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

Protocol Approve Date: 13 November 2018

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

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

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

PROTOCOL

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

Sponsor: Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited
40 Landsdowne Street
Cambridge, MA 02139 USA
Telephone: +1 (617) 679-7000
Please note: Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, may be referred to in this protocol as "Millennium", "sponsor", or "Takeda".

Study Number: TAK-788-1001

IND Number: 126,721 **EudraCT Number:** Not applicable

Compound: TAK-788 (formerly AP32788)

Date: 13 November 2018 **Amendment Number:** 03

Amendment History:

Date	Amendment Number	Amendment Type	Region
08 February 2018	Initial Protocol	Not applicable	Global
13 June 2018	01	Substantial	Global
02 November 2018	02	Substantial	Not applicable [a]
13 November 2018	03	Substantial	Global

[a] Protocol Amendment 02 was not activated.

1.0 ADMINISTRATIVE

1.1 Contacts

A separate contact information list will be provided to each site.

Serious adverse event (SAE) and pregnancy reporting information is presented in Section 10.0, as is information on reporting product complaints.

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given in Section 3.1 and relevant guidelines provided to the site.

Contact Type/Role	United States Contact
Serious adverse event and pregnancy reporting	See Section 10.0.

1.2 Approval

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation (ICH) E6 Good Clinical Practice (GCP): Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

The signature of the responsible Takeda medical officer (and other signatories, as applicable) can be found on the signature page.

Electronic signatures may be found on the last page of this document.

PPD

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the investigator's brochure, and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- ICH, E6 GCP: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.0 of this protocol.
- Terms outlined in the clinical study site agreement.
- Responsibilities of the Investigator (Appendix B).

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix C of this protocol.

_____

Signature of Investigator Date

_____

Investigator Name (print or type)

_____

Investigator's Title

_____

Location of Facility (City, State/Provence)

_____

Location of Facility (Country)

1.3 Protocol Amendment 03 Summary of Changes

Rationale for Amendment 03

This document describes the changes in reference to the protocol incorporating Amendment 03. As Protocol Amendment 02 was not activated, the changes described below are based on a comparison with Amendment 01. The primary reason for this amendment is to add Part 3 to assess the relative bioavailability of the single dose of TAK-788 160 mg administered as Process B drug-in-capsule (DiC) (test) versus a single dose of TAK-788 160 mg administered as Process A DiC (reference) in healthy subjects.

Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

For specific descriptions of text changes and where the changes are located, see Appendix E.

Changes in Amendment 03 (Compared with Amendment 01)

1. Addition of Part 3 to assess the relative bioavailability of TAK-788 capsules in healthy subjects.

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2.0 STUDY SUMMARY

Name of Sponsor: Millennium Pharmaceuticals, Inc	**Compound:** TAK-788 (formerly AP32788)	
Title of Protocol: 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	**IND No.:** 126,721	**EudraCT No.:** Not applicable
Study Number: TAK-788-1001	**Phase:** 1	

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 pharmacokinetics (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.

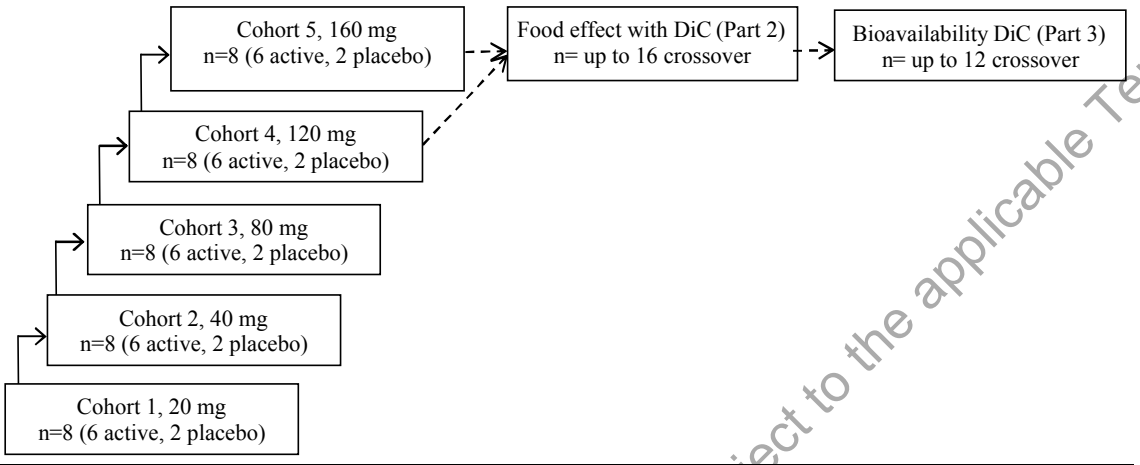
Part 1 – Dose Escalation:

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 dose-limiting toxicities following administration of TAK-788 and all Grade ≥2 treatment-related adverse events (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 the 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 from a different synthetic process (such as Process A). The dose(s) 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 non–small-cell lung cancer (Study AP32788-15-101). The highest dose tested in Part 1 of the study will not exceed the unit dose of the maximum tolerated dose identified in Study AP32788-15-101.

To mitigate the risk of treatment, pulmonary function tests (PFTs) (spirometry, lung volumes, and diffusion capacity [DLco]) and a chest computed tomography (CT) scan are required to be performed and assessed to be normal (PFTs ≥80% of predicted normal) at screening; baseline PFTs to be performed 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% of 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, and/or abnormal chest CT scan.

Study Schema for Single Rising Dose Phase (Part 1)

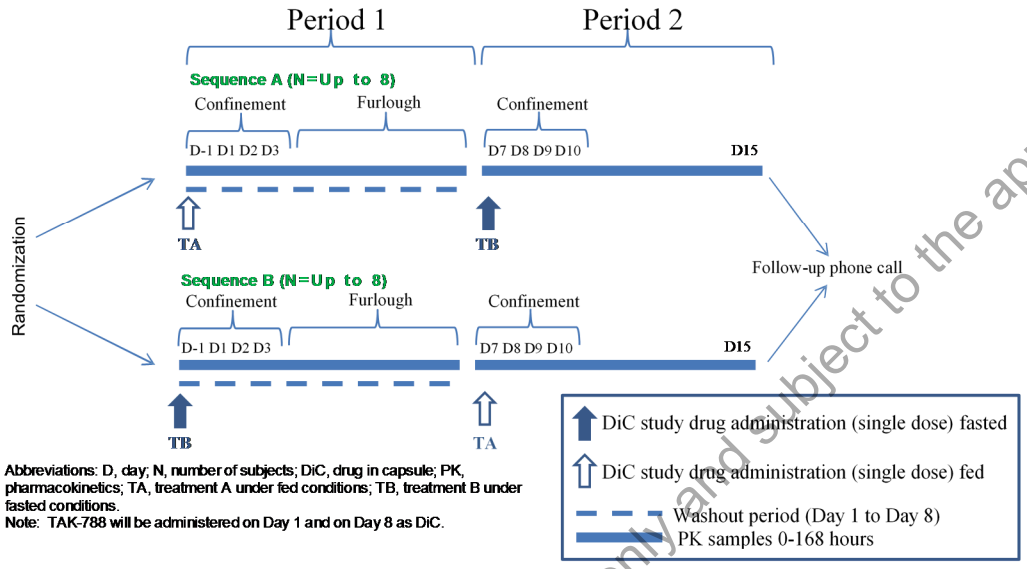


DiC, drug-in-capsule.

Part 2 – Food Effect:

In the food effect part of the study, all subjects will receive TAK-788 only. Subjects will be randomized to a crossover sequence at a 1 : 1 ratio and administered the dose of TAK-788 identified in Part 1 on Day 1 in Period 1 and on Day 8 in Period 2 with a low-fat meal (Treatment A) or under fasting conditions (Treatment B) with a washout period of ≥7 days between each dose of TAK-788. The duration of the washout period may be updated pending the PK results from Part 1. The duration of washout will be adjusted to ensure that the C_{trough} (observed plasma trough concentration at the end of a dosing interval) of TAK-788 at 168 hours postdose in Part 1 is <5% of the C_{max} (maximum observed concentration) of TAK-788 at the dose used in the food effect evaluation. The planned washout period for Part 2 is 7 days. PFTs and chest CT scan are required to be performed and assessed as normal at screening; PFTs must be performed no more than 7 days before Day 1. If pulmonary symptoms are reported, PFTs and a chest CT will be repeated 48 hours postdose before furlough. Other clinical study procedures are the same as those in the dose escalation phase.

Study Schema for Food Effect Phase (Part 2)

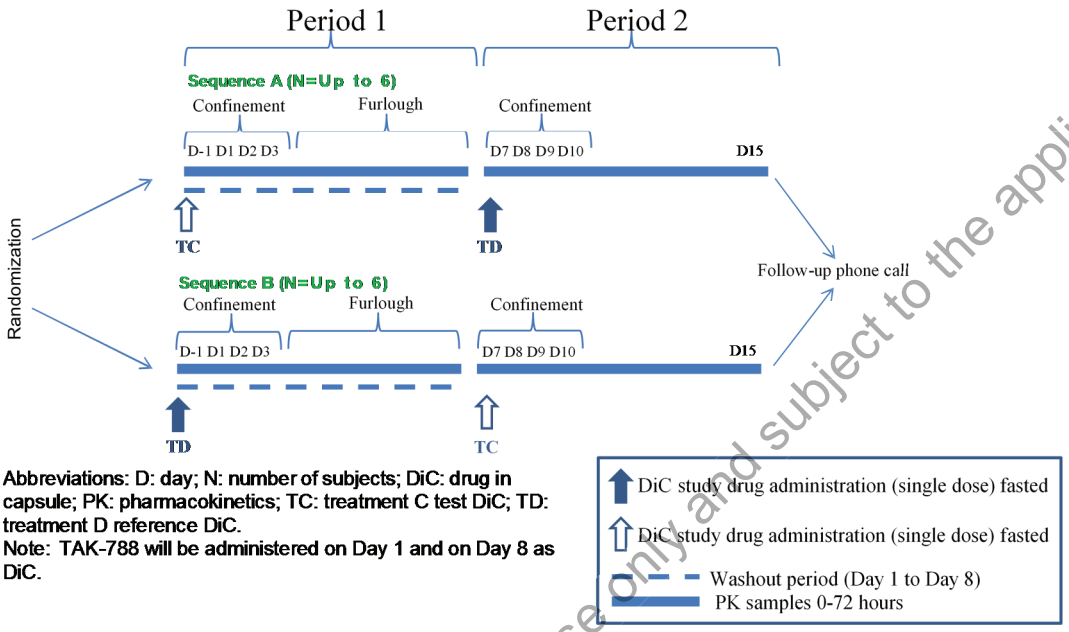


Abbreviations: D, day; N, number of subjects; DiC, drug in capsule; PK, pharmacokinetics; TA, treatment A under fed conditions; TB, treatment B under fasted conditions.
Note: TAK-788 will be administered on Day 1 and on Day 8 as DiC.

Part 3 – Bioavailability Study

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/or 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).

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.

Primary Objectives:

- Part 1: To assess safety and tolerability of TAK-788 and to identify a tolerable single oral dose of TAK-788 administered as a drug-in-capsule (DiC) formulation in healthy subjects.
- Part 2: To characterize the effect of a low-fat meal on the PK of TAK-788 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.

Secondary Objectives:.

- 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.

Exploratory Objectives:

- CCI
- [redacted]

Subject Population: Healthy subjects aged 18-55 years.

Number of Subjects:	**Number of Sites:**
Up to approximately 84 (approximately 56 in Part 1, up to 16 in Part 2, and up to 12 in Part 3)	1

Dose Levels:	**Route of Administration:**
Part 1: Single rising dose starting at 20 mg, escalating to 40, 80, 120, up to 160 mg. Part 2: A tolerable single dose identified in Part 1. Part 3: A 160 mg single dose DiC.	Oral
Duration of Treatment:	**Period of Evaluation:**
One day (single dose) for Part 1, 2 days (2 single doses separated by ≥7-day washout) for each of Parts 2 and 3.	Part 1: 30 days Part 2: 38 days Part 3: 38 days

Main Criteria for Inclusion:

- Aged 18-55 years of age at the time of informed consent.
- Healthy subjects defined as the absence of acute or chronic clinically significant deviations from normal in medical history, physical examination, electrocardiogram (ECG), and clinical laboratory determinations at screening.
- Body weight of ≥45 kg (women) or ≥55 kg (men) and a body mass index of 18.0-30.0 kg/m^2 at screening.
- Normal baseline PFTs (≥80% of predicted normal for spirometry, lung volumes, and DLco) for Parts 1, 2 and 3; and chest CT scan at screening for Parts 1 and 2.
- Nonsmoker (never smoked or >20 years from last occurrence of smoking).
- Normal organ function including hepatic, renal, and bone marrow function (please refer to study reference manual or site manual for normal ranges).

