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

NCT Number: NCT04441255

Protocol Approve Date: 09 June 2020

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

- Named persons or organizations associated with the study.
- 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.

A protocol clarification letter for the final protocol, dated 09-June-2020, explaining the discrepancies within the protocol is appended to the back of the protocol.

TAKEDA PHARMACEUTICALS

PROTOCOL

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

Study Identifier:	TAK-788-1005
Compound:	TAK-788
Date:	09 June 2020
Version/Amendment Number:	Final

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LIST OF APPENDICES

1.0 STUDY SUMMARY

Name of Sponsor: Takeda Development Center Americas, Inc. (TDC Americas) 95 Hayden Avenue Lexington, Massachusetts USA 02421 Telephone: +1 (617) 349-0200	**Compound:** TAK-788
Study Identifier: TAK-788-1005 (CA24171)	**Phase:** 1
Protocol Title: A Phase 1, Randomized, 2-Period, 2-Sequence, Crossover Study to Evaluate the Effect of High-Fat Meal on TAK-788 Pharmacokinetics in Healthy Adult Subjects	
Study Design: This is an open-label, randomized, 2-period, and 2-sequence crossover high-fat meal effect study in healthy adult subjects. Subjects will undergo screening evaluations to determine eligibility within 21 days prior to dosing. In this study, subjects will be admitted to the clinical facility the day prior to dosing in each period (Day -1). Subjects will randomized on Day 1 of Period 1 to a crossover sequence in a 1 : 1 ratio and administered a single oral dose of 160 mg TAK-788 on Day 1 with or without a high-fat meal of each period (ie, Period 1 and Period 2). Each dose will be separated by a washout period of 10 days. Blood samples for TAK-788 PK will be collected predose and up to 240 hours following each TAK-788 dose. Subjects will receive the following treatments on one occasion in a crossover fashion to evaluate the effect of a high-fat meal: • Treatment A (reference): 4 × 40 mg TAK-788 capsules, fasted conditions • Treatment B (test): 4 × 40 mg TAK-788 capsules with a high-fat meal* * 800-1000 total calories, 500-600 calories, 55-65 g, or 50% from fat (FDA FE 2019) Subjects will remain at the clinical site until the 240-hour study assessments in Period 2 are completed. All doses of TAK-788 will be administered at the clinic during this study. Spirometry as the pulmonary function test (PFT) may be performed in the event of a pulmonary adverse event (AE) and deemed clinically necessary, as determined by the Investigator or designee. A final safety follow-up phone call will occur 30 ± 2 days after the last TAK-788 dose to determine if any AEs have occurred since the last study visit. Replacement of discontinued or withdrawn subjects due to any reason will be assessed on a case by case basis by the Sponsor and PI to ensure a minimum of 12 PK-evaluable subjects complete the study.	
Study Primary Objective: • To characterize the effect of a high-fat meal on the PK of TAK-788 administered as a proposed commercial product. **Study Secondary Objective:** • To assess the PK of active metabolites AP32960 and AP32914 of TAK-788. **Study Exploratory Safety Objective:** • To collect the safety data of TAK-788 following a single oral dose in healthy adult subjects.	
Study Subject Population: Healthy male and female subjects aged 19 to 55 years inclusive, at screening. Body Mass Index (BMI) 18.5-30.0 kg/m^2, inclusive, at screening.	

Planned Number of Subjects:	**Planned Number of Sites:**
Fourteen healthy adult subjects will be enrolled, randomized, and dosed in the high-fat meal effect study.	1
Dose Levels: Treatment A (reference): 4 x 40 mg TAK-788 capsules, fasted conditions Treatment B (test): 4 x 40 mg TAK-788 capsules with a high-fat meal All doses of TAK-788 will be orally administered at the clinic with 8 fluid oz (240 mL) of water.	**Route of Administration:** Oral
Duration of Treatment: Single oral dose of TAK-788 (4 x 40 mg) on Day 1 of each period. There will be a washout period of 10 days between the dose of TAK-788 in Period 1 and Period 2.	**Planned Study Duration:** Approximately 61 days ± 2 days including screening period and follow-up.

Criteria for Inclusion:

Subjects must fulfill the following inclusion criteria to be eligible for participation in the study:

1. Healthy, adult, male or female, 19 - 55 years of age, inclusive, at screening.
2. Continuous non-smoker who has not used nicotine-containing products for at least 20 years prior to the first dosing and throughout the study, based on subject self-reporting.
3. Body mass index (BMI) ≥18.5 and ≤30.0 kg/m^2, at screening.
4. Medically healthy with no clinically significant medical history, physical examination, laboratory profiles, vital signs, or electrocardiograms (ECGs), as deemed by the Investigator or designee. Has liver function tests (LFTs) including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin less than or equal to the upper limit of normal at screening and at first check-in.
5. For a female of nonchildbearing potential, must have undergone one of the following sterilization procedures at least 6 months prior to the first dosing:
   - hysteroscopic sterilization;
   - bilateral tubal ligation or bilateral salpingectomy;
   - hysterectomy;
   - bilateral oophorectomy;

   or be postmenopausal with amenorrhea for at least 1 year prior to the first dosing and follicle stimulating hormone (FSH) serum levels consistent with postmenopausal status.
6. Female subjects of childbearing potential will be advised to remain sexually inactive or to keep the same birth control method for at least 30 days following the last TAK-788 dosing as indicated in Appendix D.
7. Female subjects must agree not to donate ova/oocytes during the study and for at least 30 days following the last TAK-788 dosing as indicated in Appendix D.
8. A non-vasectomized male subject must agree to use a condom with spermicide or abstain from sexual intercourse during the study until 30 days after the last dosing. (No restrictions are required for a vasectomized male provided his vasectomy has been performed 4 months or more prior to the first dosing of study drug. A male who has been vasectomized less than 4 months prior to study first dosing must follow the same restrictions as a non-vasectomized male).
9. Male subjects must agree not to donate sperm from the first dosing until 30 days after the last TAK-788 dosing.

10. Understands the study procedures in the informed consent form (ICF) and be willing and able to comply with the protocol.

Criteria for Exclusion:

The subject must be excluded from participating in the study if the subject:

1. Is mentally or legally incapacitated or has significant emotional problems at the time of the screening visit or expected during the conduct of the study.
2. History or presence of clinically significant medical or psychiatric condition or disease in the opinion of the Investigator or designee.
3. History of any illness (including hyperlipidemia and diabetes since high fat meal is required) that, in the opinion of the Investigator or designee, might confound the results of the study or poses an additional risk to the subjects by their participation in the study.
4. History or presence of alcoholism or drug abuse within the past 2 years prior to the first dosing.
5. History or presence of hypersensitivity or idiosyncratic reaction to the study drugs or related compounds.
6. History or presence of any previous lung disease and/or current lung infection.
7. Female subjects with a positive pregnancy test or who are lactating.
8. Positive urine drug or alcohol results at screening or first check-in.
9. Positive results at screening for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C virus (HCV).
10. Positive test result for active COVID-19.
11. Seated blood pressure is less than 90/40 mmHg or greater than 140/90 mmHg at screening.
12. Seated heart rate is lower than 40 bpm or higher than 99 bpm at screening.
13. QTcF interval is >460 msec (males) or >470 msec (females) or ECG findings are deemed abnormal with clinical significance by the Investigator or designee at screening.
14. Creatinine clearance <90 mL/min at screening (calculated using the Cockcroft-Gault formula).
15. Unable to refrain from or anticipates the use of:
    - Any drug, including prescription and non-prescription medications, herbal remedies, or vitamin supplements within 14 days prior to the first dosing and throughout the study. Medication listed as part of acceptable birth control methods will be allowed (refer to Appendix D). Thyroid hormone replacement medication may be permitted if the subject has been on the same stable dose for the immediate 3 months prior to the first dosing. Acetaminophen (up to 2 g per 24 hour period) may be permitted during the study, only after initial dosing, if necessary, to treat AEs.
    - Any drugs known to be inhibitors or inducers of cytochrome P450 (CYP)3A enzymes and/or p-glycoprotein (P-gp), including St. John's Wort, within 28 days prior to the first dosing and throughout the study. Appropriate sources (eg, Flockhart Table™) will be consulted to confirm lack of PK/pharmacodynamics interaction with study drugs.
16. Has been on a diet incompatible with the on-study diet, in the opinion of the Investigator or designee, within the 30 days prior to the first dosing and throughout the study.
17. Donation of blood or significant blood loss within 56 days prior to the first dosing.
18. Plasma donation within 7 days prior to the first dosing.
19. Participation in another clinical study within 30 days for a small molecular drug or 90 days for a biologic drug prior to the first dosing. The 30-day or 90-day window will be derived from the date of the last blood collection or dosing, whichever is later, in the previous study to Day 1 of Period 1 of the current study.

Main Criteria for Evaluation and Analyses:

Primary Endpoints

The following PK parameters will be analyzed for TAK-788.

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

Secondary Endpoints

The following PK parameters will be analyzed for active metabolites (AP32960 and AP32914) of TAK-788.

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

Exploratory Safety Endpoints

Safety will be assessed by summarizing the incidence of treatment emergent AEs (TEAEs), clinical laboratory values, physical examinations, 12-lead ECGs, and vital signs

Statistical Considerations:

Pharmacokinetics:

The PK parameters of TAK-788 and its active metabolites (AP32960 and AP32914) will be calculated based on plasma concentration - time profiles of TAK-788 and its active metabolites (AP32960 and AP32914) as described in Section 11.0, and outlined in the SAP.

A linear mixed-effects model will be used for the analysis on the natural log (ln)-transformed C_{max}, AUC_{∞}, and AUC_{last} for TAK-788 and its active metabolites (AP32960 and AP32914). The model will include sequence, treatment, and period as a fixed-effect and subject nested within sequence as a random-effect. Each model will include calculation of least squares means (LSMs) as well as the difference between treatment LSMs.

Geometric mean ratios (GMR) and 90% confidence intervals (CI), consistent with the two one sided test [Schuirmann 1987], will be calculated using the exponentiation of the difference between treatment LSMs from the analyses on the ln-transformed C_{max}, AUC_{∞}, and AUC_{last} (if it is needed) for TAK-788 and the combined molar C_{max}, AUC_{∞}, and AUC_{last} (if it is needed) for TAK-788 and its active metabolites. These ratios will be expressed as a ratio of test treatment relative to the appropriate reference treatment.

