



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

NCT Number: NCT03928327

Protocol Approve Date: 16 April 2019

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

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

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

TAKEDA PHARMACEUTICALS

PROTOCOL

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

Study Identifier: TAK-788-1006

Compound: TAK-788

Date: 16 April 2019

**Version/Amendment
Number:** Final

Property of Takeda: For non-commercial use only and subject to the applicable Terms of Use

TABLE OF CONTENTS

1.0	STUDY SUMMARY	6
2.0	STUDY SCHEMATIC	13
3.0	SCHEDULE OF STUDY PROCEDURES	15
4.0	INTRODUCTION	23
4.1	Background	23
4.1.1	TAK-788	23
4.1.2	Itraconazole	24
4.1.3	Rifampin	25
4.2	Rationale for the Proposed Study	26
4.3	Benefit/Risk Profile	27
5.0	STUDY OBJECTIVES AND ENDPOINTS	28
5.1	Hypothesis	28
5.2	Study Objectives	28
5.2.1	Study Primary Objective	28
5.2.2	Study Exploratory Objective	28
5.3	Endpoints	28
5.3.1	Primary Endpoint	28
5.3.2	Exploratory Endpoints	28
6.0	STUDY DESIGN AND DESCRIPTION	29
6.1	Study Design	29
6.2	Dose Escalation	32
6.3	Rationale for Study Design, Dose, and Endpoints	33
6.3.1	Rationale of Study Design and Dose	33
6.3.2	Rationale for Endpoints	34
6.3.3	Future Biomedical Research	34
6.3.4	Critical Procedures Based on Study Objectives: Timing of Procedures	34
6.4	Study Design/Dosing/Procedures Modifications Permitted Within Protocol Parameters	35
6.5	Study Beginning and End/Completion	35
6.5.1	Definition of Beginning of the Study	35
6.5.2	Definition of End of the Study	35
6.5.3	Definition of Study Completion	35
6.5.4	Definition of Study Discontinuation	35
6.5.5	Criteria for Premature Termination or Suspension of the Study	35
6.5.6	Criteria for Premature Termination or Suspension of a Site	35

7.0	SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS	36
7.1	Excluded Medications, Supplements, Dietary Products	36
7.2	Diet, Fluid, Activity	36
7.2.1	Diet and Fluid	36
7.2.2	Activity	37
7.3	Criteria for Discontinuation or Withdrawal of a Subject	37
7.4	Procedures for Discontinuation or Withdrawal of a Subject	37
7.5	Subject Replacement	38
8.0	CLINICAL STUDY MATERIAL MANAGEMENT	39
8.1	Clinical Study Drug	39
8.1.1	TAK-788 Capsules	39
8.1.2	Itraconazole Solution	40
8.1.3	Rifampin Capsules	40
8.1.4	Clinical Study Drug Labeling	40
8.1.5	Clinical Study Drug Inventory and Storage	41
8.1.6	Clinical Study Drug Blinding	41
8.1.7	Randomization Code Creation and Storage	41
8.1.8	Clinical Study Blind Maintenance/Unblinding Procedure	41
8.1.9	Accountability and Destruction of Sponsor-Supplied Drugs	41
9.0	STUDY PROCEDURES	42
9.1	Administrative Procedures	42
9.1.1	Informed Consent Procedure	42
9.1.2	Inclusion and Exclusion	42
9.1.3	Medical History/Demography	45
9.1.4	Concomitant Medications	45
9.2	Clinical Procedures and Assessments	45
9.2.1	Full Physical Exam	45
9.2.2	Height and Weight	45
9.2.3	BMI	46
9.2.4	Vital Signs	46
9.2.5	12-Lead ECG	46
9.2.6	Pulmonary Function Test	46
9.2.7	Study Drug Administration	47
9.2.8	AE Monitoring	48
9.2.9	Laboratory Procedures and Assessments	48
9.3	Pharmacokinetic Samples	49

9.3.1	PK Measurements	50
9.3.2	Biomarker Measurements.....	51
9.3.3	PGx Measurements	51
9.3.4	Confinement	51
10.0	ADVERSE EVENTS	52
10.1	Definitions and Elements of AEs	52
10.1.1	SAEs.....	54
10.1.2	Special Interest AEs.....	55
10.2	AE Procedures.....	55
10.2.1	Assigning Severity/Intensity of AEs.....	55
10.2.2	Assigning Causality of AEs.....	56
10.2.3	Start Date.....	56
10.2.4	End Date.....	56
10.2.5	Action Taken With Study Treatment.....	56
10.2.6	Outcome	56
10.2.7	Collection and Reporting of AEs, SAEs, Special Interest AEs, and Abnormal LFTs	57
10.2.8	Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities	59
10.2.9	Procedures for Reporting Product Complaints or Medication Errors (Including Overdose)	59
11.0	STATISTICAL METHODS.....	61
11.1	Statistical and Analytical Plans	61
11.1.1	Analysis Sets.....	61
11.1.2	Analysis of Demography and Other Baseline Characteristics	61
11.1.3	PK Analysis.....	61
11.1.4	Pharmacodynamic Analysis	62
11.1.5	Safety Analysis	62
11.2	Interim Analysis and Criteria for Early Termination	63
11.3	Determination of Sample Size.....	63
12.0	QUALITY CONTROL AND QUALITY ASSURANCE.....	64
12.1	Study-Site Monitoring Visits	64
12.2	Protocol Deviations.....	64
12.3	Quality Assurance Audits and Regulatory Agency Inspections	64
13.0	ETHICAL ASPECTS OF THE STUDY	65
13.1	IRB and/or IEC Approval	65
13.2	Subject Information, Informed Consent, and Subject Authorization	66

13.3	Subject Confidentiality	67
13.4	Publication, Disclosure, and Clinical Study Registration Policy	67
13.4.1	Publication and Disclosure	67
13.4.2	Clinical Study Registration	68
13.4.3	Clinical Study Results Disclosure	68
13.5	Insurance and Compensation for Injury	68
14.0	ADMINISTRATIVE AND REFERENCE INFORMATION	69
14.1	Administrative Information	69
14.1.1	Study Contact Information	69
14.1.2	INVESTIGATOR AGREEMENT	70
14.1.3	Study-Related Responsibilities	71
14.1.4	List of Abbreviations	71
15.0	DATA HANDLING AND RECORDKEEPING	73
15.1	CRFs	73
15.2	Record Retention	73
16.0	REFERENCES	75
17.0	APPENDICES	77

LIST OF IN-TEXT TABLES

Table 3.a	Pharmacokinetic Plasma Concentration Sampling Schedule (Part 1)	21
Table 3.b	Pharmacokinetic Plasma Concentration Sampling Schedule (Part 2)	22
Table 6.a	Part 1 TAK-788 assessment with Itraconazole	29
Table 6.b	Part 2 TAK-788 assessment with Rifampin	30
Table 6.c	Planned Doses of TAK-788, Itraconazole (Part 1), and Rifampin (Part 2)	32
Table 7.a	Excluded Medications, Supplements, and Dietary Products	36
Table 9.a	Primary Specimen Collections	49
Table 10.a	Takeda Medically Significant AE List	55

LIST OF APPENDICES

Appendix A	Responsibilities of the Investigator	77
Appendix B	Elements of the Subject Informed Consent	79
Appendix C	Investigator Consent to the Use of Personal Information	82
Appendix D	Pregnancy and Contraception	83

1.0 STUDY SUMMARY

Name of Sponsor: Millennium Pharmaceuticals, Inc. a wholly owned subsidiary of Takeda Pharmaceutical Company, Ltd 40 Landsdowne Street Cambridge, Massachusetts USA 02139 Telephone: +1 (617) 679-7000											Compound: TAK-788												
Study Identifier: TAK-788-1006 (CA24219)											Phase: 1												
Protocol Title: A Phase 1 Study of Oral TAK-788 to Evaluate the Drug-Drug Interaction with Itraconazole and Rifampin in Healthy Adult Subjects																							
Study Design: <p>This is a 2-part study. Each part will be conducted as an open-label, 2-period, fixed sequence study with TAK-788 designed to characterize TAK-788 drug-drug interaction with either a strong cytochrome P-450 (CYP)3A inhibitor, itraconazole (Part 1) or with a strong CYP3A inducer, rifampin (Part 2) in healthy adult subjects. Subjects participating in Part 1 will be different from those participating in Part 2. Additionally, Part 1 will be a sequential study design; Part 1 Cohort 2 will not start until pharmacokinetic (PK) data from Part 1 Cohort 1 (up to Period 2 Day 15) has been evaluated. The study parts may be conducted concurrently.</p> <p><u>Part 1: TAK-788 assessment with Itraconazole</u></p> <p>Part 1 will be conducted in 2 cohorts: Cohort 1 will enroll 4 subjects and will assess whether the 20 mg dose of TAK-788 is an appropriate dose for the TAK-788/itraconazole drug-drug interaction study; depending on the PK results, Cohort 2 will either continue to enroll 8 more subjects at this same dose level or enroll 12 more subjects at a revised TAK-788 dose level. Other than the dose of TAK-788, the study design will be exactly the same for each cohort.</p> <p>This study part will comprise of a screening period, 2 treatment periods and a follow-up phone call in up to 16 healthy subjects. Dose administration and PK collection scheme for the treatment period is outlined in the table below.</p>																							
		Treatment Period 1										Treatment Period 2											
Study Day	-1	1	2	3	4	5	6	8*	1*	2	3	4	5	6	7	8	9	10	11	12	13	14	15
TAK-788 PO		X											X										
Itraconazole 200 mg QD PO									X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PK Blood Samples		X	X	X	X	X	X	X*	X*				X	X	X	X	X	X		X	X		X
Overnight in Clinics	X	X	X	X								X	X	X	X								
*Since the washout period is 7 days the timing of the last PK blood draw of Period 1 will occur within 60 minutes prior to the first dose of itraconazole on Period 2 Day 1; only one PK sample will be taken. Abbreviation: PK=Pharmacokinetics; PO=per oral; QD=once daily																							
<p>On Period 1 Day 1, subjects will receive a single 20 mg oral dose of TAK-788 or a TAK-788 oral dose to be determined (TBD) (Cohort 2) as capsules (fasting). A standardized meal will be provided at least 4 hours postdose. Subjects will remain in the clinic research unit (CRU) until the morning of Day 4 after the 72-hour PK sample is collected. Additional PK samples will be taken as an outpatient up to 168 hours postdose (Period 1 Day 8, which is the same as Period 2 Day 1).</p> <p>In Period 2, subjects will receive 200 mg itraconazole once daily (QD) alone as an oral solution on an empty stomach (no food from at least 1 hour prior until at least 2 hours after dosing). Subjects will be admitted to the CRU in Period 2 Day 4. In the morning of Period 2 Day 5, subjects will receive 200 mg itraconazole together with 20 mg oral TAK-788 or TBD oral dose of TAK-788 (fasting). A standardized meal will be provided at least 4 hours postdose. Subjects will be furloughed from the CRU after the 72-hour PK sample is collected in the morning of Period 2 Day 8. There will be outpatient visits to the CRU for dosing itraconazole and/or PK sampling from Day 1 to Day 3 and Day 9 to Day 14. A final post-treatment follow-up and last PK sampling (Table 3.a) will occur at 240 hours post-Day 5 TAK-788 dose</p>																							

(Period 2 Day 15).