Main Criteria for Exclusion:

- Medical History and Concurrent Diseases
  - Ongoing or prior pulmonary disease including asthma, chronic obstructive pulmonary disease, interstitial lung disease, and pneumonitis including but not limited to drug-related pneumonitis.
  - Any history of cardiovascular disease including a history of congenital prolonged QT syndrome or unexplained cardiac arrest.
  - Manifestations of malabsorption due to prior gastrointestinal (GI) surgery, GI disease, or for an unknown other reason that may alter the PK of TAK-788.
  - Pulmonary infection ongoing or within 30 days of informed consent.
  - Current or recent (within 3 months) GI disease.
  - Any major surgery within 4 weeks before study drug administration.
  - Blood transfusion within 4 weeks before study drug administration.
  - History of bleeding disorder.
  - Inability to tolerate oral medication.
  - Inability to undergo venipuncture and/or tolerate venous access.
  - Inability to tolerate multiple blood sampling.
  - Ongoing or active infection, including but not limited to, the requirement for intravenous antibiotics.
  - Positive serology or a known history of hepatitis B virus, hepatitis C virus, and HIV.
- Physical and Laboratory Test Findings
  - Any clinically significant abnormality at screening of cardiac, hepatic, renal, respiratory, GI, endocrine, immunologic, dermatologic, hematologic, neurologic, or psychiatric disease.
  - Resting blood pressure >140/90 mmHg at screening (a single repeat measurement is allowed if the initial

measurement is outside these limits).
  - Resting pulse rate <45 beats per minute.
- Allergies and Adverse Drug Reactions
  - History of severe allergy/hypersensitivity reaction or ongoing allergy/hypersensitivity reaction, as judged by the investigator, or history of hypersensitivity to epidermal growth factor receptor/human epidermal growth factor receptor 2 inhibitors.
- Prohibited Treatments and Therapies
  - Prior exposure to TAK-788.
  - Exposure to any small molecular drug treatment, including investigational small molecular drugs, within 4 weeks or biologic drug treatment, including investigational biologics, within 16 weeks before study drug administration.
  - Use of any prescription or over-the-counter (OTC) stomach acid controllers within 2 weeks before study drug administration.
  - Use of any other drugs, including OTC medications, nutritional supplements, and herbal preparations (including St. John's wort) within 1 week before study drug administration (except occasional use of acetaminophen and ibuprofen which are allowed up to 24 hours before dosing).
  - Consumption of any food or beverages containing grapefruit, Seville oranges, blood oranges, or pomegranates within 1 week before study drug administration.

Endpoints:

- Primary:
  - Part 1: safety profile of orally administered TAK-788.
    - Number and percentage of subjects with 1 or more AE.
    - Number and percentage of subjects with 1 or more serious AE.
    - 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} (time of first occurrence of C_{max}).
    - AUC_t (area under the concentration-time curve [AUC] from time 0 to time t).
    - AUC_∞ (AUC 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 in different DiC under fasted conditions.
    - C_{max}.
    - t_{max}.
    - AUC_t.
    - $AUC_{\infty \text{ (if data permitted)}}$.
    - $t_{1/2z}$.
- Secondary:
  - 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.

- Exploratory:

CCI [redacted]

Statistical Considerations:

Pharmacokinetic Analyses

Descriptive statistics, including 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 the test versus reference treatments in Part 3 for plasma concentrations of TAK-788 and its 2 active metabolites.

Analysis of PK parameters will be performed for TAK-788 and its 2 active metabolites. The concentration versus time profiles will be analyzed via non-compartmental methods to estimate PK parameters in plasma. Descriptive statistics (number of observations, arithmetic mean, geometric mean, SD, %CV, median, minimum, and maximum values) will be presented 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 concentration), CCI [redacted].

In Part 2, PK parameters (natural log-transformed [ln]) of TAK-788 will be compared under fasted versus fed conditions using an analysis of variance (ANOVA) model. 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 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_∞.

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).

Safety Analyses

Safety assessments will include AEs, vital signs, ECGs, physical examinations, clinical laboratory tests, PFTs, from Parts 1, 2, and 3; and chest CT scan for Parts 1 and 2. The incidence of AEs will be tabulated and reviewed for clinical significance.

Safety and tolerability parameters will be listed by subject, study group, 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. Original terms used in the electronic case report forms by the investigator or designees to identify AEs will be coded using Medical Dictionary for Regulatory Activities (version 20.0 or higher) terminology.

Sample Size Justification:

- Part 1: The sample size is determined based on 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% confidence interval for the AUC ratio is expected to be in the range of 84% to 119%, using an intrasubject AUC variability of 27% in cancer patients 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 up to 16 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 2.
- Part 3: With a sample size of 10 healthy subjects, the 90% confidence interval 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 Parts 3

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the clinical study supplier list or equivalent. The identified vendors for specific study-related activities will perform these activities in full or in partnership with the sponsor.

3.2 Principal Investigator/Coordinating Investigator

Takeda will select a signatory coordinating investigator from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol, the study medication, their expertise in the therapeutic area and the conduct of clinical research and study participation. The signatory coordinating investigator will be required to review and sign the clinical study report and by doing so agrees that it accurately describes the results of the study.

3.3 List of Abbreviations

β-hCG	β-human chorionic gonadotropin
AE	adverse event
ANOVA	analysis of variance
API	active pharmaceutical ingredient
AUC	area under the plasma concentration-time curve
AUC_{24}	area under the plasma concentration-time curve from time 0 to 24 hours
$AUC_{extrap}\%$	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
CFR	Code of Federal Regulations
C_{max}	maximum observed plasma concentration
CNS	central nervous system
CRO	contract research organization
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
FDA	Food and Drug Administration
FIH	first-in-human
GCP	Good Clinical Practice
GI	gastrointestinal
GLP	Good Laboratory Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HER2	human epidermal growth factor 2
IB	investigator's brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IRB	institutional review board
IV	intravenous

ln	natural log-transformed
LSM	least-squares mean
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSCLC	non–small-cell lung cancer
NOAEL	no-observed-adverse-effect level
OTC	over-the-counter
PFT	pulmonary function test
PK	pharmacokinetic(s)
PO	*per os* (oral)
PTE	pretreatment event
QD	*quaque die* (once daily)
RP2D	recommended phase 2 dose
SAE	serious adverse event
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2z}$	terminal disposition phase half-life
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitor
t_{max}	time to first occurrence of C_{max}
UK	United Kingdom
US	United States
WHO	World Health Organization
WT	wild type

3.4 Corporate Identification

Millennium	Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited
TDC Japan	Takeda Development Center Japan
TDC Asia	Takeda Development Center Asia, Pte Ltd
TDC Europe	Takeda Development Centre Europe Ltd
TDC Americas	Takeda Development Center Americas, Inc
TDC	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable
Takeda	Millennium Pharmaceuticals, Inc, TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable

4.0 INTRODUCTION

4.1 Scientific Background

Specific genetic lesions that drive the proliferation of cancer cells, such as those resulting in activation of certain tyrosine kinases, render many cancers highly sensitive to therapeutic agents that inhibit the affected kinase (eg, tyrosine kinase inhibitors [TKIs]). These include activating mutations in the epidermal growth factor receptor (EGFR), which have been identified in 21% to 40% of patients with non–small-cell lung cancer (NSCLC) [1,2]. There are multiple classes of activating mutations in EGFR that vary widely in their degree of sensitivity to available TKIs. Because inhibition of wild-type (WT) EGFR in normal tissues is associated with dose limiting toxicities (DLTs), substantial clinical benefit has generally been associated with TKIs that inhibit specific, activated variants of EGFR more potently than they inhibit WT EGFR.

The most common activating mutations in EGFR are in-frame deletions in exon 19 and a Leu858Arg (L858R) substitution in exon 21, together accounting for approximately 90% of all EGFR activating mutations [3]. Erlotinib and gefitinib ("first generation" EGFR TKIs), and afatinib (a second-generation EGFR TKI), potently inhibit these mutants in vitro and induce high response rates of approximately 60% to 70% in patients with these mutations [4]. Although these TKIs are approved for use in patients with these specific mutations, their clinical efficacy is ultimately limited by the development of resistance, such as by mutation of the EGFR kinase domain gatekeeper residue (T790M), which occurs in 50% of patients [5,6]. Recently, osimertinib was approved for treatment of patients with metastatic EGFR T790M mutation-positive NSCLC, whose disease has progressed on or after EGFR TKI therapy.

For erlotinib and gefitinib, high response rates have largely been restricted to patients with the most common activating mutants; however, preliminary results with afatinib suggest that relatively high response rates are also achieved in patients with a second class of activating mutants, so-called "uncommon" mutants, such as those occurring at other amino acids in exons 19 and 21 (eg, G719 and L861) [7].

The final class of EGFR activating mutations, known as exon 20 insertions, accounts for approximately 9% of EGFR mutant NSCLC [8]. Unlike mutations in exons 19 or 21, almost all EGFR exon 20 insertions confer in vitro and primary clinical resistance to the 3 approved EGFR TKIs [7,9,10]. Patients with NSCLC containing EGFR exon 20 insertions exhibit clinical characteristics similar to those carrying common EGFR mutations [11] (eg, young, nonsmoker, with adenocarcinoma subtype), consistent with potential roles as driver mutations that could confer benefit to targeted therapy. In summary, while erlotinib, gefitinib, and afatinib are approved for use in NSCLC patients with common activating mutations in EGFR (ie, exon 19 deletions and L858R substitutions), no therapies are approved for patients with EGFR exon 20 insertions.

Human epidermal growth factor 2 (HER2) mutations, typically consisting of in-frame insertions in exon 20, have also been identified as potential oncogenic drivers in 2% to 4% of patients with NSCLC. These patients exhibit clinical characteristics similar to patients with EGFR mutations [12-14]. Currently, no therapies are approved for use in NSCLC patients with HER2 activating mutations.

TAK-788 is an orally administered small molecule TKI and was specifically designed to address the unmet medical need in the subset of NSCLC patients for whom no target therapy is available. This patient population includes, but is not limited to, patients whose tumors harbor EGFR exon 20 insertion mutations, HER2 exon 20 insertion mutations. In nonclinical studies, TAK-788 potently inhibited all activated forms of EGFR tested, including those containing exon 20 activating insertions, other uncommon activating mutations, and the common activating mutations (exon 19 deletions and L858R) with or without the T790M resistance mutation. TAK-788 also potently inhibits HER2 activated by exon 20 insertions and point mutations, and by amplification. TAK-788 inhibits all of these variants more potently than it inhibits WT EGFR, suggesting it may have the selectivity necessary to achieve levels of exposure required to inhibit all activated forms of these kinases [8,9,11-14]. A first-in-human (FIH) phase 1/2 study of TAK-788 (AP32788-15-101) is ongoing with the main objectives of determining the safety profile, identifying recommended phase 2 dose (RP2D) and dose-limiting toxicities (DLTs) of TAK-788, characterizing the pharmacokinetic (PK) of TAK-788, and evaluating the antitumor activity of TAK-788 in NSCLC patients with EGFR or HER2 mutations.

4.2 Nonclinical Experience

Refer to the IB.

4.3 Clinical Experience

An FIH phase 1/2 study in patients with NSCLC (AP32788-15-101) is ongoing. As of the 08 September 2017 data cut-off, a total of 34 patients have been treated with 6 different once-daily (QD) doses evaluated. Two DLTs were observed and reported in the current dose escalation cohorts, 1 each at 80 mg (Grade 3 pneumonitis) and 120 mg (Grade 5 pneumonitis). Of the 33 patients included in the clinical database reports, 21 patients (63.6%) had EGFR exon 20 insertion mutations, and 4 patients (12.1%) had HER2 exon 20 insertions or point mutations.

Preliminary PK data suggest that TAK-788 was absorbed into systemic circulation with t_{max} (median time to first occurrence of the maximum observed plasma concentration [C_{max}]) ranging from 4-6 hours following oral (PO) administration of repeated daily doses of TAK-788. The steady-state PK of TAK-788 was achieved within 1 week of TAK-788 treatment. Steady-state area under the plasma concentration-time curve (AUC) from time 0 to 24 hours (AUC_{24}) of TAK-788 increased in approximately dose-proportionally at doses ranging from 5-180 mg. Administration of TAK-788 PO QD resulted in approximately 50% accumulation in AUC_{24}. The effective half-life based on accumulation was approximately 16 hours (range, 6-28 hours).

The clinical safety data available indicated no particular safety findings that are unique compared with other EGFR TKIs. Diarrhea (33.3%) was the most common treatment-related adverse event (AE) and was the only Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term occurring in ≥20% of patients treated with TAK-788. Rash, which is commonly observed with other EGFR TKIs, was also observed with TAK-788 (12.1% of all patients).

Preliminary efficacy data showed 2 confirmed PRs and 1 PR awaiting confirmation in a total of 8 patients who had at least 1 disease assessment following treatment with TAK 788 at 80 mg QD

and 120 mg QD, respectively. All patients who responded to treatment with TAK-788 had EGFR exon 20 insertion mutations.

In mid-January 2018, 160 mg QD was identified as the maximum tolerated dose (MTD) and was the RP2D for the phase 2 expansion cohorts which include 4 histologically and molecularly defined cohorts targeting patients with NSCLC containing: (1) EGFR exon 20 insertions without active, measurable central nervous system (CNS) metastases, (2) HER2 exon 20 insertions or point mutations without active, measurable CNS metastases, (3) EGFR exon 20 insertions or HER2 exon 20 insertions or point mutations with active, measurable CNS metastases, and (4) other targets against which TAK-788 is active, with or without CNS metastases.

In summary, TAK-788 was generally well-tolerated, and preliminary anticancer activity was observed in EGFR exon 20 insertion-positive NSCLC patients who had been previously treated.

4.4 Rationale for the Proposed Study

This study is proposed to characterize safety and tolerability of a single oral dose of TAK-788, to identify a safe and tolerable dose of TAK-788 administered as a drug-in-capsule (DiC) formulation in healthy subjects, to evaluate the effects of a low-fat meal on the PK of TAK-788 and its active metabolites AP32960 and AP32916, and to assess the relative bioavailability of 2 DiCs of TAK-788. Part 1 of the study will use a randomized, double-blind, placebo-controlled, single rising dose escalation design to determine the safety and tolerability of TAK-788 and characterize the PK of TAK-788 and its active metabolites, and to identify a tolerable single dose in healthy subjects. Part 2 of the study will assess the effects of a low-fat meal on the PK of TAK-788 administered as a DiC formulation. Part 3 of the study will evaluate the relative bioavailability of a single dose of TAK-788 160 mg Process B DiC (test) versus a single dose of TAK-788 160 mg Process A DiC (reference).