Safety:

Quantitative safety data as well as the difference to baseline, when appropriate, will be summarized using the appropriate descriptive statistics.

Sample Size Justification:

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

2.0 STUDY SCHEMATIC

Screening	Study Days in Periods 1 and 2 (a)					Follow-up
	Check-in and Predose Assessments (b)	**TAK-788 Dosing, PK sampling, and Study Assessments**	**PK sampling and Study Assessments**		**PK sampling and Study Assessments (c)**	
Within 21 days prior to first dosing	Day -1	Day 1	Days 2, 3, 4	Days 6 & 8	Day 11	30 days ± 2 following last TAK-788 dose
Outpatient Visit	Confinement (d)					Outpatient Visit

(a) There is a washout of 10 days between TAK-788 dose in Period 1 and Period 2.

(b) Subjects will be confined to the CRU at the time indicated by the staff from Day -1 of Period 1.

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

(d) Subjects will start the confinement on Day -1 and will be released from confinement after the 240-hour study assessments in Period 2 are complete.

3.0 SCHEDULE OF STUDY PROCEDURES

Study Procedures [a]	S [b]	**Study Days in Periods 1 and 2** [c]																
Days in Period →		**-1**	**1**								**2**	**3**	**4**	**6**	**8**	**11** [e]	**EOS or ET** [p]	**FU** [q]
Hours →		**C-I** [d]	**0**	**0.5**	**1**	**2**	**4**	**6**	**8**	**12**	**24**	**48**	**72**	**120**	**168**	**240**		
Administrative Procedures																		
Informed Consent	X																	
Inclusion/Exclusion Criteria	X	X [f]																
Medical History	X																	
Safety Evaluations																		
Full Physical Examination [g]	X																	
Height	X																	
Weight	X	X [h]																
12-Lead Safety ECG	X		X [k]				X										X	
Vital Signs (HR and BP)	X		X [k]				X			X	X						X	
Vital Signs (RR and T)	X																X	
Pulmonary function test [i]	X																	
Hem, Serum Chem [j], and UA	X	X [l]											X				X	
Serum Pregnancy Test (♀only)	X	X																
Serum FSH (PMP ♀ only)	X																	
Urine Drug and Alcohol Screen	X	X																
HIV/Hepatitis Screen	X																	
AE Monitoring	X	X																
ConMeds Monitoring		X																

Study Procedures [a]	S [b]	**Study Days in Periods 1 and 2** [c]																
Days in Period →		**-1**	**1**								**2**	**3**	**4**	**6**	**8**	**11** [e]	**EOS or ET** [p]	**FU** [q]
Hours →		**C-I** [d]	**0**	**0.5**	**1**	**2**	**4**	**6**	**8**	**12**	**24**	**48**	**72**	**120**	**168**	**240**		
Study Drug Administration / PK																		
TAK-788 Administration			X															
Blood for TAK-788 and metabolites (AP32960 and AP32914) PK			X [m]	X	X	X	X	X	X	X	X	X	X	X	X	X [n]		
Other Procedures																		
Confinement in the CRU [o]		X																
Visit and Return Visits	X																	

a. For details on Procedures, refer to Section 9.0.
b. Within 21 days prior to the first study drug administration.
c. There will be a washout period of 10 days between the dose in Period 1 and the dose in Period 2.
d. Subjects will be admitted to the CRU on Day -1 of Period 1, at the time indicated by the CRU.
e. Day 11 of Period 1 will be the same as Day 1 of Period 2. Study procedures will only be performed once.
f. To be conducted in Period 1 only.
g. Symptom-driven physical examinations may be performed at other times, at the PI's or designee's discretion.
h. If the screening assessment was conducted within 4-7 days prior to the first dosing (Day 1 of Period 1), assessment will be conducted at check-in only if, in the opinion of the Investigator, there is reason to believe they have substantially changed.
i. Pulmonary function tests may be performed in the event of a pulmonary AE and deemed clinically necessary, as determined by the Investigator or designee.
j. Samples for serum chemistry will be obtained following a fast of at least 8 hours, however, in case of dropouts or rechecks, subjects may not have fasted for 8 hours prior to the serum chemistry sample being taken.
k. To be performed within 24 hours prior to dosing.
l. To be repeated prior to dosing in Period 2.
m. Prior to dosing.
n. The Period 1 Day 11 PK sample will serve as the pre-dose PK sample for Period 2.
o. Subjects will start confinement on Day -1 of Period 1 and will be released from confinement after the 240-hour study assessments in Period 2 are completed. At all times, subjects may be required to remain at the CRU for longer at the discretion of the Investigator or designee.
p. To be performed at the end of Period 2 or prior to early termination from the study.

Study Procedures [a]	S [b]	**Study Days in Periods 1 and 2** [c]															
Days in Period →		**-1**	**1**								**2**	**3**	**4**	**6**	**8**	**11** [e]	**EOS or ET** [p]	**FU** [q]
Hours →		**C-I** [d]	**0**	**0.5**	**1**	**2**	**4**	**6**	**8**	**12**	**24**	**48**	**72**	**120**	**168**	**240**		

q. The clinic will contact all subjects (including subjects who terminate the study early) 30 ± 2 days after the last TAK-788 dose to determine if any AEs have occurred since the last study visit.

Abbreviations: ♀ = Females, AE = Adverse events, BP = Blood pressure, C-I = Check-in, Chem = Chemistry, ConMeds = Concomitant medication, CRU = Clinical research unit, ECG = Electrocardiogram, EOS/ET = End-of-Study or early termination, FSH = Follicle-stimulating hormone, FU = Follow-up, Hem = Hematology, HIV = Human immunodeficiency virus, HR = Heart rate, PI = Principal Investigator, PK = Pharmacokinetics, PMP = Postmenopausal, Preg = Pregnancy, RR = Respiratory rate, S = Screening, T = Temperature, UA = Urinalysis

Table 3.a Pharmacokinetic Plasma Concentration Sampling Schedule

Study Day	Sample Collection Time	Time (Relative to Dosing) h: min	Plasma Concentrations of TAK-788, AP32960, and AP32914
1 (Period 1)	0 h (predose)	00:00 [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)	✓
2	0 h	24:00 (±30 min)	✓
3	0 h	48:00 (±30 min)	✓
4	0 h	72:00 (±60 min)	✓
6	0 h	120:00 (±60 min)	✓
8	0 h	168:00 (±60 min)	✓
11 (Predose Day 1 Period 2)	0 h	240:00 (±60 min) [a, b] (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)	✓
3	0 h	48:00 (±30 min)	✓
4	0 h	72:00 (±60 min)	✓
6	0 h	120:00 (±60 min)	✓
8	0 h	168:00 (±60 min)	✓
11	0 h	240:00 (±60 min)	✓
Number of samples per profile:			27

[a] The Day 1 dose must be administered shortly after the PK sample is taken.

[b] The Period 1 Day 11 PK sample will serve as the pre-dose PK sample for Period 2. The predose PK sample in Period 2 must be collected before the scheduled Period 2 Day 1 dose even though the collection window implies it can be taken after.

4.0 INTRODUCTION

4.1 Background

Aberrant activation of epidermal growth factor receptor (EGFR) and human epidermal growth factor 2 (HER2) plays a causal role in a subset of non–small cell lung cancer (NSCLC) and other cancers. As inhibition of wild-type (WT) EGFR is associated with dose-limiting toxicities, a tyrosine kinase inhibitor (TKI) that inhibits oncogenic EGFR and HER2 variants more potently than WT EGFR is more likely to be dosed at the more efficacious levels. Multiple classes of activating mutations have been identified in EGFR and HER2 that vary widely in their sensitivity to available TKIs. TAK-788, formerly known as AP32788, was designed to be a potent, selective inhibitor of all activated forms of EGFR and HER2, including exon 20 insertions (not targeted by any approved TKI), more potently than it inhibits WT EGFR.

Clinical Pharmacokinetics

The clinical development program for TAK-788 includes an ongoing phase 1/2 clinical efficacy and safety study in patients with NSCLC (AP32788-15-101), 2 completed clinical pharmacology studies: 1) Single rising dose study (Part 1), low-fat meal effect study (Part 2), and relative bioavailability study (Part 3) in healthy subjects (TAK-788-1001) and 2) a drug-drug interaction study to characterize TAK-788 drug-drug interaction with either a strong cytochrome P-450 (CYP)3A inhibitor, itraconazole (Part 1) or with a strong CYP3A inducer, rifampin (Part 2) in healthy subjects (TAK-788-1006); and 4 ongoing clinical pharmacology studies: TAK-788-1002, -1004, -1007, and -1008. The objectives and study design of these studies are presented in TAK-788 IB Edition 4 (IB 2020). Only preliminary PK results from AP32788-15-101, and final PK results from TAK-788-1001 and TAK-788-1006 are presented in this document.

In the AP32788-15-101 study, following daily oral (PO) administration of TAK-788 once daily (QD), TAK-788 was readily absorbed with a median time to reach C_{max} concentration (T_{max}) of 4 hours postdose. The single-dose C_{max} and AUC_{24} of TAK-788 increased in a dose proportional manner in the dose range of 5 to 180 mg TAK-788. However, its steady state C_{max} and AUC_{24} following multiple doses increased in a less than dose proportional manner across the dose range of 5 to 180 mg. Minimal to modest TAK-788 accumulation ratios were observed at steady state (geometric mean range 1.23 to 1.52) in the dose range of 20 to 120 mg QD. At 160 mg QD, the geometric mean accumulation ratio following repeated doses was 1.06, suggesting autoinduction of the apparent oral clearance of TAK-788 likely via induction of CYP3A.

The emerging finding of autoinduction by TAK-788 at the 160 mg QD dose is consistent with the results of in vitro induction studies that have shown concentration-dependent CYP3A induction by TAK-788 and its active metabolites, suggesting a possible risk for drug-drug interactions due to induction of CYP3A and other co-regulated enzymes/transporters by TAK-788 as a potential perpetrator. The PK of the 2 active metabolites (AP32960 and AP32914) of TAK-788 were also evaluated in clinical studies. Systemic exposures to metabolites AP32960 and AP32914 in terms of molar AUC_{24} were approximately 62% (%CV: 25%) and 8% (%CV: 13%) of parent AUC_{24} respectively.