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

Part 2: TAK-788 assessment with Rifampin

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

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

*Since the washout period is 7 days the timing of the last PK blood draw of Period 1 will occur within 60 minutes prior to the first dose of rifampin on Period 2 Day 1; only one PK sample will be taken.

Abbreviation: PK=Pharmacokinetics; PO=per oral; QD=once daily

On Period 1 Day 1, a different group of subjects from Part 1 will receive a single 160 mg oral dose of TAK-788 as capsules (fasting). A standardized meal will be provided at least 4 hours postdose. Subjects will remain in the CRU until the morning of Day 4 after the 72-hour PK sample is collected. Additional PK samples (Table 3.b) will be taken as an outpatient up to 168 hours postdose (Period 1 Day 8, which is the same as Period 2 Day 1).

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

Part 1 and Part 2:

TAK-788 and rifampin will be orally administered with approximately 240 mL of water. For itraconazole dosing, a total aqueous volume of approximately 240 mL will be administered; this will include the dose of itraconazole oral solution and two rinses of the full dose unit container with water followed by ingestion of the remaining dosing water. All doses of TAK-788, itraconazole, and rifampin will be administered at the CRU during this study, either during confinement or on an outpatient basis.

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

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

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

<p>Study Primary Objective: Part 1: To characterize the effect of itraconazole, a strong CYP3A inhibitor, on the single-dose PK of TAK-788 and its active metabolites (AP32960 and AP32914) in healthy adult subjects. Part 2: To characterize the effect of rifampin, a strong CYP3A inducer, on the single-dose PK of TAK-788 and its active metabolites (AP32960 and AP32914) in healthy adult subjects.</p> <p>Exploratory Objective: Part 1 and Part 2: To assess the safety data of TAK-788 following single oral dose with/without strong CYP3A inhibitor or inducer in healthy adult subjects.</p> <p>Study Subject Population: Healthy male and female subjects aged 18 to 55 years inclusive, at screening. Body Mass Index (BMI) 18.0-32.0 kg/m², inclusive, at screening.</p>	
<p>Planned Number of Subjects: Up to 28 healthy adult subjects will be enrolled in 2 parts (up to 16 in Part 1, and 12 in Part 2) in the drug-drug interaction study to get at least 10 PK-evaluable subjects for estimation of drug-drug interaction magnitude in each part of study.</p>	<p>Planned Number of Sites: 1</p>
<p>Dose Levels: Part 1: Cohort 1: 20 mg TAK-788, 2 single doses Cohort 2: dose TBD TAK-788, 2 single doses Cohorts 1 and 2: 200 mg itraconazole solution QD, 14 doses Part 2: 160 mg TAK-788, 2 single doses 600 mg rifampin (3 x 200 mg capsules) QD, 13 doses</p>	<p>Route of Administration: oral</p>
<p>Duration of Treatment: Part 1: <u>TAK-788 assessment with Itraconazole</u> <u>Cohort 1:</u> Period 1 Day 1, subjects will receive a single oral dose of 20 mg TAK-788; Period 2 Day 1 to Day 14, subjects will receive 200 mg itraconazole QD and coadministered on Day 5 with a single oral 20 mg TAK-788. <u>Cohort 2:</u> Period 1 Day 1, subjects will receive a single oral TBD dose of TAK-788; Period 2 Day 1 to Day 14, subjects will receive 200 mg itraconazole QD and coadministered on Day 5 with a single oral TBD dose of TAK-788. There will be a washout period of 7 days between the dose of TAK-788 on Period 1 and the first dose of itraconazole in Period 2. Part 2: <u>TAK-788 assessment with Rifampin</u> Period 1 Day 1, subjects will receive a single oral 160 mg dose of TAK-788; Period 2 Day 1 to Day 13, subjects will receive 600 mg rifampin QD and coadministered on Day 7 with a single oral dose of 160 mg TAK-788.</p>	<p>Planned Study Duration: Approximately 60 days ± 2 days including screening period and follow-up for Part 1. Approximately 60 days ± 2 days including screening period and follow-up for Part 2.</p>

There will be a washout period of 7 days between the dose of TAK-788 on Period 1 and the first dose of rifampin in Period 2.

Part 1 and Part 2:

All doses will be administered in the CRU (either during confinement or on an outpatient basis)

Criteria for Inclusion:

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

1. Healthy, adult, male or female, 18 - 55 years of age, inclusive, at screening.
2. Continuous non-smoker who has not used nicotine-containing products for at least 18 years prior to the first dosing and throughout the study, based on subject self-reporting.
3. Body mass index (BMI) ≥ 18.0 and ≤ 32.0 kg/m², 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 within the upper limit of normal at screening and at first check-in.
5. Normal baseline spirometry for FVC and FEV₁/FVC within 7 days prior to the first dosing based on the following normal FVC and FEV₁/FVC range:
 - a) 18 – 39 years of age: $\geq 80\%$
 - b) 40 – 55 years of age: $\geq 75\%$
6. 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.
7. Part 1 only: Female subjects of childbearing potential will be advised to remain sexually inactive or to keep the same birth control method for at least 60 days following the last TAK-788 dosing as indicated in [Appendix D](#).
8. Part 2 only: 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](#).
9. Part 1 only: Males subjects who are sexually active with a female partner of childbearing potential must use barrier contraception as indicated in [Appendix D](#) or abstain from sexual intercourse during the study until 94 days after the last TAK-788 dosing. Total abstinence (no sexual intercourse) may be considered an acceptable method of birth control if it agrees with his preferred and usual lifestyle.
10. Part 1 only: Male subjects must agree not to donate sperm from the first dosing until 94 days after the last TAK-788 dosing.
11. Part 2 only: Males subjects who are sexually active with a female partner of childbearing potential must use barrier contraception as indicated in [Appendix D](#) or abstain from sexual intercourse during the study until 30 days after the last TAK-788 dosing. Total abstinence (no sexual intercourse) may be considered an acceptable method of birth control if it agrees with his preferred and usual lifestyle.
12. Part 2 only: Male subjects must agree not to donate sperm from the first dosing until 30 days after the last TAK-788 dosing.

13. 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 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 chronic lung disease.
7. History or presence of an acute lung infection, within 3 months of screening.
8. Part 1 only: History or presence of any of the following, deemed clinically significant by the Investigator or designee, and as confirmed by the Sponsor:
 - Ventricular dysfunction or risk factors for Torsades de Pointes (e.g., heart failure, cardiomyopathy, family history of Long QT Syndrome);
 - Uncorrected hypokalemia (potassium levels <3.7) and/or hypomagnesemia (magnesium levels <1.9);
 - Myasthenia gravis.
9. Female subjects with a positive pregnancy test or who are lactating.
10. Positive urine drug or alcohol results at screening or first check-in.
11. Positive results at screening for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C virus (HCV).
12. Seated blood pressure is less than 90/40 mmHg or greater than 140/90 mmHg at screening.
13. Seated heart rate is lower than 40 bpm or higher than 99 bpm at screening.
14. 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.
15. Estimated creatinine clearance <90 mL/min at screening.
16. 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.
 - Any drugs known to be inhibitors or inducers of CYP3A 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 (e.g., Flockhart TableTM) will be consulted to confirm lack of PK/pharmacodynamics interaction with study drugs.
17. 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.
18. Donation of blood or significant blood loss within 56 days prior to the first dosing.
19. Plasma donation within 7 days prior to the first dosing.
20. Participation in another clinical study within 30 days prior to the first dosing. The 30-day window will be derived

from the date of the last blood collection or dosing, whichever is later, in the previous study to Period 1 Day 1 of the current study.

Main Criteria for Evaluation and Analyses:

The following PK parameters will be analyzed for TAK-788 and its active metabolites, AP32960 and AP32914, when administered alone and when coadministered with itraconazole (Part 1) or with rifampin (Part 2):

Pharmacokinetic Endpoints

The primary endpoints of the study are:

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

Additional Endpoints

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

- Terminal disposition phase half-life ($t_{1/2}$),
- Terminal disposition phase rate constant (λ_z),
- Apparent clearance after extravascular administration (CL/F) for TAK-788 only,
- Apparent volume of distribution during the terminal disposition phase after extravascular administration (V_z/F) for TAK-788 only.

Safety Endpoints

Safety will be assessed by summarizing the incidence of treatment emergent AEs (TEAEs), clinical laboratory values, physical examinations, 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 metabolites (AP32960 and AP32914) will be calculated as described in Section 11.0, and outlined in the SAP.

A linear mixed-effects model will be used for the analysis on the ln transformed C_{max} and AUC_{∞} (AUC_{last} or AUC_t if AUC_{∞} is not available) for TAK-788 and ln transformed combined molar C_{max} and AUC_{∞} for TAK-788, AP32960, and AP32914. The model will include treatment as a fixed-effect and subject as a random-effect. Each model will include calculation of least squares means (LSMs) as well as the difference between treatment LSMs.