4.4.1 Risk-Benefit Assessment

The available information suggests that the present clinical study has an acceptable benefit-risk profile.

The inclusion and exclusion criteria and safety monitoring practices employed by this protocol are adequate to protect the subjects' safety and should detect all expected treatment-emergent adverse events (TEAEs).

There will be no direct health benefit for trial participants from receipt of study drug. An indirect health benefit to the subjects enrolled in this trial is the free medical tests received at screening and during the study.

4.4.2 Rationale for Single Dose Escalation (Part 1)

This is the first single-dose experience with TAK-788 in healthy subjects. In this double-blind, randomized, placebo-controlled study, the safety, tolerability, and PK of TAK-788 and its 2 active metabolites, AP32940 and AP32916, will be evaluated. Additionally, a tolerable single dose will be identified for future clinical pharmacology studies in healthy subjects.

The starting dose of 20 mg for healthy subjects is based on clinical safety/tolerability data from phase 1 study (AP32788-15-101) in cancer patients and is supported by nonclinical safety data.

The phase 1 clinical study (AP32788-15-101) investigating the safety and PK of repeated doses of TAK-788 in patients with NSCLC started at 5 mg QD. At the time of first data cut-off in September 2017, the 120-mg QD dose was being tested. No Grade ≥2 treatment-related AEs were reported within 3 days of the repeated treatment in any patient.

In a 28-day Good Laboratory Practice (GLP)-compliant repeat-dose study in dogs (Report WIL-69513), a single dose of 1 mg/kg is considered to be the no-observed-adverse-effect level (NOAEL). The C_{av} (mean total average plasma concentration) of TAK-788 and its metabolites was 44.7 nM, which was ~4 fold the mean total C_{av} (12.6 nM) following a single dose 20 mg TAK-788 in cancer patients (data on file). Additionally, there were no TAK-788–related effects on the cardiovascular, respiratory and CNS (on the basis of monitoring in repeat-dose GLP toxicity studies), TAK-788 was neither a potent hERG inhibitor, and TAK-788 was neither mutagenic nor clastogenic in GLP-compliant bacterial reverse mutation assays (Report 9601435) and in *in vitro* mammalian chromosome aberration assays (Report 9601436). Therefore, the nonclinical safety data supports a single clinical starting dose of 20 mg.

The starting dose of TAK-788 in this study will be a single dose of 20 mg and the dose escalation steps will be similar to those in study AP32788-15-101. The highest dose tested in the dose escalation phase will not exceed the unit dose of MTD identified in Study AP32788-15-101.

The aim of Part 1 of this protocol is to determine the single-dose safety and tolerability of TAK-788 administered as DiC in healthy subjects. The dose in Part 1 of this study may be escalated up to 160 mg. The dose escalation decisions in Part 1 of the study will be guided by safety/tolerability data in previous cohorts as outlined in Section 8.3.

4.4.3 Rationale for Food Interaction (Part 2)

Typically, a clinical study in healthy subjects may provide a more accurate estimate of food effect on drug PK than a study in patients.

Information on the effects of food ingestion on TAK-788 PK will provide meal intake instructions when TAK-788 is administered to patients in future clinical studies. Food can affect oral bioavailability via various mechanisms, including altering gastric emptying rate, stimulating bile flow, altering gastrointestinal (GI) pH, increasing splanchnic blood flow, changing the luminal metabolism of drug substances, and physically or chemically interacting with drug substance or dosage form.

Food interaction is generally greatest when drug is administered shortly after food has been ingested. In addition, the nutritional and caloric content of food, volume of food, and temperature may also play a role in food-drug interactions and it is generally accepted that food that is high in calories and fat represents a worst-case scenario for this assessment. However, several recently approved oral EGFR TKIs and ALK^+ inhibitors were also studied with a standard meal or a low-fat and low-calorie meal for patients with cancer who are receiving routine oral administration of these drugs [15,16]. If possible, food effects assessments are preferably

conducted on the to-be-marketed formulation of a drug to avoid having to reassess food-drug interactions because of formulation changes. However, timely evaluation of food-drug interactions will provide important information on dosing conditions in future clinical trials.

In vitro, neither high-fat nor low-fat meals appear to increase or decrease TAK-788 absorption in a perfusion chamber study at 2 relevant clinical doses of 120 and 180 mg (data on file). Therefore, a low-fat meal is not expected to increase bioavailability.

Because TAK-788 is a Biopharmaceutics Classification System class 2 compound, there is a possibility that the magnitude of the food effect can be dose-dependent. Accordingly, it is important to conduct the food effect evaluation at or near the unit dose of the RP2D regimen. The dose used in the food effect study will be the unit doses determined in Part 1 of this study in healthy subjects to be safe and tolerable.

Since the DiC formulation will be used in the planned phase 2 pivotal clinical study, this portion of the study will be conducted with DiC of TAK-788. This part of the study will evaluate the effects of low-fat and low-calorie meal on the PK of TAK-788 administered as DiC.

4.4.4 Rationale for Relative Bioavailability Assessment (Part 3)

Process A and Process B TAK-788 drug substance (succinate salt) are chemically identical but are synthesized by different synthetic routes. The physiochemical properties of Process A and Process B TAK-788 drug substance are, however, different. The API powder prepared via Process B has larger primary particles, lower specific surface area, and a higher bulk density than the API powder prepared via Process A. The rationale for Part 3 of the study is to perform relative bioavailability assessment of Process B versus Process A DiC to enable PK bridging across the patients who are using or will be using these 2 DiCs in the TAK-788 clinical development program. CCI [redacted]

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 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 drug-in-capsule (DiC) formulation in healthy subjects.

Part 2: To characterize the effect of a low-fat meal on the PK of TAK-788 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.

5.1.2 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.

5.1.3 Exploratory Objectives

The exploratory objective is:

CCI

[redacted]

5.2 Endpoints

5.2.1 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).
- $t_{1/2z}$.

5.2.2 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.

5.2.3 Exploratory Endpoints

The exploratory endpoint is:

CCI [redacted]

CCI

[redacted]

6.0 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.

6.1 Overview of Study Design

6.1.1 Part 1 – Dose Escalation

The purpose of Part 1 of the study is to assess the safety and tolerability of TAK-788 and to identify a tolerable single dose. A single dose escalation design will be used, as detailed in Section 8.3.

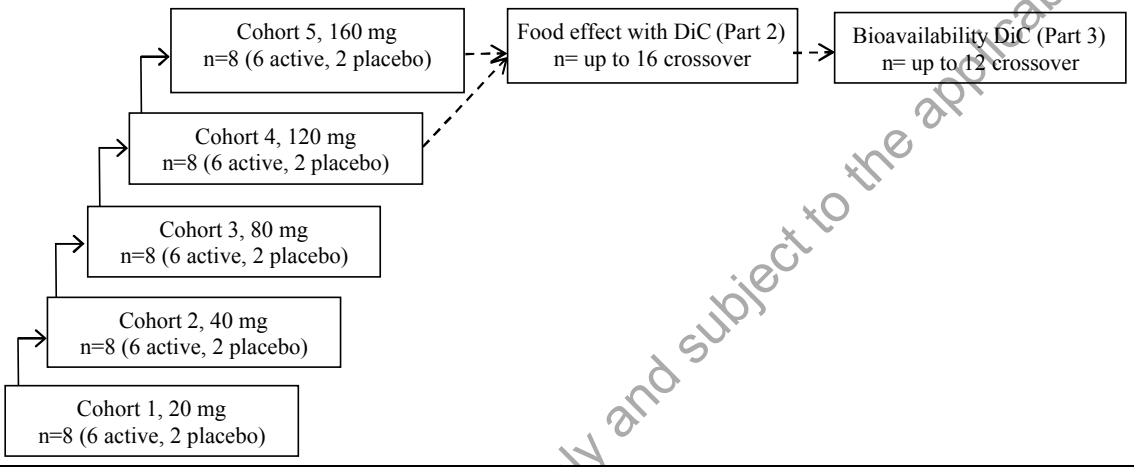
In the double-blind, randomized, placebo-controlled dose escalation phase, cohorts of 8 healthy subjects will be randomized: Under fasting conditions, 6 subjects will receive a single dose of TAK-788 and 2 subjects will receive placebo. The starting dose will be 20 mg, then with each subsequent 8-subject 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 6.a Dose Escalation Schema (Part 1)



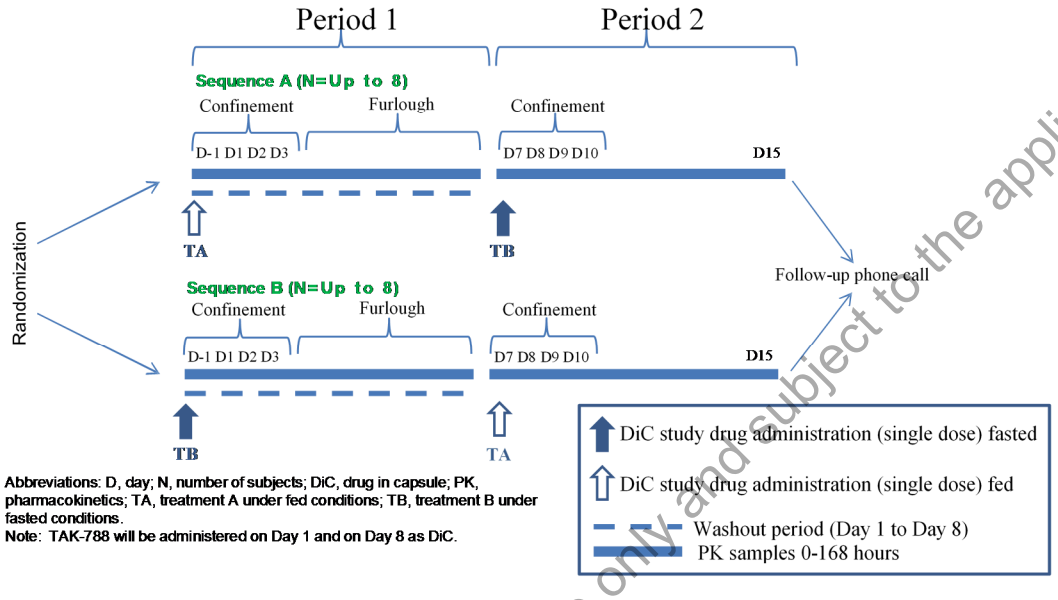
Abbreviations: DiC, drug-in-capsule.

6.1.2 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 dose used will be a tolerable single dose identified 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 Table 8.a. 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 6.b Food Effect Schema (Part 2)

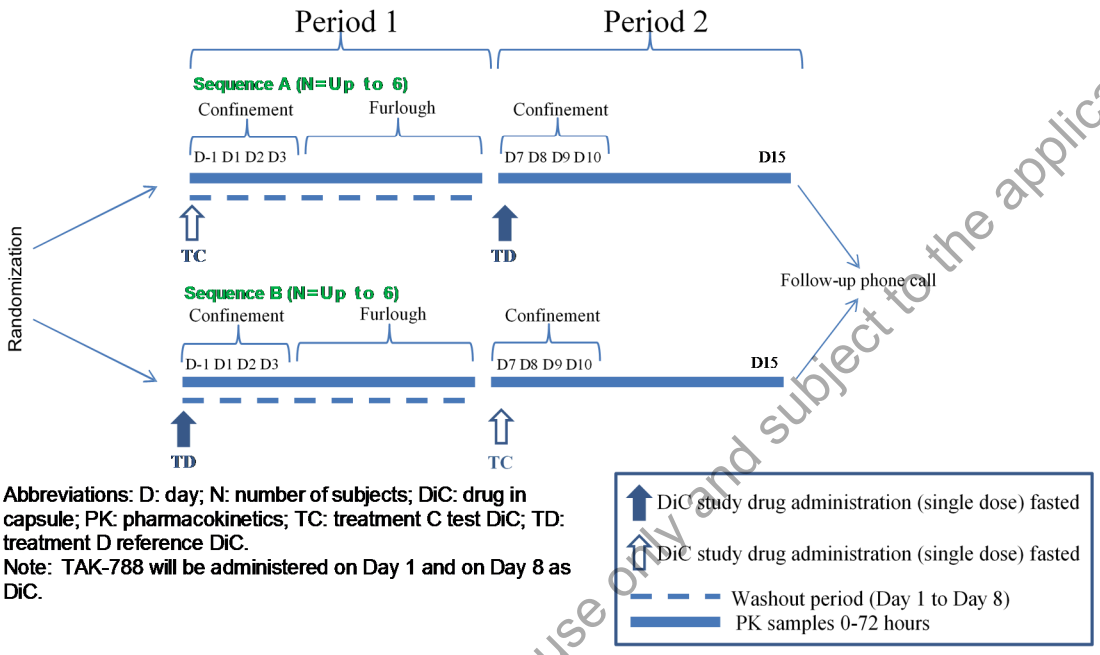


6.1.3 Part 3 – Relative Bioavailability

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 6.c Relative Bioavailability Schema (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.

6.2 Number of Subjects

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% to 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 up to 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.

6.3 Duration of Study

6.3.1 Duration of an Individual Subject's Study Participation

Subjects in the single rising dose part of the study (Part 1) will be treated for 1 day (single dose). Subjects in the food-effect part of the study (Part 2) and the relative bioavailability part of the study (Part 3) will receive 2 single doses separated by a ≥7-day washout.