In the healthy subject study TAK-788-1001, a low-fat meal (ie, ≤350 calories and ≤15% calories from fat) did not affect the PK of TAK-788 in healthy subjects. At 160 mg TAK-788, 90% CIs of the GMR with a low-fat meal versus fasted conditions for C_{max} (GMR 0.964) and AUC_{∞} (GMR 0.951) fell completely within 80 -125% range.

In the TAK-788-1006 study, a DDI between the CYP3A4 inhibitor, itraconazole, and TAK-788 was observed. Following coadministration of multiple oral doses of 200 mg itraconazole with a single oral dose of 20 mg TAK-788, overall (AUC_{∞}) and peak (C_{max}) exposures were increased by approximately 743% and 282% from the corresponding values obtained following TAK-788 alone. Similar results were observed for combined molar AUC_{∞} and combined molar C_{max} data when comparing itraconazole + TAK-788 to TAK-788 alone. A significant reduction in TAK-788 AUC_{∞} and C_{max} was observed when TAK-788 was concomitantly administered with the strong CYP3A4 inducer, rifampin. Following coadministration of multiple oral doses of 600 mg rifampin with a single oral dose of 160 mg TAK-788, overall (AUC_{∞}) and peak (C_{max}) exposures were reduced by approximately 96% and 95% compared to the corresponding values obtained following TAK-788 alone. Similar results were observed for combined molar AUC_{∞} and combined molar C_{max} data when comparing rifampin + TAK-788 to TAK-788 alone.

Refer to the Investigator's Brochure (IB) for detailed background information and safety data on TAK-788 IB Edition 4, 01-Apr-2020 (IB 2020).

4.2 Rationale for the Proposed Study

TAK-788, formerly known as AP32788, was designed to be a selective inhibitor of all mutant forms of EGFR and HER2, including exon 20 insertions, more potently than it inhibits WT EGFR. Although TAK-788 is intended for the treatment of NSCLC, it is neither a mutagenic nor genotoxic agent and was generally well tolerated in the previous clinical pharmacology studies (TAK-788-1001, TAK-788-1002, and TAK-788-1006, a total of 88 subjects) in healthy subjects in the single dose range of 20 – 160 mg.

It has been demonstrated that a low-fat meal does not impact the PK of TAK-788. (Study TAK-788-1001) so cancer patients in TAK-788 clinical development program can currently administer TAK-788 orally with or without a low-fat meal. In this study, the effect of high-fat meal on the PK of the proposed commercial product will be characterized to support the product labeling of TAK-788.

4.3 Benefit/Risk Profile

The clinical safety data from study AP32788-15-101 available as of 27 January 2020 indicated no particular safety findings that are unique to TAK-788 compared with other approved EGFR TKIs for NSCLC patients. The most common TEAEs occurring in ≥20% of NSCLC patients by preferred term (PT) overall were diarrhea 84.7%, nausea 45.3%, decreased appetite 31.0%, vomiting 31.0%, fatigue 30.0%, and anemia (23.2%). There is some variety in the characterization of TEAEs of the skin resulting in different PTs to describe it. The most common skin-related PTs were rash (30.5%), dry skin (23.6%), maculo-papular rash (17.2%), paronychia (14.8%), dermatitis acneiform (12.3%), and pruritus (10.8%) (IB 2020).

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

In Study TAK-788-1001 in healthy subjects (n=69), the most common AEs by PT (≥2 subjects overall) were nausea (12.5%), diarrhea (10.0%), headache (7.5%), and abdominal pain upper (5.0%) in Part 1 of study; and headache (31.3%), nausea (31.3%), abdominal pain upper (18.8%), feces soft (12.5%), and flatulence (12.5%) in Part 2 of study. No AEs occurred in more than 1 subject in Part 3 of study. All TEAEs recovered or resolved. One Grade ≥3 AE occurred, which was lipase increased and was assessed as not related to TAK-788 (120 mg dose, no treatment given). One subject permanently discontinued TAK-788 due to an AE of Grade 1 vomiting. The majority of TEAEs were gastrointestinal and were Grade ≤2 in severity. There were no clinically meaningful pulmonary, renal, hepatic, or cardiac abnormalities during this study. Overall, TAK-788 was well tolerated at single oral doses from 20 mg to 160 mg.

The inclusion and exclusion criteria, screening, and safety monitoring practices employed by this protocol (ie, 12 lead ECG, vital signs, clinical laboratory tests, AE questioning, and physical examination are adequate to protect the subject's safety and should detect all TEAEs.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Hypothesis

Not applicable

5.2 Study Objectives

5.2.1 Study Primary Objective

- To characterize the effect of a high-fat meal on the PK of TAK-788 administered as a proposed commercial product.

5.2.2 Study Secondary Objective

- To assess the PK of active metabolites AP32960 and AP32914 of TAK-788.

5.2.3 Study Exploratory Safety Objective

- To collect the safety data of TAK-788 following a single oral dose in healthy adult subjects.

5.3 Endpoints

5.3.1 Primary Endpoints

The following PK parameters will be analyzed for TAK-788.

- Time of first occurrence of C_{max} (T_{max}).
- Maximum observed concentration (C_{max}).

- Area under the concentration-time curve from time 0 to infinity, calculated using the observed value of the last quantifiable concentration (AUC_{∞}).
- Area under the concentration-time curve from time 0 to the time of the last quantifiable concentration (AUC_{last}).

5.3.2 Secondary Endpoints

The following PK parameters will be analyzed for active metabolites (AP32960 and AP32914) of TAK-788.

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

5.3.3 Exploratory Safety Endpoints

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

- TEAEs assessments.
- Clinical laboratory testing (hematology, serum chemistry and urinalysis).
- Physical examinations.
- 12-lead ECG.
- Vital signs.

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

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

Subjects will undergo screening evaluations to determine eligibility within 21 days prior to dosing.

Subjects will be admitted to the clinical facility the day prior to dosing in each period (Day -1). Subjects will be randomized on Day 1 of Period 1 to a crossover sequence in a 1:1 ratio and administered a single oral dose of 160 mg of TAK-788 with or without a high-fat meal on Day 1 of each period (ie, Period 1 and Period 2). Each dose will be separated by a washout period of 10 days. Blood samples for TAK-788 PK will be collected predose and up to 240 hours following each TAK-788 dose.

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

- Treatment A (reference): 4 × 40 mg TAK-788 capsules, fasted conditions
- Treatment B (test): 4 × 40 mg TAK-788 capsules with a high-fat meal

  * 800-1000 total calories, 500-600 calories, 55-65 g, or 50% from fat (FDA FE 2019)

Subjects will remain at the clinical site until the 240-hour study assessments in Period 2 are completed.

All doses of TAK-788 will be administered at the clinic during this study.

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

Replacement of discontinued or withdrawn subjects due to any reason will be assessed on a case by case basis by the Sponsor and PI to ensure a minimum of 12 PK-evaluable subjects complete the study.

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

Dose administration, PK collection, and study assessments scheme for the treatment periods are outlined in Section 2.0.

6.2 Rationale for Study Design, Dose, and Endpoints

6.2.1 Rationale of Study Design and Dose

In this study, the effect of a high-fat meal on the PK of the proposed commercial product will be characterized to support the product labeling of TAK-788. A randomized, 2-treatment (ie, fed versus fasted), 2-period, 2-way crossover design will be utilized in accordance with FDA guidance Assessing the Effects of Food on Drugs in INDs and NDAs – Clinical Pharmacology Considerations Guidance for Industry (FDA FE 2019). The washout period between doses is considered sufficient to prevent carryover effects of the treatments.

6.2.2 Rationale for Endpoints

6.2.2.1 Pharmacokinetic Endpoints

The PK endpoints are standard for this study type.

6.2.2.2 Safety Endpoints

The key safety endpoints are typical for Phase 1 studies and will be assessed through monitoring of AEs, vital signs, ECGs, laboratory assessments, and physical examinations.

6.2.3 Future Biomedical Research

Any residual plasma samples will be stored by the Sponsor or Bioanalytical facility for the maximal 5 years determined by the Sponsor following the last dosing and may be used in the future to perform metabolite profiling. Tubes or containers will be identified with a barcode using an appropriate label.

No diseases/conditions, deoxyribonucleic acid, or ribonucleic acid (RNA) will be the focus of these analyses. The analyses will focus on metabolite profiling for TAK-788 compound. Samples will not be submitted to a public database. The Sponsor and contract research organizations involved in the clinical conduct, bioanalytical analyses and PK and statistical analysis of the data will have access to the samples and/or the data that resulted from the analysis, if performed.

By signing the ICF, subjects agree to the possible future analysis of these samples. At any time, the subjects can contact the CRU staff to request destruction of the residual samples once PK assessments required to meet the primary objective of the study are completed. Any additional research on these samples unspecified by this protocol will require approval from the subjects.

6.2.4 Critical Procedures Based on Study Objectives: Timing of Procedures

For this study, the critical component is the blood collection for plasma concentrations of TAK-788 its active metabolites (AP32960 and AP32914) and samples are required to be collected, as appropriate, as close to the scheduled times defined in this protocol as possible.

6.3 Study Design/Dosing/Procedures Modifications Permitted Within Protocol Parameters

The dose and administration of the study drugs to any subject may not be modified. If necessary, a subject may be discontinued for the reasons described in in Section 7.5 and Section 7.6. Any subject who experiences emesis within 8 hours post dose will be excluded in the final PK data analysis and may be replaced with a new subject.

6.4 Study Beginning and End/Completion

6.4.1 Definition of Beginning of the Study

The beginning of the study will be defined as the beginning of the screening (ie, signing of the ICF) of the first subject.

6.4.2 Definition of End of the Study

The end of study is defined as the date of the last scheduled study procedure as outlined in the Schedule of Study Procedures (Section 3.0)

6.4.3 Definition of Study Completion

The end of the study is scheduled after completion of the evaluations in the follow-up phone call for the last subject in the study.

This time period may change in the event that the study is terminated early or the last subject is lost to follow-up.