Geometric mean ratios and 90% confidence intervals, 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} and AUC_{∞} (AUC_{last} or AUC_t if AUC_{∞} is not available) for TAK-788 as well as the combined molar C_{max} and AUC_{∞} of TAK-788, AP32960, and AP32914. These ratios will be expressed as a percentage of the following comparisons:

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

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

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

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

2.0 STUDY SCHEMATIC

Part 1

Screening	Period 1				Period 2						Follow-up
	Check-in and Predose Assessments	TAK-788 Dosing and Study Assessments	PK sampling and Study Assessments		Itraconazole Dosing and Study Assessments	Itraconazole Dosing and Study Assessments	Coadministration on (Itraconazole and TAK-788) and Study Assessments	Itraconazole dosing and PK sampling and Study Assessments		PK sampling and Study Assessments	
Within 28 days prior to first dosing	Day -1	Day 1	Day 2-4	Day 5-8 ^a	Day 1 ^{a-3}	Day 4 ^b	Day 5	Day 6-8	Day 9-14	Day 15	30 days ± 2 following last TAK-788 dose
Outpatient Visit	Confinement ^c			Outpatient Visit	Confinement ^d			Outpatient Visit			

^a Period 2 Day 1 will also be considered Period 1 Day 8. There is a washout of 7 days between TAK-788 dose in Period 1 and first itraconazole dosing in Period 2.

^b Subjects will be confined to the clinical research unit in the morning at the time indicated by the staff.

^c Subjects will start the confinement on Day -1 and be released from confinement after the 72-hour study assessments (Period 1 Day 4) are complete and will return to the study site for subsequent study procedures as per the scheduled of study procedures (Section 9.0). At all times, subject may be required to remain at the clinical research unit for longer at the discretion of the Investigator or designee.

^d Subjects will start the confinement on the morning of Day 4 and be released from confinement after the 72-hour study assessments (Period 2 Day 8) are complete and will return to the study site for subsequent dosing and/or study procedures as per the scheduled of study procedures (Section 9.0). At all times, subject may be required to remain at the clinical research unit for longer at the discretion of the Investigator or designee.

Part 2

Screening	Period 1				Period 2						Follow-up
	Check-in and Predose Assessments	TAK-788 Dosing and Study Assessments	PK sampling and Study Assessments		Rifampin Dosing and Study Assessments	Rifampin Dosing and Study Assessments	Coadministration (Rifampin and TAK-788) and Study Assessments	Rifampin dosing and PK sampling and Study Assessments		PK sampling and Study Assessments	
Within 28 days prior to first dosing	Day -1	Day 1	Day 2-4	Day 5-8 ^a	Day 1 ^{a-5}	Day 6 ^b	Day 7	Day 8-10	Day 11-13	Day 14	30 days ± 2 following last TAK-788 dose
Outpatient Visit	Confinement ^c			Outpatient Visit		Confinement ^d			Outpatient Visit		

^a Period 2 Day 1 will also be considered Period 1 Day 8. There is a washout of 7 days between TAK-788 dose in Period 1 and first rifampin dosing in Period 2.

^b Subjects will be confined to the clinical research unit in the morning at the time indicated by the staff.

^c Subjects will start the confinement on Day -1 and be released from confinement after the 72-hour study assessments (Period 1 Day 4) are complete and will return to the study site for subsequent study procedures as per the scheduled of study procedures (Section 9.0). At all times, subject may be required to remain at the clinical research unit for longer at the discretion of the Investigator or designee.

^d Subjects will start the confinement on the morning of Day 6 and be released from confinement after the 72-hour study assessments (Period 2 Day 10) are complete and will return to the study site for subsequent dosing and/or study procedures as per the scheduled of study procedures (Section 9.0). At all times, subject may be required to remain at the clinical research unit for longer at the discretion of the Investigator or designee.

3.0 SCHEDULE OF STUDY PROCEDURES

Part 1

Study Procedures ^a	S ^b	Study Days in Period 1 ^c – PART 1															
		Days in Period →	-1	1					2		3	4	5	6	8		
		Hours →	C-1 ^d	0	0.5	1	2	4	6	8	12	24	36	48	72	96	120
Administrative Procedures																	
Informed Consent	X																
Inclusion/Exclusion Criteria	X	X															
Medical History	X																
Safety Evaluations																	
Full Physical Examination ^f	X																
Height	X																
Weight	X	X ^g															
12-Lead Safety ECG	X		X ^j					X				X					
Vital Signs (HR and BP)	X		X ^j					X			X	X					
Vital Signs (RR and T)	X																
Pulmonary function test ^h	X																
Hem, Serum Chem ⁱ , and UA	X	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							
ConMeds Monitoring										X							
Study Drug Administration / PK																	
TAK-788 Administration			X														
Blood for TAK-788 and metabolites (AP32960 and AP32914) PK			X ^k	X	X	X	X	X	X	X	X	X	X	X	X	X	X ^k
Other Procedures																	
Confinement in the CRU ^l									X								
Visit and Return Visits	X														X	X	X

Study Procedures ^a	Study Days in Period 2 ^c – PART 1																				ET ^m	FU ⁿ				
	Days in Period →	1 ^c	2 - 3	4 ^d	5								6		7	8	9	10	11	12			13	14	15	
Hours →	0	0	0	0	0.5	1	2	4	6	8	12	24	36	48	72	96	120	144	168	192	216	240				
Safety Evaluations																										
12-Lead Safety ECG	X ^k			X ^k				X				X ^k											X	X		
Vital Signs (HR and BP)	X ^k			X ^k				X			X	X ^k											X	X		
Vital Signs (RR and T)																							X	X		
Hem, Serum Chem ^l , and UA	X ^k		X ^k											X ^k									X	X		
Serum Pregnancy Test (♀ only)			X ^k																							
Urine Drug and Alcohol Screen			X ^k																							
AE Monitoring																						X				
ConMeds Monitoring																						X				
Study Drug Administration / PK																										
Itraconazole QD Administration	X	X	X	X								X		X	X	X	X	X	X	X	X					
TAK-788 Administration				X																						
Blood for TAK-788 and metabolites (AP32960 and AP32914) PK	X ^k			X ^k	X	X	X	X	X	X	X	X ^k	X	X ^k	X ^k	X ^k	X ^k		X ^k	X ^k			X			
Other Procedures																										
Confinement in the CRU ^l																						X				
Return Visits	X	X														X	X	X	X	X	X	X	X			

Footnotes are on the following page.

Property of Takeda: For non-commercial use only and subject to the applicable Terms of Use

^a For details on Procedures, refer to Section 9.0.

^b Within 28 days prior to the first study drug administration.

^c There will be a washout period of 7 days between the dose of TAK-788 in Period 1 and the first dose of itraconazole in Period 2. As per site preference in agreement with Sponsor, subjects may be confined throughout the washout period and/or for the whole study. If the CRU decides to confine the subjects throughout the study, the site will still perform safety events scheduled at check-in.

^d Subjects will be admitted to the CRU on Day -1 of Period 1 and in the morning of Day 4 of Period 2, at the time indicated by the CRU.

^e Day 8 of Period 1 is the same as Day 1 of Period 2. Study procedures will only be performed once.

^f Symptom-driven physical examination may be performed, at the Investigator's or designee's discretion.

^g If the screening assessment was conducted within 4-7 days prior to dosing (Day 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.

^h To be conducted within 7 days prior to first dosing.

ⁱ 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 is taken.

^j To be performed within 24 hours prior to dosing.

^k Prior to dosing.

^l As per site preference in agreement with Sponsor, subjects may be confined throughout the washout period and/or for the whole study.

^m To be performed prior to early termination from the study.

ⁿ The CRU will contact all subjects (including subjects who terminate the study early) 30 ±2 days after the last TAK-788 dose to determine if any adverse events 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, ET = early termination, FSH = Follicle-stimulating hormone, FU = Follow-up, Hem = Hematology, HIV = Human immunodeficiency virus, HR = Heart rate, PK = Pharmacokinetics, PMP = Postmenopausal, RR = Respiratory rate, S = Screening, T = Temperature, UA = Urinalysis.

Part 2

Study Procedures ^a	S ^b	Study Days in Period 1 ^c – PART 2																
		-1	1								2		3	4	5	6	8	
		C-I ^d	0	0.5	1	2	4	6	8	12	24	36	48	72	96	120	168 ^e	
Administrative Procedures																		
Informed Consent	X																	
Inclusion/Exclusion Criteria	X	X																
Medical History	X																	
Safety Evaluations																		
Full Physical Examination ^f	X																	
Height	X																	
Weight	X	X ^g																
12-Lead Safety ECG	X		X ^j					X				X						
Vital Signs (HR and BP)	X		X ^j					X			X	X						
Vital Signs (RR and T)	X																	
Pulmonary function test ^h	X																	
Hem, Serum Chem ⁱ , and UA	X	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								
ConMeds Monitoring										X								
Study Drug Administration / PK																		
TAK-788 Administration			X															
Blood for TAK-788 and metabolites PK			X ^k	X	X	X	X	X	X	X	X	X	X	X	X	X	X ^k	
Other Procedures																		
Confinement in the CRU ^l										X								
Visit and Return Visits	X															X	X	X

Study Procedures ^a	Study Days in Period 2 ^c – PART 2																	ET ^m	FU ⁿ			
	Days in Period →	1 ^c	2 - 5	6 ^d	7							8		9	10	11	12			13	14	
	Hours →	0	0	0	0	0.5	1	2	4	6	8	12	24	36	48	72	96			120	144	168
Safety Evaluations																						
12-Lead Safety ECG	X ^k			X ^k				X				X ^k								X	X	
Vital Signs (HR and BP)	X ^k			X ^k				X			X	X ^k								X	X	
Vital Signs (RR and T)																				X	X	
Hem, Serum Chem ^l , and UA	X ^k		X ^k												X ^k					X	X	
Serum Pregnancy Test (♀ only)			X ^k																			
Urine Drug and Alcohol Screen			X ^k																			
AE Monitoring												X									X	X
ConMeds Monitoring												X									X	
Study Drug Administration / PK																						
Rifampin Administration	X	X	X	X									X		X	X	X	X	X			
TAK-788 Administration				X																		
Blood for TAK-788 and metabolites (AP32960 and AP32914) PK	X ^k			X ^k	X	X	X	X	X	X	X	X ^k	X	X ^k	X ^k	X ^k	X ^k	X ^k		X		
Other Procedures																						
Confinement in the CRU ^l																						
Return Visits	X	X															X	X	X	X		

Footnotes are on the following page.