Subjects will be followed for 30 days (window of up to 2 days after the Day 30 [Part 1] or Day 38 [Parts 2 and 3] visits) after the last dose of TAK-788. For Part 3, safety phone conferences will occur on Day 15 and 30 days after the last dose (window of up to 2 days after Day 38).

6.3.2 End of Study/Study Completion Definition and Planned Reporting

6.3.2.1 Definition of Trial Discontinuation

The trial may be discontinued for nonsafety reasons, such as:

- A finding (eg, PK, pharmacodynamic, efficacy, biologic targets) from another nonclinical or clinical trial using the trial treatment(s) results in the trial being stopped for a non–safety-related reason.
- Data from comparator(s), drug(s) of the same class, or methodology(ies) used in this trial become available and results in the trial being stopped for a non–safety-related reason.
- The trial is stopped because of nonscientific and nonsafety reasons, such as slow enrollment.

The trial may be discontinued for safety reasons:

- Early trial termination because of unanticipated concerns of safety to the trial subjects arising from nonclinical studies or clinical trials with the trial treatment(s), drug(s) of the same class, or methodology(ies) used in this trial.

6.3.2.2 Criteria for Premature Termination or Suspension of Trial Sites

A trial site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of GCP, protocol, or contractual agreement, is unable to ensure adequate performance of the trial, or as otherwise permitted by the contractual agreement.

6.3.2.3 Procedures for Premature Termination or Suspension of the Trial or the Participation of Trial Site

If the sponsor, an institutional review board (IRB), or regulatory authority elects to terminate or suspend the trial or the participation of an investigational site, a trial-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable investigational sites during the course of termination or trial suspension.

6.3.3 Time Frames for Primary and Secondary Endpoints to Support Disclosures

Please refer to Table 6.a for disclosures information for all primary and secondary endpoints.

Table 6.a Primary and Secondary Endpoints for Disclosures

Endpoint	Maximum Time Frame
Primary	
Part 1: safety profile of orally administered TAK-788.	Up to 30 days after last dose
• Number and percentage of subjects with 1 or more adverse events. • Number and percentage of subjects with 1 or more serious adverse events. • 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.	Up to 7 days following each dose
• C_{max}. • t_{max}. • AUC_t. • AUC_∞. • $t_{1/2z}$.	
Part 3: summary statistics of the PK parameters for TAK-788 with different DiC under fasted conditions.	Up to 7 days following each dose
• C_{max}. • t_{max}. • AUC_t. • AUC_∞ (if data permitted). • $t_{1/2z}$.	
Secondary	
Part 1: summary statistics of the PK parameters for TAK-788 and its 2 active metabolites, AP32960 and AP32914 under fasted conditions.	Up to 7 days
• C_{max}. • t_{max}. • AUC_t. • AUC_∞. • $t_{1/2z}$.	
Part 2: assess the safety profile of TAK-788 under fasted conditions or following a low-fat meal.	Up to 30 days after last dose
Part 3: assess the safety profile of TAK-788 under fasted.	Up to 30 days after last dose

Footnotes are on last table page.

Table 6.a Primary and Secondary Endpoints for Disclosures (continued)

Endpoint	Maximum Time Frame
Exploratory	
CCI [redacted]	

AUC_{∞}, area under the concentration-time curve from time 0 to infinity, calculated using the observed value of the last quantifiable concentration; AUC_t, area under the concentration-time curve from time 0 to time t; C_{max}, maximum observed plasma concentration; PK, pharmacokinetic; $t_{1/2z}$, terminal disposition phase half-life; t_{max}, time to first occurrence of C_{max}.

6.3.4 Total Study Duration

It is anticipated that this study will last for approximately 10 months.

7.0 STUDY POPULATION

Healthy subjects who meet all of the inclusion criteria and none of the exclusion criteria will be enrolled in this study.

7.1 Inclusion Criteria

Each subject must meet all the following inclusion criteria to be enrolled in the study.

1. Aged 18-55 years at the time of informed consent.
2. Healthy subjects defined as the absence of acute or chronic clinically significant deviations from normal in medical history, physical examination, electrocardiogram (ECG), and clinical laboratory determinations at screening.
3. Body weight of ≥45 kg (women) or ≥55 kg (men) and a body mass index of 18.0-30.0 kg/m^2 at screening.
4. Normal baseline PFTs (≥80% of predicted normal for spirometry, lung volumes, and DLco) Parts 1, 2, and 3; and chest CT scan at screening for Parts 1 and 2.
5. Nonsmoker (never smoked or >20 years from last occurrence of smoking).
6. Normal organ function including hepatic, renal, and bone marrow function.
7. Agree to practice effective contraception (see Section 8.7 for details).
8. Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the subject at any time without prejudice to future medical care.
9. The subject must be able to understand the requirements of the study and be willing to comply with the study requirements and provide their written informed consent to participate in the study.

7.2 Exclusion Criteria

Subjects meeting any of the following exclusion criteria are not to be enrolled in the study.

- Medical History and Concurrent Diseases

1. Ongoing or prior pulmonary disease including asthma, chronic obstructive pulmonary disease, interstitial lung disease, and pneumonitis including but not limited to drug-related pneumonitis.
2. Any history of cardiovascular disease including a history of congenital prolonged QT syndrome or unexplained cardiac arrest.
3. Manifestations of malabsorption due to prior GI surgery, GI disease, or for an unknown other reason that may alter the PK of TAK-788.

4. Pulmonary infection ongoing or within 30 days of informed consent.
5. Current or recent (within 3 months) GI disease.
6. Any major surgery within 4 weeks before study drug administration.
7. Blood transfusion within 4 weeks before study drug administration.
8. History of bleeding disorder.
9. Inability to tolerate oral medication.
10. Inability to undergo venipuncture and/or tolerate venous access.
11. Inability to tolerate multiple blood sampling.
12. Ongoing or active infection, including but not limited to, the requirement for intravenous (IV) antibiotics.
13. Positive serology or a known history of hepatitis B virus (HBV), hepatitis C virus (HCV), or HIV.
14. Pregnancy or breastfeeding (see Section 8.7 for details).

- Physical and Laboratory Test Findings

15. Any clinically significant abnormality at screening of cardiac, hepatic, renal, respiratory, GI, endocrine, immunologic, dermatologic, hematologic, neurologic, or psychiatric disease.
16. Resting blood pressure >140/90 mmHg at screening (a single repeat measurement is allowed if the initial measurement is outside these limits).
17. Resting pulse rate <45 beats per minute.

- Allergies and Adverse Drug Reactions

18. History of severe allergy/hypersensitivity reaction or ongoing allergy/hypersensitivity reaction, as judged by the investigator, or history of hypersensitivity to EGFR/HER2 inhibitors.

- Prohibited Treatments and Therapies

19. Prior exposure to TAK-788.
20. Exposure to any small molecule drug treatment, including investigational small molecule drugs, within 4 weeks or biologic drug treatment, including investigational biologics, within 16 weeks before study drug administration.
21. Use of any prescription or over-the-counter (OTC) stomach acid controllers within 2 weeks before study drug administration.

22. Use of any other drugs, including OTC medications, nutritional supplements, or herbal preparations (including St. John's wort) within 1 week before study drug administration (except occasional use of acetaminophen and ibuprofen, which are allowed up to 24 hours before dosing).
23. Consumption of any food or beverages containing grapefruit, Seville oranges, blood oranges, or pomegranates within 1 week before study drug administration.

8.0 STUDY DRUG

8.1 Study Drug Administration

8.1.1 Dose Escalation Phase (Part 1)

TAK-788 will be supplied as 20-mg and/or 40-mg capsules (DiC), if the 40-mg capsules are available at the time of the study.

In each cohort of 8 subjects, 6 subjects will receive a single dose of TAK-788 and 2 subjects will receive a single dose of placebo during the dose escalation phase (Part 1) under fasting conditions (see Section 8.1.2). TAK-788 dosing will begin at 20 mg (Cohort 1) and escalate to 40 mg (Cohort 2), 80 mg (Cohort 3), 120 mg (Cohort 4), up to 160 mg (Cohort 5).

All protocol-specific criteria for administering study drug must be met and documented before drug administration. Study drug will be administered only to eligible subjects under the supervision of the investigator or identified subinvestigator(s). The investigator(s) will remain blinded to the treatment in Part 1.

Subjects in Part 1 will receive a single dose of TAK-788 on Day 1 following an overnight fast (nothing to eat for at least 10 hours before and 4 hours after the TAK-788 dose). The drug product should be administered with 240 mL (8 fluid ounces) of water. No food should be allowed for at least 4 hours postdose.

Water can be allowed as desired except for 1 hour before and after drug administration. Subjects should receive standardized meals scheduled at the same time in each period of the study.

Before each dose escalation in Part 1, the investigator and sponsor will review the safety data from the previous dose cohort and will consider new safety data from nonclinical sources and the ongoing study in patients with NSCLC (AP32788-15-101).

8.1.2 Food Effects Study Phase (Part 2)

Before starting Part 2, the sponsor will evaluate the safety and tolerability of the dose identified in Part 1 and will include all available data, nonclinical and clinical, from both healthy subjects and patients in the ongoing clinical trial.

Subjects in Part 2 will receive a single dose of TAK-788 DiC formulation identified in Part 1 on Day 1, with or without a low-fat meal, followed by administration under the alternate treatment condition (fasted → fed or fed → fasted) on Day 8 (at least 7 days apart).

For fasted treatment:

- Following an overnight fast of at least 10 hours, subjects should be administered the drug product with 240 mL (8 fluid ounces) of water.
- No food should be allowed for at least 4 hours postdose.

- Water can be allowed as desired except for 1 hour before and after drug administration. Subjects should receive standardized meals scheduled at the same time in each period of the study.

For fed treatment:

- Following an overnight fast of at least 10 hours, subjects should start the recommended low-fat meal 30 minutes before administration of the drug product.
- Study subjects should eat this meal in 30 minutes or less; however, the drug product should be administered 30 minutes after the start of the meal.
- The drug product should be administered with 240 mL (8 fluid ounces) of water. No food should be allowed for at least 4 hours postdose.
- Water can be allowed as desired except for 1 hour before and after drug administration. Subjects should receive standardized meals scheduled at the same time in each period of the study.

The standard low-fat meal will be provided and served in the clinic by site personnel before dosing on Day 1 or Day 8 (or extended if the C_{trough}/C_{max} ratio is >5% at the same dose from Part 1). This meal will have the approximate composition described in Table 8.a.

Table 8.a Low-fat Meal Content

Food Item	Calories (kcal) (a)	Fat (a)	Carbohydrates (a)	Protein (a)
2 Slices of white bread, toasted	129	1.8 g	24.0 g	4.0 g
1 Teaspoon low-fat margarine	24	2.8 g	trace	Trace
1 Tablespoon jam	56	0.3 g	13.8 g	Trace
5 Ounces of apple juice	73	0.2 g	18.1 g	0.1 g
Total grams	—	5.1 g	63.3 g	9.3 g
Total calories (kcal)	336	46	253	37
% Of total calories	100	14	75	11

(a) Source; US Department of Agriculture Nutrient Database for Standard Reference, Release 18 (August 2005).

8.1.3 Relative Bioavailability (Part 3)

Subjects in Part 3 will receive a single dose of TAK-788 160 mg test DiC (Process B) or a single dose of TAK-788 160 mg reference DiC (Process A) under fasted conditions on Day 1 or Day 8 following an overnight fast of at least 10 hours. The drug product should be administered with 240 mL (8 fluid ounces) of water. No food should be allowed for at least 4 hours postdose.

Water can be allowed as desired except for 1 hour before and after drug administration. Subjects should receive standardized meals scheduled at the same time in each period of the study.

8.2 Definitions of DLT

DLTs will be summarized by category (hematologic and nonhematologic) and by MedDRA preferred term. Toxicity grade will be evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0 [17]. These criteria are provided in the study manual. A DLT is any Grade ≥3 nonhematologic toxicity, hematologic toxicity, or laboratory abnormality that occurred within 5 days following the administration of study drug and is considered by the investigator to be at least possibly related to therapy with TAK-788.

8.3 Dose Escalation Rules

For each cohort, the investigator and sponsor will confirm the safety and tolerability of the administered dose on Day 5 before proceeding to the next planned higher dose. This assessment will be based on all clinical findings such as AEs, vital signs, ECGs, PFTs, clinical laboratory tests, and physical examination. Once adequate subject safety and tolerability are confirmed, enrollment in the next dose level will proceed. The following criteria will be applied to subjects dosed with TAK-788 and must be met to proceed to next dose level:

- No DLTs have occurred at the current dose level.
- All Grade ≥2 treatment-related AEs resolve to Grade ≤1 or return to baseline by Day 5. If a Grade ≥2 treatment-related AE has 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, to ensure all Grade ≤2 treatment-related AEs have resolved to Grade ≤1 or returned to baseline before escalation to the next dose.
- If any clinically significant serious adverse reaction or other findings are observed at any dose, the investigator and sponsor may terminate dose escalation in this study.

8.4 Criteria for Tolerable Dose

The dose is considered tolerable if ≤1 of 6 subjects experiences a study drug–related DLT at the given dose within 5 days of dosing.

8.5 Excluded Concomitant Medications and Procedures

The following medications and procedures are prohibited during the study:

- Other investigational medicinal products or devices.
- Blood products or blood donation.
- Prescription medications, except as noted in Section 8.6.
- Nutraceuticals, including St. John's wort, ginseng, kava, ginkgo biloba, and melatonin.
- Immunizations.