6.4.4 Definition of Study Discontinuation

Celerion reserves the right to terminate the study in the interest of subject welfare.

The Sponsor reserves the right to suspend or terminate the study at any time.

6.4.5 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless one or more of the following criteria are satisfied that require temporary suspension or early termination of the study:

- New information or other evaluation regarding the safety or efficacy of the study medication that indicates a change in the known risk/benefit profile for the product, such that the risk is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.

6.4.6 Criteria for Premature Termination or Suspension of a Site

Not applicable.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

7.1 Inclusion Criteria

Subjects must fulfill the following inclusion criteria to be eligible for participation in the study:

1. Healthy, adult, male or female, 19 - 55 years of age, inclusive, at screening.
2. Continuous non-smoker who has not used nicotine-containing products for at least 20 years prior to the first dosing and throughout the study, based on subject self-reporting.
3. BMI $\geq$18.5 and $\leq$30.0 kg/m^2, at screening.
4. Medically healthy with no clinically significant medical history, physical examination, laboratory profiles, vital signs, or ECGs, as deemed by the Investigator or designee. Has LFTs including ALT, AST, ALP, and total bilirubin less than or equal to the upper limit of normal at screening and at first check-in.
5. For a female of nonchildbearing potential, must have undergone one of the following sterilization procedures at least 6 months prior to the first dosing:
    - hysteroscopic sterilization;
    - bilateral tubal ligation or bilateral salpingectomy;
    - hysterectomy;

- bilateral oophorectomy;

or be postmenopausal with amenorrhea for at least 1 year prior to the first dosing and FSH serum levels consistent with postmenopausal status.

6. Female subjects of childbearing potential will be advised to remain sexually inactive or to keep the same birth control method for at least 30 days following the last TAK-788 dosing as indicated in Appendix D.
7. Female subjects must agree not to donate ova/oocytes during the study and for at least 30 days following the last TAK 788 dosing as indicated in Appendix D.
8. A non vasectomized male subject must agree to use a condom with spermicide or abstain from sexual intercourse during the study until 30 days after the last dosing. (No restrictions are required for a vasectomized male provided his vasectomy has been performed 4 months or more prior to the first dosing of study drug. A male who has been vasectomized less than 4 months prior to study first dosing must follow the same restrictions as a non vasectomized male).
9. Male subjects must agree not to donate sperm from the first dosing until 30 days after the last TAK-788 dosing.
10. Understands the study procedures in the ICF and be willing and able to comply with the protocol.

7.2 Exclusion Criteria

The subject must be excluded from participating in the study if the subject:

1. Is mentally or legally incapacitated or has significant emotional problems at the time of the screening visit or expected during the conduct of the study.
2. History or presence of clinically significant medical or psychiatric condition or disease in the opinion of the Investigator or designee.
3. History of any illness (including hyperlipidemia and diabetes since high fat meal is required) that, in the opinion of the Investigator or designee, might confound the results of the study or poses an additional risk to the subject by their participation in the study.
4. History or presence of alcoholism or drug abuse within the past 2 years prior to the first dosing.
5. History or presence of hypersensitivity or idiosyncratic reaction to the study drugs or related compounds.
6. History or presence of any previous lung disease and/or current lung infection.
7. Female subjects with a positive pregnancy test or who are lactating.
8. Positive urine drug or alcohol results at screening or first check-in.
9. Positive results at screening for HIV, HBsAg, or HCV.
10. Positive test result for active COVID-19.

11. Seated blood pressure is less than 90/40 mmHg or greater than 140/90 mmHg at screening.
12. Seated heart rate is lower than 40 bpm or higher than 99 bpm at screening.
13. QTcF interval is >460 msec (males) or >470 msec (females) or ECG findings are deemed abnormal with clinical significance by the Investigator or designee at screening.
14. Creatinine clearance <90 mL/min at screening (calculated using the Cockcroft-Gault formula).
15. Unable to refrain from or anticipates the use of:
    - Any drug, including prescription and non-prescription medications, herbal remedies, or vitamin supplements within 14 days prior to the first dosing and throughout the study. Medication listed as part of acceptable birth control methods will be allowed (refer to Appendix D). Thyroid hormone replacement medication may be permitted if the subject has been on the same stable dose for the immediate 3 months prior to the first dosing. Acetaminophen (up to 2 g per 24 hour period) may be permitted during the study, only after initial dosing, if necessary, to treat AEs.
    - Any drugs known to be inhibitors or inducers of CYP3A enzymes and/or P-gp, including St. John's Wort, within 28 days prior to the first dosing and throughout the study. Appropriate sources (eg, Flockhart Table™) will be consulted to confirm lack of PK/pharmacodynamics interaction with study drugs.
16. Has been on a diet incompatible with the on-study diet, in the opinion of the Investigator or designee, within the 30 days prior to the first dosing and throughout the study.
17. Donation of blood or significant blood loss within 56 days prior to the first dosing.
18. Plasma donation within 7 days prior to the first dosing.
19. Participation in another clinical study within 30 days for small molecular drug or 90 days for a biologic drug prior to the first dosing. The 30-day or 90-day window will be derived from the date of the last blood collection or dosing, whichever is later, in the previous study to Day 1 of Period 1 of the current study.

7.3 Excluded Medications, Supplements, Dietary Products

Concomitant medications will be prohibited as listed in the exclusion criteria in Section 7.2. After the first dose, acetaminophen (up to 2 g per 24 hour period) may be administered at the discretion of the Investigator or designee. Thyroid hormone replacement medication may be permitted if the subject has been on the same stable dose for the immediate 3 months prior to the first dosing.

If deviations occur, the Investigator or designee in consultation with the Sponsor if needed will decide on a case by case basis whether the subject may continue participation in the study.

All medications taken by subjects during the course of the study will be recorded.

Use of excluded agents (prescription or non-prescription) or dietary products is outlined in Table 7.a.

Table 7.a Excluded Medications, Supplements, and Dietary Products

Category	Between Screening and First Dosing (Days -28 to predose [Day 1 of Period 1])	After First Dosing (Day 1 of Period 1) to Follow-Up
Alcohol	Prohibited from 48 hours prior to first dosing	Prohibited until end of PK collection in Period 2.
Xanthine and/or caffeine	Prohibited from 24 hours prior to first dosing [a]	Prohibited until end of PK collection in Period 2 [a].
Medications	See Sections 7.2 and 7.3.	See Sections 7.2 and 7.3.
Food substance		
Grapefruit/Seville orange	Prohibited from 28 days prior to first dosing	Prohibited until end of PK collection in Period 2.
Other Fruit Juice	Prohibited from 72 hours prior to first dosing	Prohibited until end of PK collection in Period 2.
Vegetables from the mustard green family (eg, kale, broccoli, watercress, collard greens, kohlrabi, Brussels sprouts, mustard), and charbroiled meats	Prohibited from 7 days prior to first dosing	Prohibited until end of PK collection in Period 2.

a: small amounts of caffeine derived from normal foodstuffs eg, 250 mL/8 oz/1 cup decaffeinated coffee or other decaffeinated beverage, per day, with the exception of espresso; 45 g/1.5 oz. chocolate bar, per day, would not be considered a deviation to this restriction.

7.4 Diet, Fluid, Activity

7.4.1 Diet and Fluid

Water (except water provided with each oral dosing) will be restricted 1 hour prior to and 1 hour after each study drug administration, but will be allowed *ad libitum* at all other times. Other fluids may be given as part of meals and snacks but will be restricted at all other times throughout the confinement period.

Treatment A: On Day 1 of Period 1 or Period 2 (per randomization), subjects will fast overnight for at least 10 hours prior to oral study drug administration and will continue to fast for at least 4 hours postdose.

Treatment B: On Day 1 of Period 1 or Period 2 (per randomization), subjects will be required to fast overnight for at least 10 hours until 30 minutes prior to their scheduled morning dose, when they will be given a high-fat/high-calorie breakfast which will be entirely consumed within 30 minutes. An example of high-fat/high-calorie breakfast would be 2 slices of buttered toast, 2 eggs fried in butter, 2 strips of bacon, 4 oz of hash brown potatoes, and 8 fluid oz (240 mL) of whole milk (providing approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively) (FDA FE 2019). Following dosing, subjects will fast for at least 4 hours postdose.

When confined, standard meals and snacks will be provided at appropriate times, except when they are required to fast. When confined in the CRU, subjects will be required to fast from all food and drink except water between meals and snacks.

7.4.2 Activity

Subjects will remain ambulatory or seated upright for the first 4 hours postdose on Day 1 of each period, except when they are supine or semi-reclined for study procedures or AEs.

Subjects will be instructed to refrain from strenuous physical activity which could cause muscle aches or injury, including contact sports at any time from screening until completion of the study.

7.5 Criteria for Discontinuation or Withdrawal of a Subject

Subjects are free to withdraw from the study at any time for any reason.

In addition, subjects may be withdrawn from the study by the Investigator or designee for the following reasons:

- AEs.
- A positive pregnancy test for females.
- Positive urine drug or alcohol results.
- Difficulties in blood collection.
- Taking prohibited concomitant medications.
- Emesis within 8 hours post dose.

A subject may be withdrawn by the Investigator (or designee) or the Sponsor if enrollment into the study is inappropriate, the study plan is violated, or for administrative and/or other safety reasons

7.6 Procedures for Discontinuation or Withdrawal of a Subject

The Investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.5. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the Investigator. In addition, efforts should be made to perform all procedures scheduled for the end-of-study or early termination as described in Section 3.0.

7.7 Subject Replacement

Replacement of discontinued or withdrawn subject(s) due to any reason will be assessed on a case by case basis by the Sponsor and PI to ensure a minimum of 12 PK-evaluable subjects complete the study.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

8.1 Clinical Study Drugs

TAK-788 capsule used in this clinical study is a drug-in-capsule (DiC) product without any excipient. The TAK-788 capsule product contained a nominal 40 mg (expressed as free base equivalent) of the active ingredient, provided as succinate salt and manufactured from Process C. The drug substance (DS-C) is filled into a size 2 capsule as the intended DiC commercial product (DiC-C).

All TAK-788 products will be prepared by licensed pharmacy staff at the CRU according to the procedures outlined in the pharmacy manual.