^a For details on Procedures, refer to Section 9.0.

^b Within 28 days prior to the first study drug administration.

^c There will be a washout period of 7 days between the dose of TAK-788 in Period 1 and the first dose of rifampin in Period 2. As per site preference in agreement with Sponsor, subjects may be confined throughout the washout period and/or for the whole study. If the CRU decides to confine the subjects throughout the study, the site will still perform safety events scheduled at check-in.

^d Subjects will be admitted to the CRU on Day -1 of Period 1 and in the morning of Day 6 of Period 2, at the time indicated by the CRU.

^e Day 8 of Period 1 is the same as Day 1 of Period 2. Study procedures will only be performed once.

^f Symptom-driven- physical examination may be performed, at the Investigator's or designee's discretion.

^g If the screening assessment was conducted within 4-7 days prior to dosing (Day 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

^h To be conducted within 7 days prior to first dosing.

ⁱ 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 is taken.

^j To be performed within 24 hours prior to dosing.

^k Prior to dosing.

^l As per site preference in agreement with Sponsor, subjects may be confined throughout the washout period and/or for the whole study.

^m To be performed prior to early termination from the study.

ⁿ The CRU will contact all subjects (including subjects who terminate the study early) 30 ±2 days after the last TAK-788 dose to determine if any adverse events 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, ET = Early termination, FSH = Follicle-stimulating hormone, FU = Follow-up, Hem = Hematology, HIV = Human immunodeficiency virus, HR = Heart rate, PK = Pharmacokinetics, PMP = Postmenopausal, R = Respiratory rate, S = Screening, T = Temperature, UA = Urinalysis.

Table 3.a Pharmacokinetic Plasma Concentration Sampling Schedule (Part 1)

Study Day	Sample Collection Time	Time (Relative to Dosing) h: min	Plasma Concentrations of TAK-788, AP32960, and AP32914
Period 1 Day 1	0 h (predose)	00:00 (predose)	✓
	0.5 h	00:30 (±5 min)	✓
	1 h	01:00 (±10 min)	✓
	2 h	02:00 (±10 min)	✓
	4 h	04:00 (±10 min)	✓
	6 h	06:00 (±20 min)	✓
	8 h	08:00 (±20 min)	✓
	12 h	12:00 (±20 min)	✓
2	0 h	24:00 (±30 min)	✓
	12 h	36:00 (±30 min)	✓
3	0 h	48:00 (±30 min)	✓
4	0 h	72:00 (±60 min)	✓
5	0 h	96:00 (±60 min)	✓
6	0 h	120:00 (±60 min)	✓
8	0 h	168:00 (- 60 min) Drawn prior to dosing of next period	✓
Period 2 Day 5	0 h	00:00 (predose)	✓
	0.5 h	00:30 (±5 min)	✓
	1 h	01:00 (±10 min)	✓
	2 h	02:00 (±10 min)	✓
	4 h	04:00 (±10 min)	✓
	6 h	06:00 (±20 min)	✓
	8 h	08:00 (±20 min)	✓
	12 h	12:00 (±20 min)	✓
6	0 h	24:00 (±30 min)	✓
	12 h	36:00 (±30 min)	✓
7	0 h	48:00 (±30 min)	✓
8	0 h	72:00 (±60 min)	✓
9	0 h	96:00 (±60 min)	✓
10	0 h	120:00 (±60 min)	✓
12	0 h	168:00:00 (±60 min)	✓
13	0 h	192:00 (±60 min)	✓
15	0 h	240:00 (±60 min)	✓
Number of samples per subject:			32

Table 3.b Pharmacokinetic Plasma Concentration Sampling Schedule (Part 2)

Study Day	Sample Collection Time	Time (Relative to Dosing) h: min	Plasma Concentrations of TAK-788, AP32960, and AP32914
Period 1 Day 1	0 h (predose)	00:00 (predose)	✓
	0.5 h	00:30 (±5 min)	✓
	1 h	01:00 (±10 min)	✓
	2 h	02:00 (±10 min)	✓
	4 h	04:00 (±10 min)	✓
	6 h	06:00 (±20 min)	✓
	8 h	08:00 (±20 min)	✓
	12 h	12:00 (±20 min)	✓
2	0 h	24:00 (±30 min)	✓
	12 h	36:00 (±30 min)	✓
3	0 h	48:00 (±30 min)	✓
4	0 h	72:00 (±60 min)	✓
5	0 h	96:00 (±60 min)	✓
6	0 h	120:00 (±60 min)	✓
8	0 h	168:00 (-60 min) drawn prior to dosing of next period	✓
Period 2, Day 7	0 h	00:00 (predose)	✓
	0.5 h	00:30 (±5 min)	✓
	1 h	01:00 (±10 min)	✓
	2 h	02:00 (±10 min)	✓
	4 h	04:00 (±10 min)	✓
	6 h	06:00 (±20 min)	✓
	8 h	08:00 (±20 min)	✓
	12 h	12:00 (±20 min)	✓
8	0 h	24:00 (±30 min)	✓
	12 h	36:00 (±30 min)	✓
9	0 h	48:00 (±30 min)	✓
10	0 h	72:00 (±60 min)	✓
11	0 h	96:00 (±60 min)	✓
12	0 h	120:00 (±60 min)	✓
14	0 h	168:00 (±60 min)	✓
Number of samples per subject:			30

4.0 INTRODUCTION

4.1 Background

4.1.1 TAK-788

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.

Non-Clinical Pharmacokinetics

CCI



Clinical Pharmacokinetics

CCI



CCI



Refer to the Investigator's Brochure (IB) for detailed background information and safety data on TAK-788 (IB Edition 3, 04-Jan-2019).

4.1.2 Itraconazole

Itraconazole, a synthetic triazole-derivative, is a broad spectrum antifungal agent which exerts its pharmacological action by inhibiting cytochrome P450s (CYPs)-dependent enzymes resulting in blocked ergosterol synthesis. It is indicated for the treatment of oropharyngeal and esophageal candidiasis. For patients with oropharyngeal candidiasis unresponsive/refractory to treatment with fluconazole tablets, the recommended dose is 100 mg (10 mL) twice a day. The recommended dosage of Sporanox[®] Oral Solution for esophageal candidiasis is 100 mg (10 mL) daily for a minimum treatment of 3 weeks. Treatment should continue for 2 weeks following resolution of symptoms. Doses up to 200 mg (20 mL) per day may be used based on medical judgment of the patient's response to therapy (Sporanox 2011).

Itraconazole is highly protein bound (>99%) and penetrates extensively into human tissue, but it has limited penetration into the cerebral spinal fluid. Itraconazole is extensively metabolized, predominantly by the CYP3A4 enzymes, and is known to undergo enterohepatic recirculation. Hydroxyitraconazole is the major metabolite and shows antifungal activity equal to that of the parent (Brüggemann et al. 2009).

Metabolism of itraconazole is saturable and might explain the more than proportional increase in itraconazole plasma concentration with increasing single doses and after chronic dosing.

Following multiple oral dose administration of itraconazole capsules, peak concentrations are observed at approximately 4.5 hours, with an elimination half-life of about 64 hours (compared to about 21 hours following a single oral dose). Metabolites of itraconazole are excreted into the urine (40% of metabolites) and bile (55% of metabolites) (Brüggemann et al. 2009). Itraconazole is a substrate for and an inhibitor of CYP3A4 and an inhibitor of P-gp (Sporanox 2011).

Itraconazole will be used as a strong CYP3A inhibitor in this study, as it is listed as a strong index inhibitor of CYP3A4 in the recommendations of the FDA guidance Clinical Drug Interaction Studies - Study Design, Data Analysis, and Clinical Implications Guidance for Industry (FDA 2017). An oral solution of itraconazole showed higher oral absorption than an oral capsule formulation and dosing on an empty stomach will ensure the greatest oral absorption as determined by pharmacokinetic profiles (Willems et al. 2001). The maximal inhibition of CYP3A enzymes is visible with doses of 200 mg or 400 mg (Peng et al. 2011). However, 200 mg was chosen to reduce subject exposure to unnecessary drug. Oral administration of 100–200 mg per day of itraconazole with a 3-day lead-in have shown adequately strong CYP3A4 inhibitor in several itraconazole DDI studies (Liu et al. 2016).

4.1.3 Rifampin

Rifampin is a semi-synthetic antibiotic derivative of rifamycin SV which acts by inhibiting deoxyribonucleic acid (DNA)-dependent ribonucleic acid (RNA) polymerase activity in susceptible species of *Mycobacterium tuberculosis*. Its activity does not impede mammalian enzyme RNA polymerase, therefore it is an effective treatment for both tuberculosis and meningococcus infections. Rifampin can be administered by oral route or by an IV infusion of 30 minutes to 3 hours. The IV doses are the same as oral doses (Rifadin 2013).

Rifampin is readily absorbed from the gastrointestinal tract and is considered to be a highly variable drug in healthy adults and pediatric populations. A single oral dose of 600 mg of rifampin in healthy adults has an average peak serum concentration of 7 µg/mL ranging from 4 to 32 µg/mL with an average half-life of 3.35 ± 0.66 hours. Gastric absorption with food reduces the bioavailability of rifampin by about 30%. Rifampin is widely distributed throughout the body and can reach effective concentrations in various organs and cerebrospinal fluid. Rifampin is 80% protein bound in the blood while the remaining unbound fraction is not ionized and can readily diffuse into tissues (Rifadin 2013).