- Intake of known inhibitors/inducers of cytochrome P450 3A4 (excluding study drugs) (see Appendix D).
- OTC medications, except as noted in Section 8.6.
- Vitamin supplements.
- Proton pump inhibitors (eg, omeprazole, esomeprazole, and pantoprazole).
- H2-receptor antagonists (eg, ranitidine, famotidine, cimetidine, and nizatidine).
- Medications that are known to be associated with development of torsades de pointes.

8.6 Permitted Concomitant Medications and Procedures

Occasional use of acetaminophen ≤1 g/day is permitted. Other OTC medication must be approved by the sponsor on a case-by-case basis.

Treatment with neutralizing antacids is not permitted less than 4 hours before and within 8 hours after receiving a dose of TAK-788.

Oral contraceptive pills and any other type of hormonal contraception is permitted.

Use of antiemetics is permitted per standard institutional practice, if needed to control nausea and vomiting.

Other concomitant medications will be assessed on a case-by-case basis.

All concomitant medication use must be recorded on the appropriate eCRF.

8.7 Precautions and Restrictions

It is not known what effects TAK-788 has on human pregnancy or development of the embryo or fetus. Women who are pregnant or breastfeeding will not be allowed to take part in this study. Women participating in this study should avoid becoming pregnant or nursing a baby, and men subjects should avoid impregnating a female partner for 16 weeks (4 months) after the last dose of TAK-788. Nonsterilized women of reproductive age and male subjects should use effective methods of contraception through defined periods during and after study treatment as specified below.

Women must meet 1 of the following criteria:

- Postmenopausal for at least 1 year before the screening visit, OR
- Surgically sterile, OR
- If they are of childbearing potential, agree to practice 2 effective methods of contraception from the time of signing of the informed consent form (ICF) through 16 weeks (4 months) after the last dose of study drug, OR

- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable methods of contraception.)
- Agree to not donate eggs (ova) and male subjects must agree not to donate sperm during the course of this study and for 16 weeks (4 months) after receiving their last dose of study drug.

Men, even if surgically sterilized (ie, status postvasectomy) must agree to 1 of the following:

- Agree to practice effective barrier contraception during the entire study treatment period and through 16 weeks (4 months) after the last dose of study drug, OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods for the female partner] and withdrawal are not acceptable methods of contraception.)
- Agree not to donate sperm during this study and for 120 days after receiving their last dose of study drug.

Contraception methods meeting the criteria defined above are provided in Table 8.b. If male condoms are used as a barrier method by male subjects, their partners must use an intrauterine device (Copper T, or Progesteron T) or hormonal contraceptives (combined pills) instead of spermicide.

Table 8.b Contraceptive Methods

Barrier Methods (Each Time the Subject Has Intercourse)	Intrauterine Devices	Hormonal Contraceptives
• Male condom PLUS spermicide. • Cap (plus spermicidal cream or jelly) PLUS male condom and spermicide. • Diaphragm (plus spermicidal cream or jelly) PLUS male condom and spermicide.	• Copper T PLUS condom or spermicide. • Progesterone T PLUS condom or spermicide.	• Implants. • Hormone injections. • Combined pills. • Minipills. • Patches. • Vaginal ring PLUS male condom and spermicide.

8.8 Management of Selected EGFR TKI Class AEs

8.8.1 Pneumonitis

Investigators must evaluate subjects who demonstrate potential signs/symptoms of pneumonitis, abnormal DLco (decrease of >20% from baseline), and/or abnormal chest CT scan. If clinically indicated, high-dose corticosteroid treatment should be initiated. Any DLco abnormalities and/or chest CT scan abnormalities will be followed weekly until resolution.

8.8.2 Nausea and Vomiting

Standard antiemetics may be used for the treatment of nausea and vomiting.

8.8.3 Diarrhea

Diarrhea may be treated at the investigator's discretion.

8.9 Blinding and 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 (window of up to 2 days after Day 30). 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.

8.10 Description of Investigational Agents

TAK-788 drug product is a nonsterile oral DiC formulation. The active study drug is available as 20 or 40 mg dosage strength capsules. The API has been synthesized using 2 different processes (Process A and Process B). Before Amendment 1, all subjects in Part 1 of this study received TAK-788 from Process B unmilled only with the capsule strength of 20 mg, and subjects in Part 2 received TAK-788 from Process A with capsule strength of 20 mg. After Amendment 1, some additional cohorts in Part 1 may receive TAK-788 from Process A.

Process A and Process B are the same succinate salt in chemical structure but synthesized with different processes. The API from Process B has larger particle size and higher bulk density than that from Process A.

Placebo will be commercially available empty size 2 capsules.

8.11 Preparation, Reconstitution, and Dispensation

TAK-788 study drug will be provided in appropriately labeled 30-count, 60-cc high-density polyethylene bottles, with child-resistant caps and induction seals.

Study drug bottles are considered to be bulk supplies, and are to be dispensed according to the site procedures, and according to instruction and guidelines provided in the study pharmacy manual.

TAK-788 is an anticancer drug and caution should be exercised when handling TAK-788 capsules.

8.12 Packaging and Labeling

TAK-788 study drug will be provided by Takeda and will be handled at the investigative sites as blinded material in Part 1. TAK-788 study drug is packaged in accordance with all applicable regulations.

The investigator will be notified of any expiry date or retest date extension of clinical study material during the study conduct. On expiry date notification from the sponsor or designee, the site must complete all instructions outlined in the notification, including segregation of expired clinical study material for return to the sponsor or its designee.

8.13 Storage, Handling, and Accountability

The recommended storage condition for TAK-788 is at a temperature thermostatically maintained at the usual customary working environment of 15°C-30°C, as experienced in pharmacies, hospitals, and warehouses (United States [US] Pharmacopeia 659 Packaging and Storage Requirements).

The study pharmacist or designee at the site will be responsible for handling and dispensing study drug and placebo, and for completing associated documentation. Supplies are shipped to the investigative site at appropriate intervals, depending on subject accrual. The site must use an appropriate dispensing log/accountability form provided by the sponsor, or an acceptable substitute approved by the sponsor. An unblinded site pharmacist will dispense study drug to the subjects on the day of administration. The site SOP should be followed.

All clinical trial material must be kept in an appropriate, limited-access, secure location until used or returned to the sponsor or designee. All study medication must be stored under the conditions specified on the label, and must remain in the original container until dispensed. A daily temperature log of the drug storage area must be maintained.

The investigator or designee must confirm that appropriate temperature conditions have been maintained for all TAK-788 received and that any discrepancies are reported and resolved before use of TAK-788.

The investigator is responsible for ensuring that deliveries of TAK-788 and other study materials from the sponsor are correctly received, recorded, and handled, and stored safely and properly in accordance with the Code of Federal Regulations (CFR) or national and local regulations.

The investigator or designee must ensure that the study medication is used in accordance with the approved protocol and is dispensed only to subjects enrolled in the study. To document appropriate use of study medication (TAK-788), the investigator must maintain records of all study medication delivery to the site, site inventory, use by each subject, and return to the sponsor or designee.

8.13.1 Disposition of Used Supplies

All used bottles of study drug must be destroyed in an appropriate manner according to the standard practice at each study center. Destruction of such supplies will be documented, and a representative of the sponsor will verify disposition records.

No other use of TAK-788 intended for use in this study is authorized by the sponsor. The principal investigator or designee will be responsible for the appropriate handling and disposition of residual study drug.

8.13.2 Inventory of Unused Supplies

At the completion of the trial, a final study drug accountability review will be conducted. Any discrepancies must be investigated and all unused study drug must be destroyed on site per the SOP of the investigative site.

8.14 Other Protocol-Specified Materials

Not applicable

9.0 STUDY CONDUCT

This trial will be conducted in compliance with the protocol, GCP, applicable regulatory requirements, and ICH guidelines.

9.1 Study Personnel and Organizations

The contact information for the sponsor clinician for this study, the central laboratory and any additional clinical laboratories, the coordinating investigator, and any other vendor may be found in the study manual.

9.2 Arrangements for Recruitment of Subjects

Recruitment and enrollment strategies for this study may include recruitment from the investigator's local practice or referrals from other physicians. If advertisements become part of the recruitment strategy, they will be reviewed by the IRB/independent ethics committee (IEC). It is not envisioned that prisoners (or other populations that might be subject to coercion or exploitation) will be enrolled into this study.

9.3 Treatment Group Assignments

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.

9.4 Study Procedures

Refer to the schedule of events (Appendix A) for the timing of assessments. Subjects will be admitted to the clinical site on the day before dosing days. Study drug administration will be considered time zero (starting of Day 1). Additional details are provided as necessary in the sections that follow.

9.4.1 Informed Consent

Each subject must provide written informed consent before any study-required procedures are conducted.

9.4.2 Subject Demographics

The date of birth, race, ethnicity, and sex of the subject are to be recorded during screening.

9.4.3 Medical History

During the screening period, a complete medical history will be compiled for each subject.

9.4.4 Physical Examination

A physical examination will be completed per standard of care at the times specified in the schedule of events (Appendix A). A complete physical examination must be performed at screening, the extent of which should be consistent with medical history. Subsequent physical examinations as described in the schedule of events may be directed to relevant findings.

9.4.5 Subject Height

Height will be measured during screening only (within 21 days before the first dose of TAK-788).

9.4.6 Vital Signs

Vital sign measurements including measurements of diastolic and systolic blood pressure, pulse rate, and oral temperature will be obtained at the times specified in the Schedules of Events (Appendix A). Subjects should sit quietly for at least 5 minutes before blood pressure is measured. When the timing of vital sign measurements coincides with the collection of blood samples, the vital sign measurements should be completed first. When vital sign measurements are scheduled at the same time as an ECG and a blood draw, the vital sign measurements will be obtained immediately before the ECG and the blood draw, and the blood draw will be collected at the scheduled time. If vital sign measurement results are abnormal, a repeat measure may be taken within 30 minutes.

9.4.7 Pulmonary Function Tests

PFTs include spirometry, lung volumes, and DLco. In Part 1, PFTs will be performed at screening but no more than 7 days before Day 1, and at Day 3 before furlough. In Parts 2 and 3, PFTs will be performed at screening and at Day 3, Day 10, and/or Early Termination visit if indicated on the basis of pulmonary symptoms.

9.4.8 Drug, Alcohol, and Tobacco Testing

Urine drug testing and breath alcohol testing will be performed during screening using the site's standard test panel. In addition to negative test results during screening, subjects also must have

negative urine and alcohol test results following confinement on Day -1 before the first dose of TAK-788.

To test for use of nicotine products, a urine cotinine test will be performed during screening. In addition to a negative test result during screening, subjects also must have a negative urine cotinine test result following confinement on Day -1 before the first dose of TAK-788.

In Parts 2 and 3 of the study, subjects must also have negative urine drug, breath alcohol, and urine cotinine test results the day before the second dose of TAK-788 on Day 8.

9.4.9 Pregnancy Test

In Part 1 of the study, a serum β-human chorionic gonadotropin (β-hCG) pregnancy test will be performed for women of childbearing potential during screening. In addition to a negative serum hCG pregnancy test at screening, female subjects also must have a negative serum hCG pregnancy test following confinement on Day -1 before the first dose of TAK-788 on Day 1.

In Parts 2 and 3 of the study, female subjects must have a negative serum hCG pregnancy test at screening, Day -1 (before first dose), and Day 7 (before the second dose of TAK-788 on Day 8).

9.4.10 Concomitant Medications and Procedures

Medications used by the subject and therapeutic procedures completed by the subject will recorded in the electronic case report form (eCRF) from signing of the ICF through 30 days after the last dose. See Section 8.5 and Section 8.6 for a list of medications and therapies that are prohibited and allowed, respectively, during the study.

9.4.11 AEs

AEs, serious and nonserious, will be recorded from the signing of ICF through 30 days after the last dose of study drug, with a follow-up phone call on Day 30 (window of up to 2 days after Day 30) for Part 1 subjects or on Day 38 (window of up to 2 days after Day 38) for subjects in Parts 2 and 3. Refer to Section 10.1 for details regarding definitions, documentation, and reporting of pretreatment events (PTEs), AEs, and SAEs.

9.4.12 Enrollment

A subject is considered to be enrolled in the study when the subject has met all eligibility criteria and is randomized to a study group (TAK-788 versus placebo in Part 1; fed versus fasted in Part 2; test versus reference formulation in Part 3). Procedures for completing the enrollment information are described in the study manual.

9.4.13 ECG

Triplicate 12-lead ECG will be administered at the time points specified in the Schedules of Events (Appendix A). ECG measurements must be taken at screening; on Days -1, 1, and 3 in Parts 1, 2, and 3; and on Days 7, 8, and 10 in Parts 2 and 3. On Days 1 and 8, ECG measurements will be obtained between 4 and 6 hours postdose. The clinical site's ECG machine may be used to obtain

the ECG. When the timing of an ECG coincides with the collection of blood samples, the ECG should be completed first. When an ECG is scheduled at the same time as vital signs and a blood draw, the ECG will be obtained after the vital signs and before the blood draw, and the blood draw will be collected at the scheduled time.

9.4.14 Chest CT Scan

A chest CT scan will be performed at screening (within 28 days before dosing) for Parts 1 and 2; this scan can be a low-dose scan. The follow-up chest CT scan, if needed on the basis of symptoms, should be a high-resolution chest CT scan with the appropriate dose of radiation. No IV contrast agent should be used.

