough begins on Day 3 of Part 1, the double-blind will become single-blind. The site staff, investigator(s), and sponsor will be unblinded on Day 3 but study subjects will remain blinded until after the follow-up phone call 30 days after their last dose. After furlough on Day 3, the overall randomization code will be broken for safety evaluation and reporting purposes only.

The study blind should not be broken before Day 3 of Part 1 except in a medical emergency where knowledge of the treatment administered would affect the treatment of the emergency. The decision to break the blind will be made on a case-by-case basis, at the discretion of the investigator in collaboration with the sponsor/medical monitor. The applicable site standard operating procedure (SOP) will be followed for blind-breaking procedures.

Part 2 and Part 3 are open-label.

7.4 Statistical Software

SAS version 9.4 (or higher) will be used for all analyses.

7.5 Analysis Sets

7.5.1 Randomized Population

- All subjects who are randomized to receive study treatment in Part 1, Part 2, or Part 3.

7.5.2 Safety Analysis Set

All enrolled subjects who receive any study treatment in the treatment period.

7.5.3 Pharmacokinetic (PK)-Evaluable Population

All subjects in the Safety Population who have no major protocol deviations that would affect the PK analysis and who have sufficient data to calculate PK parameters. This population will be used for the PK analyses. Data from subjects who experience emesis within the first 8 hours following dosing may be excluded from the final analysis (to be evaluated on a case-by-case basis).

7.6 Disposition of Subjects

7.6.1 Subject Disposition

Tabulations of patient disposition data will be generated by sequences.

Subject disposition data will include the number of subjects for the following categories: subjects treated, subjects in the PK-evaluable population, subjects who have completed treatment, subjects who discontinued study, and the primary reason off study. 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 populations.

Data concerning subject disposition (e.g., primary reason for discontinuation, population) will be presented in by-subject listings.

7.7 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively. Mean, SD, minimum, median and maximum will be calculated for continuous variables. Frequency and percentages will be calculated for categorical variables.

7.7.1 Demographics

Demographics will be summarized for the total safety population by treatment arm in Part 1 and sequences in Part 2 and Part 3. Demographic data to be evaluated will include age at screening, race, ethnicity, and sex.

No inferential statistics will be generated.

7.7.2 Inclusion/Exclusion Criteria

All protocol deviations will be reviewed, and major protocol deviations will be identified and listed.

7.7.3 Medical History

Medical history abnormalities will be coded to MedDRA terms (version 20.0 or higher). Physical examination abnormalities will also be listed.

7.7.4 Height

Subject height will be summarized for the total safety population by treatment/sequences.

7.7.5 Concomitant Medications

The original verbatim terms collected in the eCRF for concomitant medications will be coded using the WHO Drug Dictionary into drug class (Anatomical Therapeutic Chemical classification level 2) and preferred term. Subjects are counted once for each WHO drug generic term. Concomitant procedures will not be coded.

Concomitant medication is defined as any medication that occurs after administration of the first dose of study treatment and up through 30 days after the last dose of study drug.

Concomitant therapies with start or end dates that are completely or partially missing will be analyzed using the same imputation rules as adverse events.

Concomitant medications and procedures will be presented in separate by-subject listings.

7.8 Study Drug Exposure and Compliance

7.8.1 Extent of Exposure

Subjects in Part 1 will receive a single dose of TAK-788 or placebo. Subjects in Part 2 will receive a tolerable single dose identified in Part 1 on Day 1 in Period 1 and on Day 8 in Period 2. Subjects in Part 3 will receive a single dose of TAK-788 160 mg administered as Process B drug-in-capsule(DiC) and a single dose of TAK-788 160 mg administered as Process A DiC. All study drug administration will be listed. Meal administration and consumption will be listed.

7.8.2 Treatment Compliance and Modifications

No dose modification will occur.

7.9 Efficacy Analysis

There will be no efficacy analysis.

7.10 Pharmacokinetic Analysis

Descriptive statistics, including arithmetic mean, geometric mean, SD, coefficient of variation (%CV), minimum, median, and maximum, will be calculated and presented by dose level in Part 1, for each treatment under fasted versus fed conditions in Part 2, and for each treatment (test vs reference drug formulation) under fasted conditions in Part 3 for plasma concentrations of TAK-788 and its 2 active metabolites, AP32960 and AP32914.