Rifampin is rapidly eliminated in the bile and undergoes enterohepatic recirculation; during this process, gradual deacetylation of the drug occurs so that nearly all the drug in the bile is in this form 6 hours postdose. The deacetylated form of rifampin is active and exhibits antibacterial properties. Moreover, intestinal reabsorption is reduced by deacetylation thus promoting drug elimination.

Rifampin will be used as a strong CYP3A inducer as per the recommended in the FDA guidance Clinical Drug Interaction Studies - Study Design, Data Analysis, and Clinical Implications Guidance for Industry (FDA 2017). Rifampin dose of 600 mg QD and lead-in doses of 5 – 7 days have shown to achieve the maximal induction of CYP3A4 in humans for drug interaction studies (Duus et al. 2018, Upreti et al. 2011, Srinivas 2016). Furthermore, the level of CYP3A4 activity in modeling simulations becomes stable with 6-day dosing. Since most of the clinical DDI evaluations were carried out for approximately 5 half-life of victim drug, dosing of rifampin will continue after coadministration with a victim drug for sustainable induction of CYP3A enzymes (Duus et al. 2018).

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 (not targeted by any approved TKI), 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 and TAK-788-1002, a total of 64 subjects) in healthy subjects in the single dose range of 20 – 160 mg.

CCI



The purpose of this study is to assess the effect of co-administration of the strong CYP3A inhibitor itraconazole or the strong CYP3A inducer rifampin on the pharmacokinetics of TAK-788 to inform strategies for management of potential drug-drug interactions with strong CYP3A inhibitors or inducers in future clinical studies of TAK-788.

Itraconazole is a well characterized, competitive, strong inhibitor of CYP3A4. An oral solution of itraconazole is used in the current study instead of the capsule formulation and is administered on an empty stomach to ensure the highest oral absorption under fasting conditions and minimize gastrointestinal tract irritation during fasting. The maximal inhibition of CYP3A enzymes will be achieved with repeated doses of 200 mg itraconazole. The 4 days of lead-in administration of itraconazole ensure that CYP3A4 is maximally inhibited prior to coadministration with TAK-788.

Rifampin will be used as a strong CYP3A inducer in this study per the recommendations of the FDA guidance Clinical Drug Interaction Studies - Study Design, Data Analysis, and Clinical Implications Guidance for Industry (FDA 2017). Rifampin was selected as a 600 mg dose QD with 7 days of lead-in dosing prior to the concomitantly administered with TAK-788 in this study.

Because the half-life of AP32960 was approximately 28 hours, the longest among TAK-788 and its active metabolites, oral administration of rifampin will continue for 6 days after coadministration of TAK-788 for sustainable induction of CYP3A enzymes.

Because TAK-788 is mainly metabolized by CYP3A, it is anticipated that TAK-788 exposure will likely be increased significantly when TAK-788 is concomitantly administered with itraconazole. The itraconazole drug-drug interaction assessment portion of this study (Part 1) will consist of two

cohorts. As the magnitude of the effect of strong CYP3A inhibition on the PK of TAK-788 and its active metabolites (AP32960 and AP32914) is currently unknown, the planned dose of TAK-788 (with itraconazole) for Cohort 1 of this study will be 20 mg TAK-788, which is 8 times below the highest single dose of 160 mg evaluated in healthy subjects. PK data will be reviewed after dosing a cohort of 4 subjects in order to confirm the dose for the second cohort. TAK-788 dose in the second cohort may be modified (based on data from Cohort 1) to select a dose that would be anticipated during co-administration with itraconazole to achieve exposures similar to the previously observed exposures at the 160 mg single dose alone in healthy subjects. The dose of TAK-788 selected for the drug-drug interaction study with rifampin (Part 2) will be 160 mg (recommended Phase 2 dose).

Similar to most oncology drugs, $\leq 25\%$ loss in TAK-788 exposure when concomitantly administered with a CYP inducer and $\leq 30\%$ increase in exposure when concomitantly administered with a CYP inhibitor can be inferred not to be clinically relevant to efficacy and safety when viewed in context of moderate TAK-788 PK variability (43% CV for AUC in cancer patients) (Teo et al. 2014, IB 2019).

4.3 Benefit/Risk Profile

The clinical safety data available as of 14 September 2018 indicated no particular safety findings that are unique to TAK-788 compared with other approved EGFR TKIs. The most common treatment-emergent AEs (TEAE) occurring in $\geq 20\%$ of patients by preferred term overall were diarrhea 79 (78.2%), nausea 40 (39.6%), decreased appetite 31 (30.7%), rash 30 (29.7%), vomiting 24 (23.8%) and fatigue 23 (22.8%). The most common TEAE occurring in $\geq 20\%$ of patients overall by preferred term was diarrhea 69 (68.3%), nausea 30 (29.7%), rash 26 (25.7%), and decreased appetite 21 (20.8%) which are commonly observed with other EGFR TKIs (IB 2019).

There will be no direct health benefit for study participants from receipt of 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.

The risk of dosing itraconazole and rifampin in combination with TAK-788 is unknown in this study. However, the risk of dose of itraconazole plus TAK-788 administered in Part 1 and the dose of rifampin plus TAK-788 administered in Part 2 are anticipated to be similar to those previously reported for each of the individual drugs as reported in the TAK-788 IB, and in the full prescribing information for Sporanox[®] and Rifadin[®] since itraconazole and rifampin are administered according to the dosing recommendations found therein.

The inclusion and exclusion criteria, screening, and safety monitoring practices employed by this protocol (i.e., 12 lead ECG, vital signs, clinical laboratory tests, AE questioning, PFT (spirometry), 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

Part 1: To characterize the effect of itraconazole, a strong CYP3A inhibitor, on the single-dose PK of TAK-788 and its active metabolites (AP32960 and AP32914) in healthy adult subjects.

Part 2: To characterize the effect of rifampin, a strong CYP3A inducer, on the single-dose PK of TAK-788 and its active metabolites (AP32960 and AP32914) in healthy adult subjects.

5.2.2 Study Exploratory Objective

Part 1 and Part 2: To assess the safety data of TAK-788 following single oral dose with/without strong CYP3A inhibitor or inducer in healthy adult subjects.

5.3 Endpoints

5.3.1 Primary Endpoint

The primary endpoints of the study are:

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

5.3.2 Exploratory Endpoints

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

Part 1: TAK-788 assessment with Itraconazole

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

This study part will comprise of a screening period, 2 treatment periods and a follow-up phone call in up to 16 healthy subjects. Dose administration and PK collection scheme for the treatment period is outlined in the [Table 6.a](#) below.

Table 6.a Part 1 TAK-788 assessment with Itraconazole

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

* Since the washout period is 7 days the timing of the last PK blood draw of Period 1 will occur within 60 minutes prior to the first dose of itraconazole on Period 2 Day 1; only one PK sample will be taken.

Abbreviation: PK=Pharmacokinetics; PO=per oral; QD=once daily

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

In Period 2, subjects will receive 200 mg itraconazole QD alone as an oral solution on an empty stomach (no food from at least 1 hour prior until at least 2 hours after dosing). Subjects will be admitted to the CRU on Period 2 Day 4. In the morning of Period 2 Day 5, subjects will receive

200 mg itraconazole together with 20 mg oral TAK-788 or a TBD oral dose of TAK-788 (fasting). A standardized meal will be provided at least 4 hours postdose. Subjects will be furloughed from the CRU after the 72-hour PK sample is collected in the morning of Period 2 Day 8. There will be outpatient visits to the CRU for dosing itraconazole and/or PK sampling from Day 1 to Day 3 and Day 9 to Day 14. A final post-treatment follow-up and last PK sampling (Table 3.a) will occur at 240 hours post-Day 5 TAK-788 dose (Period 2 Day 15).

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

Part 2: TAK-788 assessment with Rifampin

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

Table 6.b Part 2 TAK-788 assessment with Rifampin

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

*Since the washout period is 7 days the timing of the last PK blood draw of Period 1 will occur within 60 minutes prior to the first dose of rifampin on Period 2 Day 1; only one PK sample will be taken.

Abbreviation: PK=Pharmacokinetics; PO=per oral; QD=once daily.

On Period 1 Day 1, a different group of subjects from Part 1 will receive a single 160 mg oral dose of TAK-788 as capsules (fasting). A standardized meal will be provided at least 4 hours postdose. Subjects will remain in the CRU until the morning of Day 4 after the 72-hour PK sample is collected. Additional PK samples (Table 3.b) will be taken as an outpatient up to 168 hours postdose (Period 1 Day 8, which is the same as Period 2 Day 1).

In Period 2, subjects will receive 600 mg rifampin QD alone as capsules (fasting). Subjects will be admitted to the CRU on Day 6. In the morning of Day 7, subjects will receive 160 mg oral TAK-788 together with 600 mg rifampin (fasting). A standardized meal will be provided at least 4 hours postdose. Subjects will be furloughed from the CRU after the 72-hour PK sample is collected in the morning of Day 10. There will be outpatient visits to the CRU for dosing rifampin

and/or PK sampling from Day 1 to Day 5 and Day 11 to Day 13. A final post-treatment follow-up and last PK sampling will occur at 168 hours post Day 7 dose (Day 14).

Part 1 and Part 2:

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

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

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

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

The planned dose levels of TAK-788, itraconazole, and rifampin to be evaluated are outlined in [Table 6.c](#).

Table 6.c Planned Doses of TAK-788, Itraconazole (Part 1), and Rifampin (Part 2)

	Cohort	Days	Dose	Route of Administration
Part 1				
Cohort 1				
Period 1				
TAK-788	1	1	20 mg	oral capsule
Period 2				
Itraconazole	1	1-14	200 mg	oral solution
Period 2				
TAK-788	1	5	20 mg	oral capsule
Cohort 2				
Period 1				
TAK-788	2	1	TBD	oral capsule
Period 2				
Itraconazole	2	1-14	200 mg	oral solution
Period 2				
TAK-788	2	5	TBD	oral capsule
Part 2				
Period 1				
TAK-788	NA	1	160 mg	oral capsule
Period 2				
Rifampin	NA	1-13	600 mg	oral capsule
Period 2				
TAK-788	NA	7	160 mg	oral capsule

NA = not applicable.