Details of the dosage form description and strengths can be found in the pharmacy manual.

8.1.1 Clinical Study Drug Labeling

TAK-788 drug product will be supplied in white high-density polyethylene bottles with child-resistant caps with liner. TAK-788 will bear the appropriate label text as required by governing regulatory agencies. At a minimum, such text will include product name, product strength, and lot number.

The pharmacy at the CRU will provide each dose in individual unit dose containers for each subject and for each study period.

8.1.2 Clinical Study Drug Inventory and Storage

The Sponsor will supply sufficient quantities of TAK-788 products to allow completion of this study.

The recommended storage condition for TAK-788 is controlled room temperature. Additional details regarding the storage and handling of TAK-788 are provided in the pharmacy manual.

Records will be made of the receipt, preparation, dispensing, and final disposition of the study drugs supplied.

8.1.3 Clinical Study Drug Blinding

This is an open-label study.

8.1.4 Randomization Code Creation and Storage

A randomization schedule will be generated by Celerion for each study part.

Subjects will be randomized to a crossover sequence in a 1:1 ratio and administered a single dose of 160 mg TAK-788 on Day 1 of each period per the randomization sequences, AB and BA.

8.1.5 Clinical Study Blind Maintenance/Unblinding Procedure

Not applicable

8.1.6 Accountability and Destruction of Sponsor-Supplied Drugs

At the conclusion of the study, any unused TAK-788 study drug will be retained by Celerion, returned to the Sponsor or designee, or destroyed, as per Sponsor instructions. If no supplies remain, this fact will be documented in the pharmacy product accountability records.

9.0 STUDY PROCEDURES

9.1 Administrative Procedures

9.1.1 Informed Consent Procedure

The purpose of the study, the procedures to be carried out and the potential hazards will be described to the subjects in non-technical terms. Subjects will be required to read, sign, and date an ICF summarizing the discussion prior to screening, and will be assured that they may withdraw from the study at any time without jeopardizing their medical care.

Subjects will be given a copy of their signed ICF.

9.1.1.1 Assignment of Screening and Allocation Numbers

Each subject will be assigned a unique identification number upon screening. Subjects who complete the study screening assessments and meet all the eligibility criteria will be assigned a unique identification number at the time of the first dosing, different from the screening number.

If replacement subjects are used, the replacement subject number will be 100 more than the original (eg, Subject No. 101 will replace Subject No. 1).

9.1.1.2 Study Drug Assignment

This is an open-label, randomized, 2-period, and 2-sequence crossover high-fat meal effect study. Subjects will receive each of the two treatments detailed in Section 9.2.7 according to the randomization scheme detailed in Section 8.1.4.

9.1.2 Inclusion and Exclusion

Each subject will be assessed through randomization, according to the eligibility criteria provided in Section 7.0.

9.1.3 Medical History/Demography

Medical history and demographic data, including name, sex, age, race, ethnicity, and history of tobacco use will be recorded.

9.1.4 Concomitant Medications

Concomitant medications will be prohibited as listed in Section 7.2 and Section 7.3. All medications taken by subjects during the course of the study will be recorded.

9.2 Clinical Procedures and Assessments

The Schedule of Study Procedures (Section 3.0) summarizes the clinical procedures to be performed at each visit. Individual clinical procedures are described in detail below. Additional evaluations/testing may be deemed necessary by the Investigator or designee and/or the Sponsor for reasons related to subject safety.

For this study, the collection of blood for TAK-788 and its metabolites PK is the critical parameter and needs to be collected as close to the exact time point as possible. All other procedures should be completed as close to the prescribed/scheduled time as possible, but can be performed prior to or after the prescribed/scheduled time (refer to Section 3.0 and Table 3.a).

COVID-19 testing and related risk assessments will be detailed in a separate document following up-to-date local regulations.

Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

9.2.1 Full Physical Exam

A full physical examination will be performed as outlined in the Schedule of Study Procedures (Section 3.0). Symptom-driven physical examinations may be performed at other times, if deemed necessary by the Investigator or designee.

9.2.2 Height and Weight

Body height (cm) and weight (kg) will be reported as outlined in the Schedule of Study Procedures (Section 3.0).

9.2.3 BMI

BMI will be calculated based on the height and weight measured at screening.

9.2.4 Vital Signs

Single measurements of body temperature, respiratory rate, blood pressure, and heart rate, will be measured as outlined in the Schedule of Study Procedures (Section 3.0). Additional vital signs may be taken at any other times, if deemed necessary.

Blood pressure and heart rate measurements will be performed with subjects in a seated position, except when they are supine or semi-reclined because of study procedures and/or AEs (eg, nausea, dizziness) or if deemed necessary by the Investigator or designee.

Blood pressure and heart rate will be measured within 24 hours prior to Period 1 and Period 2 Day 1 dosing for the predose time point. When scheduled postdose, vital signs will be performed within approximately 15 minutes of the scheduled time point.

9.2.5 12-Lead ECG

Single 12-lead ECGs will be performed as outlined in the Schedule of Study Procedures (Section 3.0). Additional ECGs may be taken at any other times, if deemed necessary by the Investigator or designee.

ECGs will be performed with subjects in a supine position. All ECG tracings will be reviewed by the Investigator or designee.

ECGs will be measured within 24 hours prior to Period 1 and Period 2 Day 1 dosing for the predose time point. When scheduled postdose, ECGs will be performed within approximately 20 minutes of the scheduled time point.

9.2.6 Pulmonary Function Test

9.2.6.1 Spirometry

Spirometry as the PFT may be performed in the event of a pulmonary AE and deemed clinically necessary, as determined by the Investigator or designee.

9.2.7 Study Drug Administration

TAK-788 oral capsules will be provided as described in Section 8.0.

Subjects will be instructed not to crush, split, or chew the TAK-788 capsules.

Treatments are described as:

Treatment A (reference)	4 × 40 mg TAK-788 capsules administered at Hour 0 on Day 1 of Period 1 or 2 per randomization following an overnight fast.
Treatment B (test)	4 × 40 mg TAK-788 capsules administered at Hour 0 on Day 1 of Period 1 or 2 per randomization with a high-fat meal.

TAK-788 will be administered following an overnight fast (Treatment A) or with a high-fat meal (Treatment B).

For Treatment B, subjects will be required to fast overnight for at least 10 hours until 30 minutes prior to their scheduled morning dose, when they will be given a high-fat/high-calorie breakfast which will be entirely consumed within 30 minutes (FDA FE 2019).

Following dosing, subjects will fast for at least 4 hours postdose (both treatments).

All study drugs will be administered with approximately 8 fluid oz (240 mL) of water. The exact clock time of oral dosing will be recorded.

The pharmacy at the CRU will provide each dose of study drug(s) in individual unit dose containers for each subject as appropriate.

9.2.8 AE Monitoring

Subjects will be monitored throughout the study for adverse reactions to the study drugs and/or procedures as described in Section 10.0.

9.2.9 Laboratory Procedures and Assessments

All tests listed below will be performed as outlined in the Schedule of Study Procedures (Section 3.0). In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the Investigator or designee.

9.2.9.1 Clinical Laboratory Tests

Hematology

Hematology will consist of the following tests:

Hemoglobin	Red blood cell count
Hematocrit	Platelet count
Total and differential leukocyte count	

Chemistry

Serum chemistry tests will be performed after at least an 8-hour fast; however, in case of dropouts or rechecks, subjects may not have fasted for 8 hours prior to when the serum chemistry sample is taken.

Chemistry evaluations will consist of the following standard chemistry panel:

Amylase	Albumin
Lipase	Sodium
Blood Urea Nitrogen	Potassium
Bilirubin (total and direct)	Chloride
ALP	Glucose
AST	Creatinine *
ALT	Magnesium

* At screening, creatinine clearance will be calculated using the Cockcroft-Gault formula.

Urinalysis

Urinalysis will consist of the following tests:

pH	Bilirubin
Specific gravity	Blood *
Protein *	Nitrite *
Glucose	Urobilinogen
Ketones	Leukocyte esterase *

* If urinalysis is positive for protein, blood, nitrite and/or leukocyte esterase, a microscopic examination (for red blood cells, white blood cells, bacteria, casts, and epithelial cells) will be performed.

Other

HIV test	Urine drug screen – Opiates (includes morphine, heroin (diacetylmorphine), codeine, 6-acetylmorphine, dihydrocodeine, hydrocodone, thebaine, and, hydromorphone) – Amphetamines – Barbiturates – Benzodiazepines – Cocaine – Cannabinoids
HBsAg	
HCV *(if antibody positive, confirm RNA negative)*	
COVID-19 test	
Urine alcohol screen	
Serum pregnancy test (for females only)	
FSH (for postmenopausal females only)	

9.3 Pharmacokinetic Samples

Instructions for plasma samples processing and handling will be provided in a separate document.

Primary specimen collection parameters are provided in Table 9.a.

Table 9.a Primary Specimen Collections

Specimen Name	Primary Specimen	Description of Intended Use	Sample Collection
Plasma sample for TAK-788 and metabolites PK	Plasma	Plasma sample for TAK-788 and metabolites PK analysis	Mandatory

9.3.1 PK Measurements

9.3.1.1 Plasma PK Measurements

PK parameters from plasma concentrations of TAK-788 and its metabolites, AP32960 and AP32914, will be calculated as follows, as appropriate, following oral administration:

AUC_{last}:	The area under the concentration versus time curve, from time 0 to the last observed non-zero concentration, as calculated by the linear trapezoidal method.
AUC_{∞}:	The area under the concentration versus time curve, from time 0 extrapolated to infinity. AUC_{∞} is calculated as AUC_{last} plus the ratio of the last measurable blood concentration to the elimination rate constant.
$AUC_{\%extrap}$:	Percent of AUC_{∞} extrapolated, represented as $(1 - AUC_{last}/AUC_{\infty})*100$.
CL/F:	Apparent total plasma clearance after oral (extravascular) administration, calculated as Dose/AUC_{∞} (TAK-788 only).
C_{max}:	Maximum observed concentration.
t_{max}:	Time to reach C_{max}. If the maximum value occurs at more than one time point, t_{max} is defined as the first time point with this value.
$t_{½z}$:	Apparent first-order terminal disposition phase half-life will be calculated as $0.693/\lambda_z$.
$\lambda_{z:}$	Apparent first order terminal disposition phase rate constant calculated from a semilog plot of the plasma concentration versus time curve.
Vz/F:	Apparent volume of distribution during the terminal disposition phase after oral (extravascular) administration, calculated as Dose/(AUC_{∞}x λ_z) (TAK-788 only).