Analysis of PK parameters will be performed for TAK-788, AP32960, and AP32914. The concentration-time profiles will be analyzed using noncompartmental methods to estimate PK parameters in plasma. The number of observations, arithmetic mean, geometric mean, SD, %CV, median, minimum, and maximum values will be calculated for the PK parameters C_{max}, t_{max}, AUC_t, AUC_∞, $t_{1/2z}$, AUC_{extrap}% (area under the curve from the last quantifiable concentration to infinity calculated using the observed value of the last quantifiable concentration, expressed as a percentage of AUC_∞), CL/F (apparent clearance after extravascular administration, calculated using the observed value of the last quantifiable concentration), V_z/F (apparent volume of distribution during the terminal disposition phase after extravascular administration, calculated using the observed value of the last quantifiable [CCI redacted]. Dose proportionality analysis by the power model will be performed for C_{max} and AUC in Part 1.

In Part 2, PK parameters (natural log-transformed [ln]) of TAK-788, AP32960, and AP32914 will be compared under fasted versus fed conditions using an analysis of variance (ANOVA) model separately by each dose. The ANOVA model will include fasted versus fed condition, period, and sequence as fixed effects and subject nested within sequence as a random effect. Each ANOVA will calculate the least-squares mean (LSM), the difference between treatment LSMs, and the standard error associated with the difference. Residual, subject nested within sequence, and intersubject variance, along with the intrasubject and intersubject CV, will be reported. Ratios of LSM will be calculated using the exponential function of the difference between treatment LSMs from the analyses on the ln-transformed C_{max}, AUC_t, and AUC_∞.

In Part 3, PK parameters (ln-transformed) of TAK-788 for the test formulation (Process B DiC) and the reference formulation (Process A DiC) will be compared using an ANOVA model. The ANOVA model will include treatment (test versus reference), period, and sequence as fixed effects and subject nested within sequence as a random effect. Each ANOVA will calculate the LSM, the difference between treatment LSMs, and the SE associated with the difference. Residual, subject nested within sequence, and intersubject variance, along with the intrasubject and intersubject CV, will be reported. Ratios of LSM will be calculated using the exponential function of the difference between treatment LSMs from the analyses on the ln-transformed C_{max}, AUC_t, and AUC_∞ (if data permitted).

Low-fat meal effect in Part 2 and similarity of 2 formulations in Part 3 will be concluded if the 90% confidence interval (CI) for the ratio of population geometric means of primary PK parameters Cmax, AUC∞, and AUCt (only if AUC∞ is not available) between the 2 treatments (fasted versus fed in part 2 and Process A DIC vs Process B DIC) is contained in the equivalence limits of 80% to 125%.

T_{max} will not be transformed and will be analyzed using non-parametric analysis (Walsh averages and appropriate quartile of the Wilcoxon signed-rank test). Median (range) for each treatment and p-value will be presented.

7.11 Pharmacogenetic Analysis

Not applicable.

7.12 Safety Analysis

Safety and tolerability parameters will be listed by subject, study part, and treatment group, and displayed in summary tables using descriptive statistics. All subjects receiving placebo in Part 1 will be pooled and analyzed as one placebo group.

Safety analyses will be conducted separately for subjects who received TAK-788 and placebo.

Physical Examinations will be listed. Follow up Telephone contacts will be listed.

7.12.1 Adverse Events

Original terms used in the eCRFs by the investigator or designees to identify AEs will be coded using MedDRA (version 20.0 or higher) terminology.

The number and percentage of subjects with TEAEs will be summarized by MedDRA System Organ Class and Preferred Term and study group and by study group by maximum severity and relationship to study treatment. A TEAE is any AE that is new in onset or was aggravated in severity or frequency following the first dose of study drug, up to and including the last visit of the study.

Adverse events with start dates that are completely or partially missing will be analyzed as described in section 7.1.6.