9.4.15 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed locally. Additional laboratory samples may be taken at the discretion of the investigator (eg, if the results of any tests fall outside reference ranges or if clinical symptoms necessitate testing). Handling and shipment of clinical laboratory samples will be outlined in the study manual. Clinical laboratory evaluations will be performed as outlined below:

9.4.15.1 Clinical Chemistry, Hematology, and Urinalysis

Blood samples for analysis of the clinical chemistry and hematology parameters shown in Table 9.a and urine samples for analysis of the parameters shown in Table 9.b will be obtained as specified in the schedule of events.

Table 9.a Clinical Chemistry and Hematology Tests

Hematology	Serum Chemistry (a)	
Hemoglobin	Albumin	Creatine phosphokinase
CBC with 5-part differential	Alkaline phosphatase	γ-Glutamyl transferase
Platelet count	Alanine aminotransferase	Glucose
RBC count	Amylase	Lactate dehydrogenase
Reticulocyte count	Aspartate aminotransferase	Lipase
	Bilirubin, direct	Magnesium
	Bilirubin, total	Phosphate, inorganic
	Blood urea nitrogen	Potassium
	Calcium	Protein, total
	Carbon dioxide	Sodium
	Chloride	Urate
	Creatinine	

CBC, complete blood count; RBC, red blood cell.
(a) For screening serum chemistry, subjects must be fasting (nothing except water) for 8 hours before the measurement.

Fasting serum glucose will be measured at screening only. Subjects are required to fast overnight (nothing except water and/or protocol allowed medications [see Section 8.6] after midnight or for a minimum of 8 hours) for each of these measurements.

In addition to fast serum glucose, serum glucose will also be measured at the time points specified in the Schedules of Events (Appendix A). Subjects are not required to fast for these measurements.

The Cockcroft-Gault formula will be used to estimate creatinine clearance as follows:

$$Estimated\ creatinine\ clearance = [(140 - Age) \bullet Mass(kg)\ ] / [72 \bullet serum\ creatinine(mg/dL)]$$

For female subjects, the result of the formula above should be multiplied by 0.85.

Table 9.b Clinical Urinalysis Tests

Bilirubin	Occult blood
Glucose	pH
Ketones	Protein
Leukocytes	Specific gravity
Nitrite	Urobilinogen

9.4.15.2 Serology

Serology tests performed at screening will include anti-HIV antibodies, HBV surface antigen, and anti-HCV antibody.

9.4.15.3 Coagulation

Prothrombin international normalized ratio will be measured only if alanine aminotransferase or aspartate aminotransferase is>3 times the upper limit of normal (ULN).

9.4.16 PK Measurements

Blood samples for PK analysis of TAK-788 will be collected over a 7-day period (0-168 hours) for Parts 1 and 2 and over a 3-day period (0-72 hours) for Part 3 following the dose of TAK-788. Time points are specified in the PK blood sampling schedules (Appendix A). While the primary purpose of collecting PK samples is for measuring plasma concentrations of TAK-788 and its active metabolites, AP32960 and AP32914, if deemed necessary and pending technical feasibility, the samples collected may also be used for future performance of exploratory measurements of TAK-788 metabolite levels to further understand TAK-788 metabolism in humans. The dates and exact times of administration of TAK-788 before collection of the blood sample for PK analysis and the dates and exact times of the postdose PK sample collection will be recorded on the eCRF.

Urine samples for PK analysis of the renal clearance of TAK-788 will be obtained at the time points specified in the PK plasma and urine sampling schedules (Appendix A). While the primary purpose of collecting urine PK samples is for measuring urine concentrations of TAK-788, if deemed necessary and pending technical feasibility, the urine samples collected may also be used

for future performance of exploratory measurements of TAK-788 metabolite levels to further understand TAK-788 metabolism in humans. The date and exact time of the predose voids; the dates and exact times of administration of TAK-788 before the start of urine sample collection for PK analysis; and the total volume of each voided sample following administration of TAK-788 will be recorded on the eCRF.

For subjects in Parts 2 and 3, the morning dose on Day 8 should occur at approximately the same time as the morning dosing time on Day 1. When the timing of a PK or safety laboratory blood sample coincides with the timing of ECG measurements, the ECG will be completed before the blood sample collection.

9.5 Completion of Study Treatment for Individual Subjects

Subjects will be enrolled into Part 1, Part 2, or Part 3 of the study and will be considered to have completed study treatment after they have received the prescribed study drug treatments in Part 1, Part 2, or Part 3 of this study (single dose for Part 1 and two separated doses for Parts 2 and 3).

9.6 Discontinuation of Treatment With Study Drug and Subject Replacement

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:

- Occurrence of intolerable AE, as assessed by the investigator or designee.
- Clinically significantly abnormal vital signs, ECG, clinical laboratory, or physical examination assessments, as assessed by the investigator.
- Pregnancy.
- Withdrawal of consent.
- Lost to follow-up.
- Administrative reasons (eg, sponsor decision).
- Major protocol violation.
- If, in the opinion of the investigator, it is in the best interest of the subject.
- Non-compliance with study requirements and restrictions.
- Use of a concomitant medication that, in the opinion of the investigator, could interfere with the study procedures or data integrity or compromise the safety of the subject.
- Positive urine drug screen, CO breath test, or breath alcohol test at admission to any study visit.
- Emesis within 8 hours of drug ingestion (to be evaluated by the investigator or designee on a case-by-case basis).
- Termination of the study.

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 Parts 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.

9.7 Study Compliance

Study drug will be administered or dispensed only to eligible subjects by an unblinded site pharmacist and will be under the supervision of the investigator or identified subinvestigator(s). The pharmacist will be unblinded in Part 1. The appropriate study personnel will maintain records of study drug receipt and dispensing. Subject compliance with study drug administration will be confirmed according to standard procedures at the clinical site.

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 PTE

A PTE is any untoward medical occurrence in a subject who has signed informed consent to participate in a study but before administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

10.1.2 AE Definition

AE means any untoward medical occurrence in a subject or subject administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug.

An abnormal laboratory value will not be assessed as an AE unless that value is considered by the investigator to be a clinically significant change from baseline.

10.1.3 SAE Definition

An SAE is any untoward medical occurrence that, at any dose:

- Results in **death.**
- Is **life-threatening** (refers to an AE in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe).
- Requires in-patient **hospitalization or prolongation of an existing hospitalization** (see clarification in the paragraph in Section 10.2 on planned hospitalizations).
- Results in **persistent or significant disability or incapacity**. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**.
- Is a **medically important event**. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, on the basis of appropriate medical judgment, may jeopardize the subject, require medical or surgical intervention to prevent one of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency department or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle

(eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

In this study, intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE, version 5.0, effective date 27 November 2017 [17]. Clarification should be made between an SAE and an AE that is considered severe in intensity (Grade 3 or 4), because the terms *serious* and *severe* are *not* synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is *not* the same as *serious*, which is based on subject/event outcome or action criteria described above, and is usually associated with events that pose a threat to a subject's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm^3 to less than 2000/mm^3 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

10.2 Procedures for Recording and Reporting AEs and SAEs

All AEs spontaneously reported by the subject and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the appropriate page of the eCRF (see Section 10.3 for the period of observation). Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as 1 comprehensive event.

Regardless of causality, SAEs and serious PTEs (as defined in Section 10.1) must be reported (see Section 10.3 for the period of observation) by the investigator to the Takeda Global Pharmacovigilance department or designee (contact information provided below). This should be done by faxing the SAE form within 24 hours after becoming aware of the event. The SAE Form, created specifically by Takeda, will be provided to each clinical study site. A sample of the SAE Form may be found in the study manual. Follow-up information on the SAE or serious pretreatment event may be requested by Takeda. SAE report information must be consistent with the data provided on the eCRF.

SAE Reporting Contact Information

CCI [redacted]

Planned hospital admissions or surgical procedures for an illness or disease that existed before study drug was given are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (eg, surgery was performed earlier or later than planned). For both serious and nonserious AEs, the investigator must determine both the severity (toxicity grade) of the event and the relationship of the event to study drug administration. For serious PTEs, the

investigator must determine both the severity (toxicity grade) of the event and the causality of the event in relation to study procedures.

Severity (toxicity grade) for each AE, including any lab abnormality, will be determined using the NCI CTCAE, version 5.0, effective date 27 November 2017 [17]. The criteria are provided in the study manual. Selected asymptomatic laboratory values may also constitute AEs as defined by the NCI CTCAE.

10.3 Monitoring of AEs and Period of Observation

AEs, both nonserious and serious, will be monitored throughout the study as follows:

- AEs will be reported from the signing of informed consent through 30 days after administration of the last dose of study drug and recorded in the eCRFs.
- SAEs will be monitored throughout the study as follows:
  - Serious PTEs will be reported to the Takeda Global Pharmacovigilance department or designee from the time of the signing of the ICF up to first dose of study drug, and will also be recorded in the eCRF.
  - Related and unrelated treatment-emergent SAEs will be reported to the Takeda Global Pharmacovigilance department or designee from the first dose of study drug through 30 days after administration of the last dose of study drug and recorded in the eCRF. After this period, only related SAEs must be reported to the Takeda Global Pharmacovigilance department or designee. SAEs should be monitored until they are resolved or are clearly determined to be due to a subject's stable or chronic condition or intercurrent illness(es).

10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and permanently discontinue study drug. The sponsor must also be contacted immediately by faxing a completed pregnancy form to the Takeda Global Pharmacovigilance department or designee (see Section 10.2). The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male subject becomes pregnant during the male subject's participation in this study, the sponsor must also be contacted immediately by faxing a completed pregnancy form to the Takeda Global Pharmacovigilance department or designee (see Section 10.2). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

10.5 Procedures for Reporting Product Complaints or Medication Errors (Including Overdose)

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately report this via the phone numbers or e-mail addresses provided below.

A medication error is a preventable event that involves an identifiable subject and that leads to inappropriate medication use, which may result in subject harm. While overdoses and underdoses constitute medication errors, doses missed inadvertently by a subject do not. Individuals who identify a potential medication error (including overdose) situation should immediately report this via the phone numbers or e-mail addresses provided below.

Call center	Phone number	E-mail	Fax
CCI [redacted]			

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE form should be completed and sent to CCI [redacted] (refer to Section 10.2).

10.6 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, investigators, and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as an expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal product's administration or in the overall conduct of the trial. The investigational site also will forward a copy of all expedited reports to its IRB or IEC in accordance with national regulations.

11.0 STUDY COMMITTEES

Not applicable.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the data management plan. If selected for coding, AEs, PTEs, medical history, and concurrent conditions will be coded using MedDRA. Drugs will be coded using the World Health Organization (WHO) Drug Dictionary.

12.1 eCRFs

Completed eCRFs are required for each subject who signs an ICF.

The sponsor or its designee will supply investigative sites with access to eCRFs and will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor, contract research organization (CRO) partners, and regulatory authorities. Investigative sites must complete eCRFs in English.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designees) and will be answered by the site.

Any change of, modification of, or addition to the data on the eCRFs should be made by the investigator or appropriate site personnel. Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change.

The investigator must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated ICFs, subject authorization forms regarding the use of personal health information (if separate from the ICFs), electronic copy of eCRFs, including the audit trails, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor, or its designees. Any source documentation printed on degradable thermal-sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long term legibility. Furthermore, ICH E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years

after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the clinical study site agreement between the investigator and sponsor.

Refer to the clinical study site agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

Refer to the clinical study site agreement for the sponsor's requirements on record retention. The investigator and the head of the institution should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan will be prepared and finalized before database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

13.1.1 Analysis Sets

The study analysis populations will consist of the following:

- Randomized population: All subjects who are randomized to receive study treatment in Part 1, Part 2, or Part 3.
- Safety population: All enrolled subjects who receive any study treatment in the treatment period.
- PK 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).

13.1.2 Analysis of Demographics 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.

13.1.3 PK 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 concentration), CCI [redacted]

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. 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).

13.1.4 Safety Analysis

Safety and tolerability parameters will be listed by subject, study group, 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. 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.

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). Vital sign abnormalities and PFTs will be listed with a flag for clinical significance based on investigator judgment. Oral temperature data will be listed.

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

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.

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 clinical significance based on investigator judgment.

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

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. These data will be listed.

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

13.2 Determination of Sample Size

Part 1: The 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% to 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 up to 16 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 2.

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 allows for 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.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the sponsor or its designee (eg, CRO) and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or designee (as long as blinding is not jeopardized), including but not limited to the investigator's binder, study medication, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information (if separate from the ICFs), and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or IEC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the US Food and Drug Administration [FDA], the United Kingdom [UK] Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" listed in Appendix B. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable state and federal requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. US sites that are unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the US Department of Health and Human Services.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the investigator's brochure, a copy of the ICF, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study (ie, before shipment of the sponsor-supplied drug or study specific screening activity). The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, ICF) reviewed; and state the approval date. The sponsor will notify site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the trial. Until the site receives notification, no protocol activities including screening may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the ICF, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB or IEC and sponsor.

15.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The ICF and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The ICF will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the ICF and if applicable, the subject authorization form. The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor before use.

The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language that is fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the ICF, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. In the event the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject, or the subject's legally acceptable representative, determines that he or she will participate in the study, then the ICF and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and before the subject enters into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink pen. The investigator must also sign and date the ICF and subject authorization (if applicable) at the time of consent and before subject entering into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original ICF, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the subject signs the ICF in the subject's medical record. Copies of the signed ICF, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed

consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised ICF.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will be linked to the sponsor's clinical study database or documentation only via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, US FDA, UK Medicines and Healthcare products Regulatory Agency, Japan Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents) including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization by the subject as part of the informed consent process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected on the subject's eCRF).