No value for λ_z, AUC_{∞}, $AUC_{\%extrap}$, CL/F, Vz/F, or $t_{½z}$ will be reported for cases that do not exhibit a linear terminal log-linear phase in the concentration versus time profile.

No PK parameters will be calculated for subjects with detectable concentrations at 2 or fewer consecutive time points.

Individual and mean plasma concentration-curves (both linear and log-linear) will be included in the final report.

9.3.2 Biomarker Measurements

Not applicable

9.3.3 PGx Measurements

Not applicable

9.3.4 Confinement

In each period, subjects will be housed on Day -1, at the time indicated by the CRU, until after the 240-hour PK sample is collected and scheduled safety assessments in Period 2 are completed.

Subjects will return for study assessments/PK blood sampling as indicated in the Section 3.0. At all times, a subject may be required to remain at the CRU for longer at the discretion of the Investigator or designee.

The CRU will contact all subjects (including subjects who terminate the study early) 30 ± 2 days after the last TAK-788 administration to determine if any AEs have occurred since the last study visit.

10.0 ADVERSE EVENTS

10.1 Definitions and Elements of AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study; it does not necessarily have to have a causal relationship with the treatment.

An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, whether or not it is considered related to the drug.

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a preexisting condition. (Intermittent events for pre-existing conditions or underlying disease should not be considered AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study medication or a concomitant medication.
- Be considered unfavorable by the Investigator for any reason.

Diagnoses versus signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG parameters maybe considered AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the Investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory re-test and/or continued monitoring of an abnormal value are not considered an intervention. In

addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.

- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), the diagnosis only should be reported appropriately as an AE.

Pre-existing conditions:

- A pre-existing condition (present at the time of signing of informed consent) is considered a concurrent medical history condition and should NOT be recorded as an AE. A baseline evaluation (eg, laboratory test, ECG, X-ray) should NOT be recorded as an AE unless related to a study procedure. However, if the subject experiences a worsening or complication of such a concurrent medical history condition, the worsening or complication should be recorded appropriately as an AE (worsening or complication occurs after informed consent is signed). Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of…").
- If a subject has a pre-existing episodic condition (eg, asthma, epilepsy), any occurrence of an episode should only be captured as an AE if the episodes become more frequent, serious, or severe in nature, that is, Investigators should ensure that the AE term recorded captures the change from Baseline in the condition (eg "worsening of…").
- If a subject has a degenerative concurrent condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be captured as an AE if occurring to a greater extent to that which would be expected. Again, Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Worsening of AEs:

- If the subject experiences a worsening or complication of an AE after the first administration of study medication or after any change in study medication, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Changes in severity of AEs:

- If the subject experiences a change in the severity of an AE that is not associated with a change in study medication, the event should be captured once with the maximum severity recorded.

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered AEs. However, if a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be captured appropriately as an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as AEs but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Overdose:

- An overdose is defined as a known deliberate or accidental administration of investigational drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol. It is up to the Investigator or the reporting physician to decide whether a dose is to be considered an overdose, in consultation with the Sponsor.
- All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the CRF, in order to capture this important safety information consistently in the database. AEs associated with an overdose will be documented on AE CRF(s) according to Section 10.0.
- Serious adverse events (SAEs) of overdose should be reported according to the procedure outlined in Section 10.2.7.
- In the event of drug overdose, the subject should be treated symptomatically.

10.1.1 SAEs

An SAE is defined as any untoward medical occurrence that at any dose:

1. Results in DEATH.
2. Is LIFE THREATENING.
    - The term "life threatening" refers to an event 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.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Is a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
    - May require intervention to prevent items 1 through 5 above.
    - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.

AEs that fulfill 1 or more of the serious criteria above are to be considered SAEs and should be reported and followed up in the same manner (see Sections 10.1.1 and 10.2.7.3).

Table 10.a Takeda Medically Significant AE List

Term	
Acute respiratory failure/acute respiratory distress syndrome	Hepatic necrosis
	Acute liver failure
Torsade de pointes / ventricular fibrillation / ventricular tachycardia	Anaphylactic shock
	Acute renal failure
Malignant hypertension	Pulmonary hypertension
Convulsive seizures	Pulmonary fibrosis
Agranulocytosis	Confirmed or suspected endotoxin shock
Aplastic anemia	Confirmed or suspected transmission of infectious agent by a medicinal product
Toxic epidermal necrolysis/ Stevens-Johnson syndrome	Neuroleptic malignant syndrome / malignant hyperthermia
	Spontaneous abortion / stillbirth and fetal death

AEs that fulfill 1 or more of the serious criteria above are to be considered SAEs and should be reported and followed up in the same manner (see Sections 10.1 and 10.1.1).

10.1.2 Special Interest AEs

There are no AEs of Special Interest for this study.

10.2 AE Procedures

10.2.1 Assigning Severity/Intensity of AEs

In this study, intensity for each AE, including any laboratory abnormality, will be determined using the National Cancer Institute, Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0, dated 27 November 2017 [CTCAE 2017]. 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 <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.

10.2.2 Assigning Causality of AEs

The relationship of each AE to study medication(s) will be assessed using the following categories:

Related: An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which a causal relationship is at least a reasonable possibility, ie, the relationship cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant drugs and concurrent treatments, may also be responsible.

Not Related: An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant medications and concurrent treatments.

10.2.3 Start Date

The start date of the AE is the date that the first signs/symptoms were noted by the subject and/or Investigator.

10.2.4 End Date

The end date of the AE is the date at which the subject recovered, the event resolved but with sequelae or the subject died.

10.2.5 Action Taken With Study Treatment

- Drug withdrawn – a study medication is stopped due to the particular AE.
- Dose not changed – the particular AE did not require stopping a study medication.
- Unknown – only to be used if it has not been possible to determine what action has been taken.
- Not applicable – a study medication was stopped for a reason other than the particular AE eg, the study has been terminated, the subject died, dosing with study medication had not yet started or dosing with study medication was already stopped before the onset of the AE.
- Drug interrupted – the dose was interrupted due to the particular AE.

10.2.6 Outcome

- Recovered/resolved – subject returned to first assessment status with respect to the AE.

- Recovering/resolving – the intensity is lowered by one or more stages: the diagnosis has or signs/symptoms have almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to the baseline value; the subject died from a cause other than the particular AE with the condition remaining "recovering/resolving."
- Not recovered/not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/symptoms or laboratory value on the last day of the observed study period has become worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE state remaining "Not recovered/not resolved."
- Recovered/Resolved with sequelae – the subject recovered from an acute AE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis).
- Fatal – an AE that is considered as the cause of death.
- Unknown – the course of the AE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

10.2.7 Collection and Reporting of AEs, SAEs, Special Interest AEs, and Abnormal LFTs

10.2.7.1 Collection Period

Collection of AEs (ie, AEs, SAEs, Special Interest AEs, and Abnormal LFTs) will commence at the time the subject signs the informed consent. Routine collection of AEs will continue until the follow-up phone call 30 $\pm$ 2 days after the last dose of TAK-788. For subjects who discontinue prior to the administration of TAK-788, AEs will be followed until the subject discontinues study participation.

10.2.7.2 Reporting AEs

At each study visit, the Investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study. Subjects experiencing an SAE prior to the first exposure to investigational product must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to Baseline or there is a satisfactory explanation for the change. Non-serious AEs that begin prior to the first exposure to investigational product, related or unrelated to the study procedure, need not be followed-up for the purposes of the protocol.

All subjects experiencing AEs, whether considered associated with the use of the study medication or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to Baseline or until there is a satisfactory explanation for the changes observed. All AEs will be documented in the AE page of the CRF, whether or not the Investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

- Event term.
- Start and end date and time.
- Pattern of AE (frequency).
- Severity/Intensity.
- Causality (Investigator's opinion of the causal relationship between the event and administration of study drug[s]).
- Action taken with Study drug.
- Outcome of event.
- Seriousness.

10.2.7.3 Reporting SAEs

When an SAE occurs through the AE collection period it should be reported according to the procedure outlined below:

A Takeda SAE form must be completed, in English and signed by the Investigator immediately or within 24 hours of first onset or notification of the event. The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious.
- Subject identification number.
- Investigator's name.
- Name of the study medication(s).
- Causality assessment.

The SAE form should be transmitted within 24 hours to the attention of the contact listed in Section 14.1.1.

Any SAE spontaneously reported to the Investigator following the AE collection period should be reported to the Sponsor if considered related to study participation.

Reporting of SAEs that begin before first administration of investigational product will follow the same procedure for SAEs occurring on treatment.

10.2.7.3.1 SAE Follow-Up

If information is not available at the time of the first report becomes available at a later date, the Investigator should complete a follow-up SAE form or provide other written documentation and fax it immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

10.2.7.4 Reporting Special Interest AEs

Not applicable

10.2.7.5 Reporting of Abnormal LFTs

If a subject has elevated ALT ≥3x upper limit of normal (ULN) with concurrent elevated total bilirubin >2× ULN ***or*** elevated international normalized ratio (INR) >1.5, contact the sponsor's medical monitor within 24 hours.

For any subject with ALT ≥3x ULN and total bilirubin >2x ULN or INR >1.5x ULN for which an alternative etiology has not been found, report the event as an SAE (Section 10.2.7.3) and contact the sponsor immediately.

10.2.8 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 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 products administration or in the overall conduct of the Study. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

10.2.9 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 email addresses provided below.

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

Product	Call Center	Phone Number	Email	Fax
TAK-788	Dohmen Life Science Services, or DLSS (formerly known as MedComm)	1-844-662-8532 Non-toll-free number: 1-510-740-1273	GlobalOncologyMedinfo@takeda.com	1-800-881-6092

Product complaints and medication errors in and of themselves are not AEs. If a product complaint or a medication error results in an SAE, the SAE should be reported.