7.12.1.1 Overall Summary

An overall summary treatment-emergent AE table will include numbers and percentages of subjects who had any treatment-emergent AE, treatment-related treatment-emergent AE, grade 3 or higher treatment-emergent AE, grade 3 or higher treatment-related treatment-emergent AE, serious AE (SAE), treatment-related SAE, treatment-emergent AE resulting in discontinuation, and on-study deaths.

7.12.1.2 Serious Adverse Events

The number and percentage of subjects experiencing at least one treatment emergent serious AE (SAE) will be summarized by MedDRA SOC and PT. Similar summary will be generated for treatment emergent treatment-related SAEs.

By-subject listings of the SAEs will be presented (the subject listing will contain all SAEs regardless of treatment emergent AE status). The treatment-related SAEs will also be presented.

7.12.1.3 DLTs

DLTs are not captured in the eCRFs.

7.12.1.4 Deaths

By-subject listings of the deaths will be presented. All deaths occurring on-study will be displayed (regardless of treatment emergent AE status). On-study death is defined as the death that occurs between the first dose of study drug and 30 days after the last dose of study drug.

7.12.1.5 Adverse Events Resulting in Discontinuation of Study Drug

The number and percentage of subjects experiencing at least one adverse event resulting in discontinuation of study drug will be summarized by MedDRA SOC and PT.

By-subject listing of AEs resulting in discontinuation of study drug will be presented. All AEs resulting in discontinuation of study drug occurring on-study will be displayed (regardless of treatment emergent AE status).

7.12.2 Clinical Laboratory Evaluations

For the purposes of summarization, all laboratory values will be converted to standardized units. If a lab value is reported using a non-numeric qualifier (eg, less than (<) a certain value, or greater than (>) a certain value), the given numeric value will be used in the summarization, ignoring the non-numeric qualifier.

If a subject has repeated laboratory values for a given time point, the value from the last evaluation will be used.

Laboratory data will be summarized by the type of laboratory test and chronological time point. Descriptive statistics and the number of subjects with laboratory test results below, within, and above normal ranges will be tabulated by scheduled time. Abnormal findings in laboratory data will be listed with a flag for Low, High or Abnormal.

7.12.3 Vital Signs

Descriptive statistics will be calculated for vital signs (blood pressure, pulse rate, and respiratory rate) and PFTs (spirometry, lung volumes, and DLco), and will be presented for each time point by study group (absolute values and change from baseline). PFT abnormalities will be listed with a derived flag for any subject whose DLco has decreased by >20% from baseline. Vital sign

abnormalities will be listed with a derived flag for abnormalities based on the criteria specified in the following tables.

Table 7.a Abnormal values for vital signs

Vital Sign Parameter	Unit	Lower Criteria	Upper Criteria
Pulse	bpm	<50	>120
Systolic Blood Pressure (BP)	mm Hg	<85	>180
Diastolic BP	mm Hg	<50	>110
Temperature	°F (°C)	<96.1 (<35.6)	>99.9 (>37.7)

7.12.4 CT Scans

Chest CT scan results will be described narratively if abnormalities are reported during the study.

7.12.5 12-Lead ECGs

ECG results (absolute values and change from baseline) will be summarized using descriptive statistics; frequencies (numbers and percentages) will be calculated for the overall evaluation by scheduled time and study group. ECGs are taken as triplicates. All triplicates and mean of triplicates will be listed. The mean values will be used for summaries. ECG abnormalities will be listed with a flag for Low, High or Abnormal.

Table 7.b Abnormal values for 12-Lead ECGs

ECG Parameter	Unit	Lower Criteria	Upper Criteria
Heart Rate	bpm	<50	>120
PR Interval	msec	<120	>196
QRS Duratin	msec	<72	>112
RR Interval	msec	<600	>1200
QTcB	msec	<350	>446
QTcF	msec	<351	>438

7.13 Interim Analysis

No interim analysis is planned.

7.14 Changes in the Statistical Analysis Plan

Not applicable.

8.0 REFERENCES

Not applicable.

9.0 APPENDICES

Not applicable.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Biostatistics Approval	29-Mar-2019 20:42 UTC