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the clinical study site agreement. In the event of any discrepancy between the protocol and the clinical study site agreement, the clinical study site agreement will prevail.

15.4.2 Clinical Trial Registration

To ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum register interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites on or before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing.

As needed Takeda and investigator/site contact information may be made public to support participant access to trials via registries. In certain situations/registries, Takeda may assist participants or potential participants with finding a clinical trial by helping them locate trial sites closest to their homes by providing the investigator name, address, and phone number via email/phone or other methods to those requesting trial information. Once subjects receive investigator contact information, they may call the site to request enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

Any investigator who objects to Takeda providing this information to callers must provide Takeda with a written notice requesting that their information not be listed on the registry site.

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov or other publicly accessible websites (including the Takeda corporate site) and registries, as required by Takeda Policy/ Standard, applicable laws and/or regulations.

15.4.4 Data Sharing

The sponsor is committed to responsible sharing of clinical data with the goal of advancing medical science and improving subject care. Qualified independent researchers will be permitted to use data collected from subjects during the study to conduct additional scientific research, which may be unrelated to the study drug or the subject's disease. The data provided to external researchers will not include information that identifies subjects personally.

15.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study subjects. Refer to the clinical study site agreement for the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

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Appendix A Schedule of Events

Table 1 – Single Rising Dose Study (Part 1)

	Screening [a]	Day -1	Day 1	Day 2	Day 3	Day 8	Follow-up [b]
Informed consent	X						
Inclusion/exclusion criteria	X	X					
Demographics	X						
Medical history	X						
Physical examination [c]	X	X			X		
Height	X						
Weight [c]	X	X					
Vital signs [d]	X	X	X	X	X		
Chest CT scan [e]	X				(X)		
Pulmonary function tests [f]	X				X		
Concomitant medications and procedures [g]	← continuous →						X
Adverse event reporting [h]	← continuous →						X
Electrocardiogram [i]	X	X	X		X		
Admission to clinical site [j]		X					
TAK-788 administration			X				
Pregnancy test [k]	X	X					
Hematology/chemistry/coagulation [l]	X	X	X		X		
Urinalysis [l]	X	X	X		X		
Pharmacokinetic sampling [m]			X	X	X	X	
Drug, alcohol, and tobacco testing [n]	X	X					
Serology [l]	X						
Follow-up questionnaire						X	X

Footnotes are on last table page.

Abbreviations: CT, computed tomography; ICF, informed consent form.
An "X" in parentheses indicates that a procedure or test may be done under certain conditions. If extenuating circumstances prevent a subject from beginning treatment or completing a scheduled procedure or assessment within this time, the subject may continue the study only with the permission of the medical monitor.
[a] Unless otherwise noted, the screening visit must occur within 21 days before the day of the first dose of study drug (Day 1). The ICF may be signed 2-28 days before Day 1, and the chest CT scan may be within 28 days from Day 1 dosing.
[b] Follow-up phone call to query subject about possible adverse events. This contact should take place 30 days after the last dose (window of up to 2 days after Day 30).
[c] The Day -1 physical examination and weight assessment are not required if the screening physical examination and weight assessment were conducted within 4-7 days before administration of the first dose of study drug (Day 1) and in the opinion of the investigator, there is no reason to believe they have substantially changed.
[d] Perform vital sign measurement before dosing. On Day 1 only, perform vital signs measurements between 4 and 6 hours postdose. Blood pressure should be determined with the subject in a seated position after sitting quietly for 5 minutes. See Section 9.4.6 for timing in relation to other tests and procedures. If vital sign measurement results are abnormal, a repeat measure may be taken within 30 minutes.
[e] The screening chest CT scan can be a low-dose CT scan within 28 days from Day 1 dosing. The follow-up chest scan, if needed based on symptoms, should be a high-resolution chest CT scan with the appropriate dose of radiation. No IV contrast agent should be used. CT is to be performed on Day 3 if indicated based on pulmonary symptoms.
[f] See Section 9.4.7. Part 1: Spirometry, lung volumes, and diffusion capacity at screening but no more than 7 days before Day 1 and on Day 3.
[g] See Section 9.4.10.
[h] See Section 9.4.11.
[i] See Section 9.4.13. Triplicate 12-lead ECG measurements must be taken at screening and on Day -1, Day 1, and Day 3. On Day 1 only, perform ECG measurements between 4 and 6 hours postdose.
[j] Subjects should be admitted to the clinical site on the day before each dosing day.
[k] A serum β-human chorionic gonadotropin pregnancy test will be performed only for subjects of childbearing potential during screening and again at Day -1 (baseline) if the screening test was performed more than 4 days before the first dose of any study drug. The results must be negative within 4 days before the first dose of TAK-788 is administered (ie, within the 4 days before Day 1), or as otherwise required by local regulations. Additional pregnancy testing may be performed during the study at the discretion of the investigator, upon request from an independent ethics committee/institutional review board, or if required by local regulations. See Section 9.4.9.
[l] Evaluations to be performed are listed in Table 9.a. On Day 1 only, perform these laboratory tests between 4 and 6 hours postdose unless the timing of test is specified in Section 9.4.15.
[m] Time points for blood samples for PK analysis will be collected as specified in Appendix A, Table 3.
[n] See Sections 9.4.8.

Table 2 – Food Effect Study (Part 2)

	Screening [a]	Period 1 → / Period 2 →	Day -1 / Day 7	Day 1 / Day 8	Day 2 / Day 9	Day 3 / Day 10	Day 8 / Day 15	Follow-up [b]
Informed consent	X							
Inclusion/exclusion criteria	X		X					
Demographics	X							
Medical history	X							
Physical examination [c]	X		X			X		
Height	X							
Weight [c]	X		X					
Vital signs [d]	X		X	X	X	X		
Chest CT scan [e]	X					(X)		
Pulmonary function tests [f]	X					(X)		
Concomitant medications and procedures [g]			← continuous →					X
Adverse event reporting [h]			← continuous →					X
Electrocardiogram [i]	X		X	X		X		
Admission to clinical site [j]			X					
TAK-788 administration				X				
Pregnancy test [k]	X		X					
Hematology/chemistry/coagulation [l]	X		X	X		X		
Urinalysis [l]	X		X	X		X		
Pharmacokinetic sampling [m]				X	X	X	X	
Drug, alcohol, and tobacco testing [n]	X		X					
Serology [l]	X							
Follow-up questionnaire							X	X

Footnotes are on last table page.

CT, computed tomography; ICF, informed consent form.
An "X" in parentheses indicates that a procedure or test may be done under certain conditions. Note: If extenuating circumstances prevent a subject from beginning treatment or completing a scheduled procedure or assessment within this time, the subject may continue the study only with the permission of the medical monitor.
[a] Unless otherwise noted, the screening visit must occur within 21 days before the day of the first dose of study drug (Day 1). The ICF may be signed 2-28 days before Day 1, and the chest CT scan may be within 28 days from Day 1 dosing.
[b] Follow-up phone call to query subject about possible adverse events. This contact should take place 30 days after the last dose (window of up to 2 days after Day 38).
[c] The Day-1 physical examination and weight are not required if the screening physical examination and weight were conducted within 4-7 days before administration of the first dose of study drug (Day 1) and in the opinion of the investigator, there is no reason to believe they have substantially changed.
[d] Perform vital sign measurement before dosing. On Day 1 and Day 8, perform vital signs measurements between 4 and 6 hours postdose. Blood pressure should be determined with the subject in a seated position after sitting quietly for 5 minutes. See Section 9.4.6 for timing in relation to other tests and procedures. If vital sign measurement results are abnormal, a repeat measure may be taken within 30 minutes.
[e] The screening chest CT scan can be a low-dose CT scan within 28 days from Day 1 dosing. The follow-up chest scan, if needed based on symptoms, should be a high-resolution chest CT scan with the appropriate dose of radiation. No IV contrast agent should be used. CT is to be performed on Day 3 or Day 10 if indicated based on pulmonary symptoms.
[f] See Section 9.4.7. Perform spirometry, lung volumes, and diffusion capacity at screening but no more than 7 days before Day 1.
[g] See Section 9.4.10.
[h] See Section 9.4.11.
[i] See Section 9.4.13. Triplicate 12-lead ECG measurements must be taken at screening and on Days -1, 1, 3, 7, 8, and 10. On Day 1 and Day 8, perform ECG measurements between 4 and 6 postdose.
[j] Subjects should be admitted to the clinical site on the day before each dosing day.
[k] A serum β-human chorionic gonadotropin (β-hCG) pregnancy test will be performed only for subjects of childbearing potential during screening and again at Day -1 (baseline) if the screening test was performed more than 4 days before the first dose of any study drug. The results must be negative within 4 days before the first dose of TAK-788 is administered (ie, within the 4 days before Day 1), or as otherwise required by local regulations. In Period 2, the results must be negative on Day 7 before the second single-dose of TAK-788 on Day 8 is administered. Additional pregnancy testing may be performed during the study at the discretion of the investigator, upon request of an independent ethics committee (IEC)/institutional review board (IRB), or if required by local regulations. See Section 9.4.9.
[l] Evaluations to be performed are listed in Table 9.a. On Day 1 only, perform these laboratory tests between 4 and 6 hours postdose unless the timing of test is specified in Section 9.4.15.
[m] Time points for blood samples for PK analysis will be collected as specified in Appendix A, Table 4.
[n] See Sections 9.4.8.

Table 3 Relative Bioavailability Study (Part 3)

	Screening [a]	Period 1 → / Period 2 →	Day -1 / Day 7	Day 1 / Day 8	Day 2 / Day 9	Day 3 / Day 10	Day 8 / Day 15	Follow-up [b]
Informed consent	X							
Inclusion/exclusion criteria	X		X					
Demographics	X							
Medical history	X							
Physical examination [c]	X		X			X		
Height	X							
Weight [c]	X		X					
Vital signs [d]	X		X	X	X	X		
Pulmonary function tests [e]	X					(X)		
Concomitant medications and procedures [f]			← continuous →					X
Adverse event reporting [g]			← continuous →					X
ECG [h]	X		X	X		X		
Admission to clinical site [i]			X					
TAK-788 administration				X				
Pregnancy test [j]	X		X					
Hematology/chemistry/coagulation [k]	X		X	X		X		
Urinalysis [k]	X		X	X		X		
PK sampling [l]				X	X	X		
Drug, alcohol, and tobacco testing [m]	X		X					
Serology [k]	X							
Follow-up questionnaire							X [n]	X

Footnotes are on last table page.

ECG, electrocardiogram; ICF, informed consent form; PK, pharmacokinetic.
An "X" in parentheses indicates that a procedure or test may be done under certain conditions. Note: If extenuating circumstances prevent a subject from beginning treatment or completing a scheduled procedure or assessment within this time, the subject may continue the study only with the permission of the medical monitor.
[a] Unless otherwise noted, the screening visit must occur within 21 days before the day of the first dose of study drug (Day 1). The ICF may be signed 2-28 days before Day 1.
[b] Follow-up phone call to query subject about possible adverse events. This contact should take place 30 days after the last dose (window of up to 2 days after Day 38).
[c] The Day -1 physical examination and weight are not required if the screening physical examination and weight were conducted within 4-7 days before administration of the first dose of study drug (Day 1) and, in the opinion of the investigator, there is no reason to believe they have substantially changed.
[d] Perform vital sign measurement before dosing. On Day 1 and Day 8, perform vital sign measurements between 4 and 6 hours postdose. Blood pressure should be determined with the subject in a seated position after sitting quietly for 5 minutes. See Section 9.4.6 for timing in relation to other tests and procedures. If vital sign measurement results are abnormal, a repeat measure may be taken within 30 minutes.
[e] See Section 9.4.7. Perform spirometry, lung volumes, and diffusion capacity at screening but no more than 7 days before Day 1.
[f] See Section 9.4.10.
[g] See Section 9.4.11.
[h] See Section 9.4.13. Triplicate 12-lead ECG measurements must be taken at screening and on Days -1, 1, 3, 7, 8, and 10. On Day 1 and Day 8, perform ECG measurements between 4 and 6 postdose.
[i] Subjects should be admitted to the clinical site on the day before each dosing day.
[j] A serum β-human chorionic gonadotropin pregnancy test will be performed only for subjects of childbearing potential during screening and again at Day -1 (baseline) if the screening test was performed more than 4 days before the first dose of any study drug. The results must be negative within 4 days before the first dose of TAK-788 is administered (ie, within the 4 days before Day 1), or as otherwise required by local regulations. In Period 2, the results must be negative on Day 7 before the second single-dose of TAK-788 on Day 8 is administered. Additional pregnancy testing may be performed during the study at the discretion of the investigator, upon request of an independent ethics committee/institutional review board, or if required by local regulations. See Section 9.4.9.
[k] Evaluations to be performed are listed in Table 9.a. On Day 1 only, perform these laboratory tests between 4 and 6 hours postdose unless the timing of test is specified in Section 9.4.15.
[l] Time points for blood samples for PK analysis will be collected as specified in Appendix A, Table 4.
[m] See Sections 9.4.8.
[n] Day 15 safety conference call.