11.0 STATISTICAL METHODS

11.1 Statistical and Analytical Plans

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a statistical analysis plan (SAP). The SAP will be prepared by Celerion and agreed upon with the Sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoints definition and/or its analysis will also be reflected in a protocol amendment. Additional statistical analyses other than those described in this section may be performed if deemed appropriate.

11.1.1 Analysis Sets

11.1.1.1 PK Set

Samples from all subjects will be assayed even if the subjects do not complete the study. All subjects who comply sufficiently with the protocol and display an evaluable PK profile (eg, exposure to treatment, availability of measurements and absence of major protocol violations) will be included in the statistical analyses. Any subject who experiences emesis within 8 hours post dosing with TAK-788 will be excluded in the final data analysis.

11.1.1.2 Safety Set

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

11.1.1.3 Pharmacodynamic Set

Not applicable.

11.1.2 Analysis of Demography and Other Baseline Characteristics

Continuous demographic data (ie, age, weight, height, and BMI) will be listed and summarized using appropriate summary statistics. Categorical demographic data (ie, gender, race, and ethnicity) will also be listed and tabulated.

11.1.3 PK Analysis

The plasma TAK-788 and its active metabolites (AP32960 and AP32914) concentrations will be listed and plotted against sample collection times. PK parameters derived from the plasma concentrations of TAK-788 and its active metabolites (AP32960 and AP32914) and sample collection times will be calculated as described in Section 9.3.1.1 using appropriate summary statistics to be fully outlined in the SAP.

11.1.3.1 Analysis of Variance

A linear mixed-effects model will be used for the analysis on the ln-transformed C_{max}, AUC_{∞}, and AUC_{last} for TAK-788 and its active metabolites (AP32960 and AP32914). The model will include sequence, treatment, and period as a fixed-effect and subject nested within sequence as a random-effect. Each model will include calculation of LSMs as well as the difference between treatment LSMs.

11.1.3.2 Ratios and Confidence Intervals

GMR and 90% CI, consistent with the two one sided test [Schuirmann 1987], will be calculated using the exponentiation of the difference between treatment LSMs from the analyses on the ln-transformed C_{max}, AUC_{∞}, and AUC_{last} (if it is needed) for TAK-788 and the combined molar C_{max}, AUC_{∞}, and AUC_{last} (if it is needed) for TAK-788 and its active metabolites. These ratios will be expressed as a ratio of test treatment relative to the appropriate reference treatment.

11.1.4 Pharmacodynamic Analysis

Not applicable.

11.1.5 Safety Analysis

All safety data will be populated in the individual CRFs.

Dosing dates and times will be listed by subject.

Quantitative safety data as well as the difference to baseline, when appropriate, will be summarized using the appropriate descriptive statistics.

11.1.5.1 AEs

AEs will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA®) available at Celerion and summarized by treatment for the number of subjects reporting the TEAE and the number of TEAEs reported. A by-subject AE data listing including verbatim term, coded term, treatment, severity, and relationship to treatment will be provided.

11.1.5.2 Clinical Laboratory Evaluation

Clinical laboratory results will be summarized by treatment and point of time of collection and a shift table describing out of normal range shifts will be provided.

11.1.5.3 Vital Signs

Vital signs assessments will be summarized by treatment and point of time of collection.

11.1.5.4 Other Safety Parameters

Physical examination findings will be presented in the data listings.

ECGs will be summarized by treatment and point of time of collection.

Medical history, and concurrent conditions will be coded using the MedDRA® and concomitant medications will be coded using the World Health Organization drug and will be listed by subject.

11.2 Determination of Sample Size

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

12.0 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 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 CRFs. Source documents are defined as original documents, data, and records. The Investigator and study site guarantee access to source documents by the Sponsor or its designee (Clinical Research Organization) and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the Sponsor or the Sponsor's designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, Study drug, subject medical records, informed consent documentation, and review of CRFs 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.

12.2 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.

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.

12.3 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 FDA, the United Kingdom 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 guarantees access for quality assurance auditors to all study documents as described in Section 12.1.

13.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual subjects (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the International Council on Harmonisation (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" that are listed in Appendix A. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and Investigator responsibilities.

13.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable state and federal/local 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. Those Americas sites 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 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 informed consent form, 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, informed consent form) reviewed; and state the approval date. The Sponsor will ship drug/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 Study. Until the site receives drug/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 informed consent form, 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.

13.2 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 informed consent form, 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 informed consent form 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 informed consent form 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 informed consent form and, if applicable, the subject authorization form. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the Sponsor prior to use.

The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the Investigator to explain the detailed elements of the informed consent form, 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 he or she will participate in the study, then the informed consent form 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 prior to the subject entering 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. The Investigator must also sign and date the informed consent form and subject authorization (if applicable) at the time of consent and prior to 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 informed consent form, 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 informed consent in the subject's medical record. Copies of the signed informed consent form, 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 informed consent form.

13.3 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 only be linked to the Sponsor's clinical study database or documentation 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, FDA, Medicines and Healthcare products Regulatory Agency, 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 of the subject as part of the informed consent process (see Section 13.2).

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

13.4 Publication, Disclosure, and Clinical Study Registration Policy

13.4.1 Publication and Disclosure

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/or 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.

13.4.2 Clinical Study Registration

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

For some registries, Takeda will assist callers in locating study sites closest to their homes by providing the Investigator name, address, and phone number to the callers requesting Study information. Once subjects receive Investigator contact information, they may call the site requesting enrollment into the Study. The investigative sites are encouraged to handle the Study inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of Study enrollment, they should be referred to the Sponsor.

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

13.4.3 Clinical Study Results Disclosure

Takeda will post the results of clinical studies on ClinicalTrials.gov or other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws and/or regulations.

13.5 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 study subjects. Refer to the study site agreement regarding 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.

14.0 ADMINISTRATIVE AND REFERENCE INFORMATION

14.1 Administrative Information

14.1.1 Study Contact Information

Contact Type/Role	Contact
Serious adverse event and pregnancy reporting	**SAE Reporting Contact Information** **Cognizant** **US and Canada** Toll-free fax #: 1-800-963-6290 E-mail: takedaoncocases@cognizant.com

Please refer to Safety Management Plan.

14.1.2 INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, package insert 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.
- International Council on Harmonisation, E6 [R2] Good Clinical Practice: 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 10.2.8 of this protocol.
- Terms outlined in the study site agreement.
- Responsibilities of the Investigator (Appendix A).

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)

14.1.3 Study-Related Responsibilities

The Sponsor will perform all study-related activities with the exception of those identified in the Study-Related Responsibilities template. The vendors identified for specific study-related activities will perform these activities in full or in partnership with the Sponsor.

14.1.4 List of Abbreviations

AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC_{last}	Area under the concentration-time curve, from time 0 to the last observed non-zero concentration
AUC_{∞}	Area under the concentration-time curve, from time 0 extrapolated to infinity
BMI	Body mass index
bpm	Beats per minute
C_{av}	Average concentration
CFR	Code of Federal Regulations
CI	Confidence interval
CL/F	Apparent clearance after extravascular administration
cm	Centimeter
C_{max}	Maximum observed concentration
CRA	Clinical Research Associate
CRF	Case report form
CRU	Clinical Research Unit
CV	Coefficient of variation
CYP	Cytochrome P450
DDI	Drug-drug interaction
DiC	Drug-in-Capsule
ECG	Electrocardiogram
EGFR	Epidermal growth factor receptor
EMEA	European Medicines Agency
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
g	Gram
GCP	Good Clinical Practice
GMR	Geometric mean ratio
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HDPE	High-density polyethylene
HER2	Human epidermal growth factor 2

HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
kg	Kilogram
LFT	Liver function test
LSM	Least square mean
m^2	Meters squared
MedDRA®	Medical Dictionary for Regulatory Activities®
mg	Milligram
min	Minute
mL	Milliliter
mmHg	Millimeter of mercury
msec	Millisecond
NSCLC	Non–small cell lung cancer
oz	Ounce
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
PFT	Pulmonary function test
PT	Preferred term
QD	Once daily
QTcF	QT interval corrected for heart rate using Fridericia's formula
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SUSAR	Suspected unexpected serious adverse reaction
$t_{½z}$	Apparent first-order terminal disposition phase half-life
TBD	To be determined
TEAE	Treatment-emergent adverse event
TKI	Tyrosine kinase inhibitor
t_{max}	Time to reach C_{max}
ULN	Upper limit of normal
US	United States
USA	United States of America
Vz/F	Apparent volume of distribution after extravascular administration
WHO	World Health Organization
WT	Wild-type
λ_z	Apparent first order terminal disposition phase rate constant

15.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan.

15.1 CRFs

Celerion standard CRFs will be supplied. CRFs are produced, stored electronically, and are available to the designated study team members. Each CRF is reviewed and signed by the PI. The final signed CRFs are provided to the Sponsor in the format as decided upon between Celerion and the Sponsor (eg, CD, flashdrive, SFTP). This will be documented in the Data Management Plan (if applicable).

After completion of the entry process, edit checks are then performed for appropriate databases as a validation routine using SAS® or comparable statistical program to check for missing data, data inconsistencies, data ranges, etc. Corrections are made prior to database lock.

Corrections 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. Reasons for significant corrections should additionally be included.

After the lock of the clinical study database, any change of, modification of, or addition to the data on the CRFs should be made by the Investigator/designee with use of change and modification records of the CRFs. The Principal Investigator must review the data change for completeness and accuracy, and must sign and date.

CRFs 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 CRFs. The completed CRFs 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.

15.2 Record Retention

The Investigator agrees to keep the records stipulated in Section 15.1 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 informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), electronic copy of CRFs, including the audit trail, 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 [R2] Section 4.9.5 requires the Investigator to retain essential documents specified in ICH E6 [R2] (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 [R2] 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 and the head of the institution should contact and receive written approval from the Sponsor before disposing of any such documents.

16.0 REFERENCES

European Medicines Agency Committee for Medicinal Products for Human Use: Guideline on the Investigation of Bioequivalence. January 2010. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-bioequivalence-rev1_en.pdf

National Cancer Institute, Common Terminology Criteria for Adverse Events (CTCAE), Revised: Nov-2017 (v5.0). Available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf.