6.2 Dose Escalation

Part 1 will be conducted in 2 cohorts: Cohort 1 will enroll 4 subjects and will assess whether the 20 mg dose of TAK-788 is an appropriate dose for the TAK-788/itraconazole drug-drug interaction study (see Section 4.2); depending on the PK results, Cohort 2 will either continue to enroll 8 more subjects at this same dose level (20 mg) or enroll 12 more subjects at a revised TAK-788 dose level (TBD dose TAK-788). Other than the dose of TAK-788, the study design will be exactly the same for each cohort.

A sequential dosing design was selected to dose subjects in 2 cohorts. The first cohort of 4 subjects will be studied until the end of Period 2 Day 15 and PK will be reviewed. The dose may be maintained for Cohort 2 or raised to a maximum of 160 mg while ensuring the drug interaction between TAK-788 and itraconazole does not exceed the exposure of TAK-788 levels previously seen in healthy adult subjects. The dose level for TAK-788 in Cohort 2 will be a dose anticipated during coadministration with itraconazole to achieve exposures similar to the previously observed exposures at the 160 mg single dose alone in healthy subjects.

There will be no dose modifications for Part 2.

6.3 Rationale for Study Design, Dose, and Endpoints

6.3.1 Rationale of Study Design and Dose

Part 1:

Because TAK-788 is mainly metabolized by CYP3A, it is anticipated that TAK-788 exposure will likely be increased significantly when TAK-788 is concomitantly administered with itraconazole. The itraconazole drug-drug interaction assessment portion of this study (Part 1) will consist of two cohorts. As the magnitude of the effect of strong CYP3A inhibition on the PK of TAK-788 and its active metabolites (AP32960 and AP32914) is currently unknown, the planned dose of TAK-788 (with itraconazole) for Cohort 1 of this study will be 20 mg TAK-788, which is 8 times below the highest single dose of 160 mg evaluated in healthy subjects. PK data will be reviewed after dosing a cohort of 4 subjects in order to confirm the dose for the second cohort. TAK-788 dose in the second cohort may be modified (based on data from Cohort 1) to select a dose that would be anticipated during co-administration with itraconazole to achieve exposures similar to the previously observed exposures at the 160 mg single dose alone in healthy subjects. The dose of TAK-788 selected for the drug-drug interaction study with rifampin (Part 2) will be 160 mg (recommended Phase 2 dose).

In this first study part, subjects will be dosed with TAK-788 alone and then in combination with itraconazole after 4 consecutive days of dosing itraconazole alone. It has been well established in the literature that itraconazole is a strong CYP3A inhibitor and that dosing 200 mg of itraconazole for 3 to 5 days to achieve maximum CYP3A inhibition in order to detect a drug-drug interaction [Varis et al. 2000, Yoshizato et al. 2012]. Dosing of itraconazole after Day 5 until the end of the PK sampling time will ensure continued inhibition of CYP3A. [Varis_2000](#) [Yoshizato_2012](#)

No clinically significant drug-drug interaction may be conclusive if $\leq 30\%$ increase in exposure to TAK-788 or combined molar exposure to TAK-788, AP32960, and AP32914 will occur when concomitantly administered with a strong CYP3A inhibitor. A change of this magnitude may be inferred not to be clinically relevant to safety when viewed in the context of moderate TAK-788 PK variability (approximately 43% CV for AUC₂₄ in cancer patients).

Part 2:

In the second study part, subjects will be dosed with TAK-788 alone and then in combination with 600 mg rifampin after 6 consecutive days of dosing rifampin alone. It has been well established in the literature that rifampin has maximum CYP3A induction after 5 – 7 days of lead-in dosing [Duus et al. 2018, Upreti et al. 2011, Srinivas 2016]. A dose of 600 mg oral rifampin daily is used to achieve CYP3A induction in previous literature. Rifampin will continue to be administered until the end of the PK sampling time in Period 2 to maintain induction levels.

The dose of TAK-788 selected for the drug-drug interaction study with rifampin (Part 2) will be 160 mg (recommended Phase 2 dose). Since a reduction in exposure is anticipated the coadministration of these two study drugs should be well-tolerated.

A $\leq 25\%$ loss in TAK-788 exposure or combined molar exposure to TAK-788, AP32960, and AP32914 when concomitantly administered with a strong CYP inducer may be inferred not to be clinically relevant to efficacy when viewed in context of moderate TAK-788 PK variability (approximately 43% CV for AUC₂₄ in cancer patients).

Part 1 and Part 2:

On PK days, all study medication (TAK-788 alone, TAK-788 plus itraconazole, or TAK-788 plus rifampin) will be given after an overnight fast of at least 10 hours followed by at least a 4-hour fast after dosing to avoid interference of food. On other dosing days, itraconazole will be administered on an empty stomach (no food from at least 1-hour prior until at least 2 hours after dosing) and rifampin will be administered under fasted conditions.

6.3.2 Rationale for Endpoints

6.3.2.1 Pharmacokinetic Endpoints

The pharmacokinetic endpoints are standard for this type of study.

6.3.2.2 Safety Endpoints

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

6.3.3 Future Biomedical Research

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

No diseases/conditions, deoxyribonucleic acid, or ribonucleic acid 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.

6.3.4 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.

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

Part 1 only: The dose of TAK-788 for Cohort 2 will be determined based on the exposure data of Cohort 1.

For itraconazole in Part 1 and rifampin and TAK-788 in Part 2, 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 Section 7.3 and Section 7.4.

6.5 Study Beginning and End/Completion

6.5.1 Definition of Beginning of the Study

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

6.5.2 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)

6.5.3 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.

6.5.4 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.

6.5.5 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.

6.5.6 Criteria for Premature Termination or Suspension of a Site

Not applicable.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

7.1 Excluded Medications, Supplements, Dietary Products

Concomitant medications will be prohibited as listed in the exclusion criteria in Section 9.1.2.2. 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])	After First Dosing (Day 1) to Follow-Up
Alcohol	Prohibited from 48 hours prior to first dosing	Prohibited throughout the study.
Xanthine and/or caffeine	Prohibited from 24 hours prior to first dosing ^a	Prohibited throughout the study ^a .
Medications	See Sections 7.1 and 9.1.2.2	See Sections 7.1 and 9.1.2.2
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 e.g., 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.

7.2 Diet, Fluid, Activity

7.2.1 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.

On Period 1 Day 1 and Period 2 Day 5 (Part 1) or Period 1 Day 1 and Period 2 Day 7 (Part 2): subjects will fast overnight for at least 10 hours prior to each oral study drug administration and will continue to fast for at least 4 hours postdose.

On all other dosing days in Period 2 in Part 1 subjects will administer itraconazole on an empty stomach (no food from at least 1-hour prior until at least 2 hours after dosing). On all other dosing days in Period 2 in Part 2 subjects will administer rifampin after an overnight fast of at least 10 hours followed by at least a 4-hour fast after dosing to avoid interference of food.

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.

7.2.2 Activity

Subjects will remain ambulatory or seated upright for the first 4 hours postdose on Period 1 Day 1 (Part 1 and Part 2) and Period 2 Day 5 (Part 1) or Day 7 (Part 2), except when they are supine or semi-reclined for study procedures or AEs. There is no activity restriction on other dosing days.

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.

7.3 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.

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

7.4 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 7.3. 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.

7.5 Subject Replacement

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 10 PK-evaluable subjects complete in each part of study.

Property of Takeda: For non-commercial use only and subject to the applicable Terms of Use

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

8.1 Clinical Study Drug

8.1.1 TAK-788 Capsules

Part 1:

A single 20 mg TAK-788 capsule (1 x 20 mg TAK-788) or a dose up to 160 mg dose of 1 or more capsules of TAK-788 will be administered on Period 1 Day 1 and Period 2 Day 5 for Cohorts 1 and 2, respectively.

Part 2:

A single 160 mg dose of TAK-788 capsules (4 x 40 mg TAK-788) will be administered on Period 1 Day 1 and Period 2 Day 7.

Oral dose of TAK-788 drug product is a nonsterile, oral, capsule dosage form, supplied in a hard gelatin capsule of TAK-788 succinate salt. TAK-788 succinate salt is the active pharmaceutical ingredient. The drug product is supplied as a hard gelatin capsule shell. No other ingredients are included in the drug product.

TAK-788 (AP32788) 20 mg: Size 2, Swedish-orange, opaque, gelatin capsules, 30 capsules per bottle

TAK-788 (AP32788) 40 mg: Size 1, white, opaque, hard gelatin capsules 30 capsules per bottle

Capsules are packaged in: White, 60-cc, round HDPE bottles that are induction sealed with a silver foil, tamper evident seal. White, child-resistant caps with pictorial instructions.

Bottles will be labelled with a single panel label with a minimum of the following information:

- Protocol number.
- Contents.
- Storage conditions.
- Lot Number.
- A caution and warning statement.
- Sponsor information.

Investigational Product Shipment Receipt

- Open box, remove and stop the Temptale temperature recorder.
- Inspect the Temptale according to the Temptale instructions.
- Verify that the number, dosage, and lot numbers of the TAK-788 (AP32788) bottles match the packing list.
- Inspect the TAK-788 (AP32788) for any signs of damage.

- Verify the bottle ID numbers against the packing list and file the forms in the site files.
- Properly store the bottles of TAK-788 (AP32788). Store below 30°C (86°F).
 - Do not refrigerate or freeze.

If there are signs of damage, please do the following:

- Physically quarantine the shipment (quarantine according to the required storage).
- Email the packing list to Clinical Supply Chain at ClinicalSupply788@takeda.com to describe the observation.
- Clinical Supply Chain will confirm receipt of issue.
- Clinical Supply Chain will generate an email to the site on outcome.
- Any and all discrepancies are to be reported to TAKEDA Pharmaceuticals and XERIMIS without delay, they should be listed on the packing list.

8.1.2 Itraconazole Solution

Itraconazole will be supplied as a 10 mg/mL Sporanox[®] oral solution (brandname only).