Table 4 Pharmacokinetic Plasma and Urine Concentration Sampling Schedule for Part 1

Study Day	Sample Collection Time	Time (Relative to Dosing) h:min	Plasma Concentrations of TAK-788, AP32960, and AP32914	Urine Concentrations of TAK-788, AP32960, and AP32914
1	0 h (predose)	00:00 (predose)	✓	✓ (predose void)
	0.5 h	00:30 (±5 min)	✓	
	1 h	01:00 (±10 min)	✓	
	2 h	02:00 (±10 min)	✓	
	4 h	04:00 (±10 min)	✓	
	6 h	06:00 (±20 min)	✓	
	8 h	08:00 (±20 min)	✓	
	12 h	12:00 (±20 min)	✓	✓ (0-12 h ±30 min)
2	0 h	24:00 (±30 min)	✓	✓ (12-24 h ±30 min)
	12 h	36:00 (±30 min)	✓	✓ (24-36 h ±30 min)
3	0 h	48:00 (±30 min)	✓	✓ (36-48 h ±30 min)
4	0 h	72:00 (±60 min)	✓	
5	0 h	96:00 (±60 min)	✓	
8	0 h	168:00 (±60 min)	✓	
Number of samples per profile:			14	4

When the timing of a PK or safety laboratory blood sample coincides with the timing of ECG measurements, the ECG will be completed before the collection of the blood sample.
The timing of the morning visit on Days 4, 5, and 8 should occur at approximately the same time as the morning dosing time on Day 1.

Table 5 Pharmacokinetic Plasma Concentration Sampling Schedule for Parts 2 and 3

Study Day	Sample Collection Time	Time (Relative to Dosing) h:min	Plasma Concentrations of TAK-788, AP32960, and AP32914
1	0 h (predose)	00:00 (predose)	✓
	0.5 h	00:30 (±5 min)	✓
	1 h	01:00 (±10 min)	✓
	2 h	02:00 (±10 min)	✓
	4 h	04:00 (±10 min)	✓
	6 h	06:00 (±20 min)	✓
	8 h	08:00 (±20 min)	✓
	12 h	12:00 (±20 min)	✓
2	0 h	24:00 (±30 min)	✓
	12 h	36:00 (±30 min)	✓
3	0 h	48:00 (±30 min)	✓
4	0 h	72:00 (±60 min)	✓
5 [b]	0 h	96:00 (±60 min)	✓
8 [c]	0 h	168:00 (±60 min) [a] (predose)	✓
	0.5 h	00:30 (±5 min)	✓
	1 h	01:00 (±10 min)	✓
	2 h	02:00 (±10 min)	✓
	4 h	04:00 (±10 min)	✓
	6 h	06:00 (±20 min)	✓
	8 h	08:00 (±20 min)	✓
	12 h	12:00 (±20 min)	✓
9	0 h	24:00 (±30 min)	✓
	12 h	36:00 (±30 min)	✓
10	0 h	48:00 (±30 min)	✓
11	0 h	72:00 (±60 min)	✓
12 [b]	0 h	96:00 (±60 min)	✓
15 [b]	0 h	168:00 (±60 min)	✓
Number of samples per profile:			Part 2: 27 Part 3: 24

Note: The timing of the morning visit on Days 4, 5, and 8 should occur at approximately the same time as the morning dosing time on Day 1. Similarly, the timing of the morning visit on Days 11, 12, and 15 should occur at approximately the same time as the morning dosing time on Day 8. When the timing of a PK or safety laboratory blood sample coincides with the timing of ECG measurements, the ECG will be completed before the collection of the blood sample.

[a] The predose PK sample must be collected before the next dose even though the collection window implies it can be taken after. The Day 8 dose must be administered shortly after the PK sample is taken.

[b] Part 3 removed PK sampling at 96-hour and 168-hour timepoints. Part 3 last PK sample is at the 72-hour timepoint

[c] Day 8, Part 3 will have predose sample, not the 168-hour sample.

Appendix B Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all applicable local laws and regulations. The responsibilities imposed on investigators by the US FDA are summarized in the "Statement of Investigator" (Form FDA 1572), which must be completed and signed before the investigator may participate in this study.

The investigator agrees to assume the following responsibilities by signing a Form FDA 1572:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. Ensure that study related procedures, including study specific (nonroutine/nonstandard panel) screening assessments are NOT performed on potential subjects, before the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
5. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 CFR Part 56 ICH, and local regulatory requirements.
6. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
7. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50 ICH and local regulations, are met.
8. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each ICF should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an ICF does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
9. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.
10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.

11. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.
12. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

Appendix C Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of investigator, including his or her name, address, and other personally identifiable information. In addition, investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the UK, US, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

Investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study medication.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study details and results on publicly accessible clinical trial registries, databases, and websites.

Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in the investigator's own country.

Investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

Appendix D List of Strong Inhibitors and Inducers of CYP3A

Strong Inhibitors [a]	Strong Inducers [b]
Boceprevir	Carbamazepine
Clarithromycin	Enzalutamide
Cobicistat	Mitotane
Conivaptan	Phenytoin
Danoprevir and ritonavir	Rifampin
Diltiazem	St. John's wort
Elvitegravir and ritonavir	
Grapefruit juice	
Idelalisib	
Indinavir and ritonavir	
Itraconazole	
Ketoconazole	
Lopinavir and ritonavir	
Nefazodone	
Nelfinavir	
Paritaprevir and ritonavir and (ombitasvir and/or dasabuvir)	
Posaconazole	
Ritonavir	
Saquinavir and ritonavir	
Telaprevir	
Tipranavir and ritonavir	
Troleandomycin	
Voriconazole	

Abbreviation: CYP, cytochrome P450.
[a] fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table3-2 (accessed 18 January 2018).
[b] fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table3-3 (accessed 18 January 2018).

Appendix E Detailed Description of Amendments to Text

The primary section(s) of the protocol affected by the changes in Amendment 03 are indicated. The corresponding text has been revised throughout the protocol.

Change 1: Addition of Part 3 to assess the relative bioavailability of TAK-788 capsules in healthy subjects.

The primary change occurs in the following sections:

- Section 4.4 Rationale for the Proposed Study.
- Section 4.4.4 Rationale for Relative Bioavailability Assessment (Part 3).
- Section 5.0 STUDY OBJECTIVES AND ENDPOINTS.
- Section 6.0 Study Design.
- Section 6.1 Overview of Study Design.
- New Section 6.1.3 Part 3 – Relative Bioavailability.
- Section 6.2 Number of Subjects.
- New Section 8.1.3 Relative Bioavailability (Part 3).
- Section 8.10 Description of Investigational Agents.
- Section 9.3 Treatment Group Assignments.
- Section 9.4.7 Pulmonary Function Tests
- Section 13.1.3 PK Analysis.
- Section 13.2 Determination of Sample Size.
- Appendix A Schedule of Events.

Added text: **Section 4.4 Rationale for the Proposed Study:**

This study is~~,~~ proposed to ~~identify~~ **characterize** safety and tolerability of a single oral dose of TAK-**788, to identify a safe and tolerable dose of TAK**-788 administered as a drug-in-capsule (DiC) formulation in healthy subjects ~~and~~**,** to evaluate the effects of a low-fat meal on the PK of TAK-788 and its active metabolites~~,~~ AP32960 and AP32916**, and to assess the relative bioavailability** of 2 DiCs of TAK-788. Part 1 of the study will use a randomized, double-blind, placebo-controlled, single rising dose escalation design to determine the safety and tolerability of TAK-788 and characterize the PK of TAK-788 and its active metabolites, and to identify a tolerable single dose in healthy subjects. Part 2 of the study will assess the effects of a low-fat meal on the PK of TAK-788 administered as a DiC formulation. **Part 3 of the study will evaluate the relative bioavailability of a single dose of TAK-788 160 mg Process B DiC (test) versus a single dose of TAK-788 160 mg Process A DiC (reference).**

Section 4.4.4 Rationale for Relative Bioavailability Assessment (Part 3)
Process A and Process B TAK-788 drug substance (succinate salt) are chemically identical but are synthesized by different synthetic routes. The physiochemical properties of Process A and Process B TAK-788 drug substance are, however, different. The API powder prepared via Process B has larger primary particles, lower specific surface area, and a higher bulk density than the API powder prepared via Process A. The rationale for Part 3 of the study is to perform relative bioavailability assessment of Process B versus Process A DiC to enable PK bridging across the patients who are using or will be using these 2 DiCs in the TAK-788 clinical development program. Part 3 of this study was added in Amendment 2 to assess the relative bioavailability of TAK-788 encapsulated in Process B DiC (test) and Process A DiC (reference) in healthy subjects.

Section 5.0 STUDY OBJECTIVES AND ENDPOINTS

Section 5.1.1 Primary Objectives

The primary objectives are:

Part 1: ~~to~~ **To** assess safety and tolerability of TAK-788 and to identify a tolerable single oral dose of TAK-788 administered as a **drug-in-capsule (**DiC**)** formulation in healthy subjects.

Part 2: ~~to~~**To** characterize the effect~~s~~ 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.

Section 5.1.2 Secondary Objectives

The secondary objectives are:

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

Part 2: ~~to~~**/ Part 3**: To assess the safety of TAK-788 following a single dose of TAK-788 ~~with or without a low-fat meal, administered as a DiC formulation~~ in healthy subjects.

Section 5.1.3 Exploratory Objectives

The exploratory objective is:

CCI [redacted]

Section 5.2 Endpoints

Section 5.2.1 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 ~~and its 2 active metabolites, AP32960 and AP32914~~ 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).**
- **$t_{1/2z.}$**

Section 5.2.2 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.

- $C_{max.}$
- $t_{max.}$
- $AUC_{t.}$
- $AUC_{\infty.}$
- $t_{1/2z.}$

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.

Section 5.2.3 Exploratory Endpoints

The exploratory endpoint is:

CCI

CCI

[redacted]

~~Section 6.1 Overview of Study Design~~

This is a **randomized,** double-blind, ~~randomized,~~ placebo-controlled~~,~~ single rising dose study**,** followed by ~~a~~**an open-label,** crossover evaluation of the effects of a low-fat meal on the PK of TAK-788 ~~PK~~ 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**.

Section 6.1 Overview of the Design

…

Section 6.1.3 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/or 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 6.c Relative Bioavailability Schema (Part 3)

[New figure depicting Part 3 schema]

Section 6.2 Number of Subjects

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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.

Section 8.1.3 Relative Bioavailability (Part 3)

Subjects in Part 3 will receive a single dose of TAK-788 160 mg test DiC (Process B) or a single dose of TAK-788 160 mg reference DiC (Process A) under fasted conditions on Day 1 or Day 8 following an overnight fast of at least 10 hours. The drug product should be administered with 240 mL (8 fluid ounces) of water. No food should be allowed for at least 4 hours postdose.

Water can be allowed as desired except for 1 hour before and after drug administration. Subjects should receive standardized meals scheduled at the same time in each period of the study.

Section 8.10 Description of Investigational Agents

TAK-788 drug product is a nonsterile oral DiC formulation. The active study drug is available as 20 or 40 mg dosage strength capsules. The API has been synthesized using 2 different processes (Process A and Process B). Before Amendment 1, all subjects in Part 1 of this study received TAK-788 from Process B unmilled only **with the capsule strength of 20 mg**, and subjects in Part 2 received TAK-788 from Process A **with capsule strength of 20 mg**. After Amendment 1, some additional cohorts in Part 1 may receive TAK-788 from Process A.

Process A and Process B are the same succinate salt in chemical structure but **synthesized with** different ~~physical properties. Process B incorporates optimizations in scale up, solvents, and reagents and implements a new step.~~**processes**. The API from Process B has larger particle size and higher bulk density than that from Process A. ~~At the time of Amendment 1, preliminary PK data from this study and a phase 1/2 study in patients with NSCLC (Study AP32788-15-101) indicate approximately 30% to 60% lower exposures (TAK-788 AUC_{24}) in healthy subjects receiving Process B unmilled TAK-788 DiC compared with patients with NSCLC receiving Process A TAK-788 DiC.~~

Section 9.3 Treatment Group Assignments

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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.

Section 9.4.7 Pulmonary Function Tests

PFTs include spirometry, lung volumes, and DLco. In Part 1, PFTs will be performed at screening but no more than 7 days before Day 1, and at Day 3 before furlough. In Parts 2 and 3, PFTs will be performed at screening and at Day 3**, Day 10, and/or Early Termination visit** if indicated on the basis of pulmonary symptoms.

Section 13.1.3 PK 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 ~~and~~**,** 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.

...

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).

Section 13.2 Determination of Sample Size

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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 allows for 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.

Appendix A Schedule of Events

[Addition of Table 3 Relative Bioavailability Study (Part 3)]

[Revised Table 5 Pharmacokinetic Plasma Concentration Sampling Schedule for

Parts 2 and 3 to include PK sampling for Part 3]

Rationale for Change: The rationale for Part 3 of the study is to perform relative bioavailability assessment of Process B versus process A DiC to enable PK bridging across the patients who are using or will be using these 2 DiCs in the TAK 788 clinical development program.

The following sections also contain this change:

- Study title.
- Section 2.0 STUDY SUMMARY.
- Section 6.3.1 Duration of an Individual Subject's Study Participation.
- Table 6.a Primary and Secondary Endpoints for Disclosures.
- Section 7.1 Inclusion Criteria.
- Section 9.4.7 Pulmonary Function Tests.
- Section 9.4.8 Drug, Alcohol, and Tobacco Testing.
- Section 9.4.9 Pregnancy Test.
- Section 9.4.11 AEs.
- Section 9.4.12 Enrollment.
- Section 9.4.13 ECG.
- Section 9.4.14 Chest CT Scan.
- Section 9.4.16 PK Measurements.
- Section 9.5 Completion of Study Treatment for Individual Subjects.
- Section 9.6 Discontinuation of Treatment With Study Drug and Subject Replacement.
- Section 13.1.1 Analysis Sets.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Biostatistics Approval	13-Nov-2018 19:30 UTC
	Clinical Pharmacology Approval	13-Nov-2018 19:49 UTC
	Clinical Approval	13-Nov-2018 20:27 UTC