Schuirmann DJ. A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. J Pharmacokinet Biopharm 1987;15: 657-680.

TAK-788. Millennium Pharmaceuticals, Inc. Global Investigator Brochure. Edition 4.0, 01-April-2020.

U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Draft Guidance Bioavailability Studies Submitted in NDAs or INDs — General Considerations Guidance for Industry. February 2019. https://www.fda.gov/media/121311/download

U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Draft Guidance Assessing the Effects of Food and Drugs in INDs and NDAs — Clinical Pharmacology Considerations Guidance for Industry. February 2019. https://www.fda.gov/media/121313/download

17.0 APPENDICES

Appendix A Responsibilities of the Investigator

Clinical research studies sponsored by the Sponsor are subject to ICH GCP and all the applicable local laws and regulations. The responsibilities imposed on Investigators by the 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 that will assist in the protocol.
3. If the Investigator/institution retains the services of any individual or party to perform Study-related duties and functions, the Investigator/institution should ensure that this individual or party is qualified to perform those Study-related duties and functions and should implement procedures to ensure the integrity of the Study-related duties and functions performed and any data generated.
4. Ensure that study related procedures, including study specific (nonroutine/nonstandard panel) screening assessments are NOT performed on potential subjects, prior to the receipt of written approval from relevant governing bodies/authorities.
5. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
6. 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.
7. 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.
8. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
9. 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 informed consent form 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 informed consent form 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.

10. Prepare and maintain adequate case histories of all persons entered into the study, including CRFs, 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.
11. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
12. Maintain current records of the receipt, administration, and disposition of Sponsor-supplied drugs, and return all unused Sponsor-supplied drugs to the Sponsor.
13. Report adverse reactions to the Sponsor promptly. In the event of an SAE, notify the Sponsor within 24 hours.

Appendix B Elements of the Subject Informed Consent

In seeking informed consent, the following information shall be provided to each subject:

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the subject's participation.
4. A description of the procedures to be followed, including invasive procedures.
5. The identification of any procedures that are experimental.
6. The estimated number of subjects involved in the study.
7. A description of the subject's responsibilities.
8. A description of the conduct of the study.
9. A statement describing the treatment(s).
10. A description of the possible side effects of the treatment that the subject may receive.
11. A description of any reasonably foreseeable risks or discomforts to the subject and, when applicable, to an embryo, fetus, or nursing infant.
12. A description of any benefits to the subject or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
13. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject and their important potential risks and benefits.
14. A statement describing the extent to which confidentiality of records identifying the subject will be maintained, and a note of the possibility that regulatory agencies, auditor(s), IRB/IEC, and the monitor may inspect the records. By signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.
15. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
16. The anticipated prorated payment(s), if any, to the subject for participating in the study.
17. The anticipated expenses, if any, to the subject for participating in the study.
18. An explanation of whom to contact for answers to pertinent questions about the research (Investigator), subject's rights, and IRB/IEC and whom to contact in the event of a research-related injury to the subject.

19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject otherwise is entitled, and that the subject or the subject's legally acceptable representative may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
21. A statement that the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
22. A statement that results of PGx analysis will not be disclosed to an individual, unless prevailing laws require the Sponsor to do so.
23. The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated.
24. A written subject authorization (either contained within the informed consent form or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the study. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:
    a) that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs/IECs;
    b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer subjects the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;
    c) that personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the study medication(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical studies;
    d) that subjects agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and
    e) that the subject's identity will remain confidential in the event that study results are published.

25. Female subjects of childbearing potential (eg, nonsterilized, premenopausal female subjects) who are sexually active must use highly effective contraception (as defined in the informed consent) from signing the informed consent and throughout the duration of the study, and for 30 days after the last dose of study drug. Regular pregnancy tests will be performed throughout the study for all female subjects of childbearing and non-childbearing potential. If a subject is found to be pregnant during study, study drug will be discontinued and the Investigator will offer the subject the choice to receive unblinded treatment information.
26. Male subjects must use highly effective contraception (as defined in the informed consent) from signing the informed consent throughout the duration of the study and for 30 days after the last dose of study drug. If the partner or wife of the subject is found to be pregnant during the study, the Investigator will offer the subject the choice to receive unblinded treatment information.
27. A statement that clinical Study information from this Study will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix C Investigator Consent to the 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 United Kingdom, United States, 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 Study 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 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 Pregnancy and Contraception

Contraception and Pregnancy Avoidance Procedure

TAK-788 may pose a risk to developing fetuses or to babies who are being breastfed. Because TAK-788 may affect an unborn baby, female participants should not become pregnant while in this study, and male participants should not conceive with their female partner(s) while in this study. Women who are pregnant or breastfeeding will not be allowed to take part in this study.

Women of childbearing potential and male patients must use medically acceptable birth control. Avoiding sexual activity is the only certain way to prevent pregnancy.

Males Subjects and Their Female Partners:

It is not known whether the study medication will affect sperm or an unborn baby. Based on animal studies, taking TAK-788 may lead to testicular changes that could impact reproduction. For this reason, to be in the study males must agree not to father a child or donate sperm during the study and for 30 days after the last dose of TAK-788.

If a male has not had a vasectomy and is sexually active with any person who is pregnant, or could get pregnant, he must use a condom with spermicide each time he has sex during the study and for 30 days after last dose of TAK-788. No restrictions are required for a vasectomized male provided his vasectomy has been performed 4 months or more prior to the first dosing of study drug. A male who has been vasectomized less than 4 months prior to study first dosing must follow the same restrictions as a non vasectomized male and must agree to use an appropriate method of barrier contraception (latex condom with a spermicidal agent) during the entire study, and for 30 days after his last dose of TAK-788. Or, he should completely avoid having heterosexual intercourse.

If a female partner does become pregnant while a male subject is taking part in the study, the subject must tell the study doctor immediately.

In this situation, the female partner should be under medical supervision during her pregnancy, and the baby should be under supervision after it is born. The female partner may be asked to give her consent to the collection of information related to both herself as well as the baby.

Acceptable birth control for males with female partners includes any of the following:

- total abstinence (no sexual intercourse) if it agrees with his preferred and usual lifestyle
- a barrier method (latex condom with a spermicidal agent)

Males must use acceptable birth control during the study treatment period and for at least 30 days after their last dose of TAK-788 and should tell their female partner(s) that they are in research study.

Females:

Females must agree not to become pregnant, breastfeed a baby or donate an egg or eggs (ova) during the study and for 30 days after the last dose of TAK-788. Women of childbearing potential must use acceptable birth control from the time of signing the informed consent form until at least 30 days after their last dose of TAK-788.

If a female has been surgically sterilized or is postmenopausal, she does not need to meet any contraception requirements to take part in this study. If a female is of childbearing potential and is sexually active with a male partner, she must be willing to use an acceptable method of contraception during the study and for 30 days after the last dose of TAK-788.

TAK-788 may decrease effectiveness of hormonal contraceptives, therefore, women of childbearing potential must use effective non-hormonal methods of contraception. Acceptable birth control for women of childbearing potential with male partners must include one form of highly effective non-hormonal contraception and one additional effective (barrier) method, as described below:

<table>
<tr><th>Highly effective non-hormonal methods</th><th>Additional effective (barrier) methods</th></tr>
<tr><td>Non-hormonal intrauterine device</td><td rowspan="2">Male or female condom with or without spermicide (female and male condoms should not be used together)</td></tr>
<tr><td>Vasectomised sole sexual partner (removal of the tube that carries sperm from the testicle to the penis)</td></tr>
<tr><td>Sexual abstinence (no sexual intercourse, additional effective barrier method therefore not applicable)</td><td>Cap, diaphragm or sponge with spermicide</td></tr>
</table>

Total abstinence (no sexual intercourse) may be considered an acceptable method of birth control if it agrees with her preferred and usual lifestyle.

In order to enter the study, all females must have a pregnancy test to confirm that she is not pregnant. This test will be repeated just before she starts taking the first study medication and then regularly throughout the study, at each check-in. If a pregnancy test during the study shows that she may be pregnant, she will be withdrawn from the study and the treatment will end. She will be asked for the results of any tests and procedures carried out during pregnancy and up to the birth. She may also be asked for the results from any evaluation of the baby after the birth.

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

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical Pharmacology Approval	09-Jun-2020 20:39 UTC
	Clinical Science Approval	09-Jun-2020 20:53 UTC
	Biostatistics Approval	10-Jun-2020 00:36 UTC

Protocol Clarification Letter for Celerion Study No.: CA24171
Takeda Pharmaceuticals Study No.: TAK-788-1005
Date of Final Protocol: 09-Jun-2020
Date of Protocol Clarification Letter: 24-Jun-2020

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

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There will not be a pharmacy manual provided for this study as there is no compounding required for the investigational product. This protocol clarification letter is written to remove reference to the pharmacy manual in Section 8.1 – Clinical Study Drugs and in Section 8.1.2 – Clinical Study Drug Inventory and Storage:

In Section 8.1 – Clinical Study Drugs, modifications to the second and third paragraphs will be made as noted below (deletion noted with ~~strikethrough~~):

> All TAK-788 products will be prepared by licensed pharmacy staff at the CRU~~according to the procedures outlined in the pharmacy manual~~.
>
> ~~Details of the dosage form description and strengths can be found in the pharmacy manual~~.

In Section 8.1.2 – Clinical Study Drug Inventory and Storage, the second sentence in the second paragraph will be deleted as noted below (deletion noted with ~~strikethrough~~):

> The recommended storage condition for TAK-788 is controlled room temperature. ~~Additional details regarding the storage and handling of TAK-788 are provided in the pharmacy manual.~~

The final protocol, dated 09-Jun-2020 was not amended to incorporate this change, therefore, this protocol clarification letter is being written. However, should an amendment for this protocol be required at some point in the future, this change will be included in that amendment.

PPD

PPD

25-Jun-2020
Date

25 Jun 2020
Date

29-Jun-2020 | 22:38:22 JST
Date

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Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

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Envelope Summary Events	Status	Timestamps
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Signing Complete	Security Checked	29-Jun-2020 | 22:38
Completed	Security Checked	29-Jun-2020 | 22:38

Payment Events	Status	Timestamps