Itraconazole 200 mg (approximately 20 mL) will be administered QD in Period 2 Part 1 at each dosing. Itraconazole will be stored and prepared according to the product label.

Subjects will be dosed with itraconazole and the dosing container will be rinsed with dosing water twice. The remaining volume of the 240 mL of dosing water will be ingested by the subject subsequently.

8.1.3 Rifampin Capsules

Rifampin will be supplied as 200 mg Rifadin[®] capsules (brandname only).

Rifampin 600 mg (3 x 200 mg capsules) will be dosed QD in Period 2 Part 2. Rifampin will be stored according to the product label.

8.1.4 Clinical Study Drug Labeling

TAK-788 capsule containers will be affixed with a clinical label in accordance with local regulatory requirements.

Itraconazole and rifampin will be affixed with a clinical label in accordance with local regulatory requirements.

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

8.1.5 Clinical Study Drug Inventory and Storage

TAK-788 capsules

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

- Store below 30°C (86°F).
- Do not refrigerate or freeze – Normal room temperature.
- Keep away from cold or heat sources.
- Keep out of reach and sight of children.

Rifampin capsules and Itraconazole solution

Celerion will provide sufficient quantities of the Sporanox[®] itraconazole oral solution and Rifadin[®] rifampin capsules to allow completion of the study. The same lot number will be used throughout the study. The lot numbers and expiration dates (where available) of the study drugs supplied will be recorded in the final report. Rifampin and itraconazole will be stored according to the product labels provided with the product.

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

8.1.6 Clinical Study Drug Blinding

This is an open-label study.

8.1.7 Randomization Code Creation and Storage

Not applicable

8.1.8 Clinical Study Blind Maintenance/Unblinding Procedure

Not applicable

8.1.9 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 (see Section 8.1.1). Any remaining supplies that were purchased by Celerion will be destroyed. 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 a fixed-sequence study. Within each study part/cohort, all subjects will receive the treatments as detailed in Section 8.1.

9.1.2 Inclusion and Exclusion

9.1.2.1 Inclusion Criteria

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

1. Healthy, adult, male or female, 18 - 55 years of age, inclusive, at screening.
2. Continuous non-smoker who has not used nicotine-containing products for at least 18 years prior to the first dosing and throughout the study, based on subject self-reporting.
3. BMI ≥ 18.0 and ≤ 32.0 kg/m², 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 within the upper limit of normal at screening and at first check-in.
5. Normal baseline spirometry for FVC and FEV₁/FVC within 7 days prior to the first dosing based on the following normal FVC and FEV₁/FVC range:
 - c) 18 – 39 years of age: $\geq 80\%$
 - d) 40 – 55 years of age: $\geq 75\%$

6. 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.
7. Part 1 only: Female subjects of childbearing potential will be advised to remain sexually inactive or to keep the same birth control method for at least 60 days following the last TAK-788 dosing as indicated in [Appendix D](#).
8. Part 2 only: 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](#).
9. Part 1 only: Males subjects who are sexually active with a female partner of childbearing potential must use barrier contraception as indicated in [Appendix D](#) or abstain from sexual intercourse during the study until 94 days after the last TAK-788 dosing. Total abstinence (no sexual intercourse) may be considered an acceptable method of birth control if it agrees with his preferred and usual lifestyle.
10. Part 1 only: Male subjects must agree not to donate sperm from the first dosing until 94 days after the last TAK-788 dosing.
11. Part 2 only: Males subjects who are sexually active with a female partner of childbearing potential must use barrier contraception as indicated in [Appendix D](#) or abstain from sexual intercourse during the study until 30 days after the last TAK-788 dosing. Total abstinence (no sexual intercourse) may be considered an acceptable method of birth control if it agrees with his preferred and usual lifestyle.
12. Part 2 only: Male subjects must agree not to donate sperm from the first dosing until 30 days after the last TAK-788 dosing.
13. Understands the study procedures in the ICF and be willing and able to comply with the protocol.

9.1.2.2 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 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 chronic lung disease.
7. Presence of an acute lung infection, within 3 months of screening.
8. Part 1 only: History or presence of any of the following, deemed clinically significant by the Investigator or designee, and as confirmed by the Sponsor:
 - Ventricular dysfunction or risk factors for Torsades de Pointes (e.g., heart failure, cardiomyopathy, family history of Long QT Syndrome);
 - Uncorrected hypokalemia (potassium levels <3.7) and/or hypomagnesemia (magnesium levels <1.9);
 - Myasthenia gravis.
9. Female subjects with a positive pregnancy test or who are lactating.
10. Positive urine drug or alcohol results at screening or first check-in.
11. Positive results at screening for HIV, HBsAg, or HCV.
12. Seated blood pressure is less than 90/40 mmHg or greater than 140/90 mmHg at screening.
13. Seated heart rate is lower than 40 bpm or higher than 99 bpm at screening.
14. 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.
15. Estimated creatinine clearance <90 mL/min at screening.
16. 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.
 - 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 (e.g., Flockhart Table™) will be consulted to confirm lack of PK/pharmacodynamics interaction with study drugs.

17. 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.
18. Donation of blood or significant blood loss within 56 days prior to the first dosing.
19. Plasma donation within 7 days prior to the first dosing.
20. Participation in another clinical study within 30 days prior to the first dosing. The 30-day window will be derived from the date of the last blood collection or dosing, whichever is later, in the previous study to Period 1 Day 1 of the current study.

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 7.1 and 9.1.2.2. 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 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 Table 6.a and Table 6.b).

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 (e.g., 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 Day 1 dosing for the predose time point. At all other predose time points blood pressure and heart rate will be measured within 2 hours prior to dosing. 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 Day 1 dosing Period 1 for the predose time point. At all other predose time points ECG will be measured within 2 hours prior to dosing. 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 measures will be taken at screening (within 7 days prior to first dosing) using a standard calibrated spirometer to determine the parameters detailed below. Spirometry may be repeated during the study in response to pulmonary symptoms at the discretion of the Investigator or designee.

- FEV₁ (forced expiratory volume);
- FVC (forced vital capacity);
- FEV₁/FVC.

9.2.7 Study Drug Administration

TAK-788 oral capsules, itraconazole oral solution, and rifampin capsules will be provided as described in Section 8.0.

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

Treatments A - F are described as:

Part 1:	
Treatment A	Cohort 1, Period 1: 20 mg TAK-788 (1 x 20 mg) administered at Hour 0 on Day 1 following an overnight fast.
Treatment B	Cohort 1, Period 2: 200 mg itraconazole oral solution administered every 24 hours for 14 consecutive days (within ± 1 hour of Day 1 dosing) with a single dose of 20 mg TAK-788 administered at Hour 0 on Day 5 following an overnight fast.
Treatment A or E	Cohort 2, Period 1: TBD TAK-788 administered at Hour 0 on Day 1 following an overnight fast.
Treatment B or F	Cohort 2, Period 2: 200 mg itraconazole oral solution administered every 24 hours for 14 consecutive days (within ± 1 hour of Day 1 dosing) with a single dose of TBD TAK-788 administered at Hour 0 on Day 5 following an overnight fast.
Part 2:	
Treatment C	Period 1: 160 mg TAK-788 (4 x 40 mg) capsule administered at Hour 0 on Day 1 following an overnight fast.
Treatment D	Period 2: 600 mg rifampin (3 x 200 mg capsules) administered every 24 hours for 13 consecutive days (within ± 1 hour of Day 1 dosing) with a single dose of 160 mg TAK-788 (4 x 40 mg) capsule administered at Hour 0 on Day 7 following an overnight fast.

TAK-788 will be administered following an overnight fast. When itraconazole is administered alone, it will be administered on an empty stomach with no food from at least 1 hour prior to dosing and for at least 2 hours after dosing. When rifampin is administered alone, it will be administered following an overnight fast.

All study drugs will be administered with approximately 240 mL of water or a total aqueous volume of approximately 240 mL for itraconazole oral solution plus water. The exact clock time of

oral dosing will be recorded. Itraconazole will be dosed with a container which will be rinsed twice with water ingested by subjects and the remaining dosing water will be ingested by subjects.

The pharmacy at the CRU will provide each dose of study drug(s) in individual unit dose containers and the oral solution dose in a glass bottle 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
Alkaline phosphatase	Glucose
Aspartate aminotransferase	Creatinine *
Alanine aminotransferase (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
HBsAg	– Opiates (includes morphine, heroin (diacetylmorphine), codeine, 6-acetylmorphine, dihydrocodeine, hydrocodone, thebaine, and, hydromorphone)
HCV (<i>if antibody positive, confirm RNA negative</i>)	
Urine alcohol screen	
Serum pregnancy test (for females only)	– Amphetamines
FSH (for postmenopausal females only)	– Barbiturates
	– Benzodiazepines
	– Cocaine
	– Cannabinoids

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 for plasma TAK-788 and metabolites AP32960 and AP32914 concentrations 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 _t	Area under the concentration-time curve from time 0 to time t
AUC _∞ :	The area under the concentration versus time curve, from time 0 extrapolated to infinity. AUC _∞ is calculated as AUC _t or AUC _{last} plus the ratio of the last measurable blood concentration to the elimination rate constant.
AUC _{%extrap} :	Percent of AUC _∞ extrapolated, represented as $(1 - AUC_t \text{ or } AUC_{last} / AUC_{\infty}) * 100$.
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 _{1/2} :	Apparent first-order terminal elimination half-life will be calculated as $0.693/\lambda_z$. Where λ_z is the apparent first order terminal elimination rate constant calculated from a semilog plot of the plasma concentration versus time curve. The parameter will be calculated by linear least-squares- regression analysis using the maximum number of points in the terminal log-linear phase (e.g., three or more non-zero plasma concentrations).
Vz/F	Apparent volume of distribution during the terminal elimination phase after oral (extravascular) administration, calculated as $Dose / (AUC_{\infty} \times \lambda_z)$ (TAK-788 only).

No value for λ_z , AUC_∞, AUC_{%extrap}, CL/F, Vz/F, or t_{1/2} will be reported for cases that do not exhibit a 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

Part 1:

In Period 1, subjects will be housed on Day -1, at the time indicated by the CRU, until the morning of Day 4 after the 72-hour PK sample is collected.

In Period 2, subjects will be housed on Day 4, in the morning, at the time indicated by the CRU, until the morning of Day 8 after the 72-hour PK sample is collected.

Part 2:

In Period 1, subjects will be housed on Day -1, at the time indicated by the CRU, until the morning of Day 4 after the 72-hour PK sample is collected.

In Period 2, subjects will be housed on Day 6 Period 2, in the morning, at the time indicated by the CRU, until the morning of Day 10 after the 72-hour PK sample is collected.

Part 1 and 2:

Subjects will return for dosing and/or study procedures 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 adverse events have occurred since the last study visit.

As per site preference and in agreement of Sponsor, subjects may be confined throughout the washout period and/or for the whole study. If the CRU decides to confine the subjects throughout the study, the site will still perform safety events scheduled at check-in.

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 may be 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, etc) 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/mm³ to <2000/mm³ 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, i.e., 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.
- Dose reduced – the dose was reduced due to the particular AE.
- Dose increased – the dose was increased due to the particular 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 days \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.

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 $\geq 3x$ upper limit of normal (ULN) with concurrent elevated total bilirubin $>2 \times$ ULN *or* elevated international normalized ratio (INR) >1.5 , contact the sponsor's medical monitor within 24 hours.

For any subject with ALT $\geq 3x$ 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	PPD [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

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.

Property of Takeda: For non-commercial use only and subject to the applicable Terms of Use

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 (e.g., exposure to treatment, availability of measurements and absence of major protocol violations) will be included in the statistical analyses. Any subject who experiences emesis within 8 hours post dosing with TAK-788 will be excluded in the final data analysis.

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

11.1.3 PK Analysis

Values will be calculated for the plasma TAK-788 and metabolites concentrations. PK parameters for plasma concentrations of TAK-788 and metabolites (AP32960 and AP32914) will be calculated as described in Section 9.3.1.1, and 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} and AUC_{∞} (AUC_{last} or AUC_t if AUC_{∞} is not available) for TAK-788 and ln transformed combined molar C_{\max} and AUC_{∞} for TAK-788, AP32960, and AP32914. The model will include treatment as a

fixed-effect and subject as a random-effect. Each model will include calculation of LSMs as well as the difference between treatment LSMs.

11.1.3.2 Ratios and Confidence Intervals

Geometric mean ratios (GMR) and 90% confidence intervals, 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} and AUC_{∞} (AUC_{last} or AUC_t if AUC_{∞} is not available) for TAK-788 and ln transformed combined molar C_{max} and AUC_{∞} for TAK-788, AP32960, and AP32914. These ratios will be expressed as a percentage of the following comparisons:

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

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

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

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 Interim Analysis and Criteria for Early Termination

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

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

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

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 CRE).

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 Studys 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 Studys it Sponsors anywhere in the world on ClinicalStudys.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 Americas 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 Studys on ClinicalStudys.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	PPD [REDACTED]

Please refer to Safety Management Plan.

Property of Takeda: For non-commercial use only and subject to the applicable Terms of Use

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 B](#)).

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in [Appendix D](#) of this protocol.

Signature of Investigator

Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Province)

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 _t	Area under the concentration-time curve from time 0 to time t
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
CYP	Cytochrome P450
DDI	Drug-drug interaction
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
EGFR	Epidermal growth factor receptor
FEV ₁	Forced expiratory volume
FSH	Follicle stimulating hormone
FVC	Forced vital capacity
g	Gram
GCP	Good Clinical Practice
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
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
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
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
PFT	Pulmonary function test
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 _{1/2}	Apparent first-order terminal elimination half-life
TBD	To be determined
TEAE	Treatment-emergent adverse event
TKI	Tyrosine kinase inhibitor
ULN	Upper limit of normal
US	United States
USA	United States of America
V _z /F	Apparent volume of distribution after extravascular administration
WHO	World Health Organization
WT	Wild-type
λ _z	Apparent first order terminal elimination 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

The Sponsor or its designee will supply investigative sites with access to CRFs. The Sponsor or its designee will train appropriate site staff in the use of the CRF. These forms are used to transmit the information collected in the performance of this study to the Sponsor and regulatory authorities. CRFs must be completed in English.

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

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.

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

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

- Brüggemann RJ, Alffenaar JW, Blijlevens NM, et al. Clinical relevance of the pharmacokinetic interactions of azole antifungal drugs with other coadministered agents. *Clin Infect Dis*. 2009;15;48:1441-1458.
- Duus E, Matson MA, and Bernareggi A. Effects of strong cytochrome P450 (CYP)3A4 inducers/inhibitors on the pharmacokinetic (PK) profile of anamorelin in healthy volunteers. *Journal of Clinical Oncology* 2018 36:15_suppl, e22180-e22180
- Liu L, Bello A, Dresser MJ, Heald D, Komjathy SF, O'Mara E, Rogge M, Stoch SA, Robertson SM. Best practices for the use of itraconazole as a replacement for ketoconazole in drug-drug interaction studies. *J Clin Pharmacol*. 2016 Feb;56(2):143-51. doi: 10.1002/jcph.562.
- 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.
- Peng CC, Templeton I, Thummel KE, Davis C, Kunze KL, and Isoherranen N. Evaluation of 6 β -hydroxycortisol, 6 β -hydroxycortisone and their combination as endogenous probes for inhibition of CYP3A4 in vivo. *Clin Pharmacol Ther*. 2011 Jun; 89(6): 888–895.
- Rifadin[®] (Rifampin capsules or for injection), monograph by Sanofi-Aventis U.S. LLC, full prescribing information (electronic monograph/ revised February 2013) published on the FDA website at <http://www.accessdata.fda.gov/scripts/cder/drugsatfda>
- Schuirman 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.
- Sporanox[®] (itraconazole oral solution) product monograph from Ortho-McNeil-Janssen Pharmaceuticals, Inc., (revised November 2011). Available at:
<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/>.
- Srinivas RN, Pharmacokinetic Interaction of Rifampicin with Oral Versus Intravenous Anticancer Drugs: Challenges, Dilemmas and Paradoxical Effects Due to Multiple Mechanisms. *Drug R D* (2016) 16:141-148.
- TAK-788. Millennium Pharmaceuticals, Inc. Global Investigator Brochure. Edition 3.0, January 2019.
- Teo YL, Han Kiat Ho, and Alexandre Chan. Metabolism-related pharmacokinetic drug–drug interactions with tyrosine kinase inhibitors: current understanding, challenges and recommendations. *Br J Clin Pharmacol*. 2014 Feb; 79(2): 241–253.

U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Draft Guidance Clinical Drug Interaction Studies — Study Design, Data Analysis, and Clinical Implications Guidance for Industry October 2017 <https://www.fda.gov/downloads/drugs/guidances/ucm292362.pdf> (accessed on 26 March 2019).

Upreti VV, Boulton DW, Li L, Ching A, Su H, LaCreta FP, and Patel CG. Effect of rifampicin on the pharmacokinetics and pharmacodynamics of saxagliptin, a dipeptidyl peptidase-4 inhibitor, in healthy subjects. *Br J Clin Pharmacol.* 2011 Jul; 72(1): 92–102.

Varis T, Kivistö KT, Backman JT, and Neuvonen PJ. The cytochrome P450 3A4 inhibitor itraconazole markedly increases the plasma concentrations of dexamethasone and enhances its adrenal-suppressant effect. *Clin Pharmacol Ther.* 2000 Nov;68(5):487-94.

Willems L, van der Geest R, de Beule K. Itraconazole oral solution and intravenous formulations: a review of pharmacokinetics and pharmacodynamics. *J Clin Pharm Ther.* 2001 Jun;26(3):159-69. Review.

Yoshizato T, Kotegawa T, Imai H, Tsutsumi K, Imanaga J, Ohyama T, Ohashi K. Itraconazole and domperidone: a placebo-controlled drug interaction study. *Eur J Clin Pharmacol.* 2012 Sep;68(9):1287-94.

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 28 days after the last dose of study drug. Regular pregnancy tests will be performed throughout the study for all female subjects of 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 94 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 ClinicalStudies.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:

Part 1:

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 94 days after the last dose of TAK-788.

If a male has not had a vasectomy and are sexually active with any person who is pregnant, or could get pregnant, he must use a condom with spermicidal cream or jelly each time he has sex during the study and for 94 days after last dose of TAK-788. If a male is surgically sterilized (i.e., have had a vasectomy) he must agree to use an appropriate method of barrier contraception (latex condom with a spermicidal agent) during the entire study, and for 94 days after his last dose of TAK-788. Or, he should completely avoid having heterosexual intercourse.

Part 2:

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 are sexually active with any person who is pregnant, or could get pregnant, he must use a condom with spermicidal cream or jelly each time he has sex during the study and for 30 days after last dose of TAK-788. If a male is surgically sterilized (i.e., have had a vasectomy) he 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.

Part 1 and 2:

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 94 days (Part 1) or for at least 30 days (Part 2) after their last dose of TAK-788 and should tell their female partner(s) that they are in research study.

Females:

Part 1

Females must agree not to become pregnant, breastfeed a baby or donate an egg or eggs (ova) during the study and for 60 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 60 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 60 days after the last dose of TAK-788.

Part 2:

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.

Part 1 and 2:

TAK-788 may decrease effectiveness of hormonal contraceptives, therefore, women must use an 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:

Highly effective non-hormonal methods	Additional effective (barrier) methods
Nonhormonal intrauterine device	Male or female condom with or without spermicide (female and male condoms should not be used together)
Bilateral tubal occlusion (a surgical procedure that blocks the fallopian tubes to prevent the ovum (egg) from being fertilized) or bilateral salpingectomy	
Hysteroscopic sterilization	
Hysterectomy	
Bilateral oophorectomy	
Vasectomised sole sexual partner (removal of the tube that carries sperm from the testicle to the penis)	
Sexual abstinence (no sexual intercourse)	Cap, diaphragm or sponge with spermicide

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

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical Pharmacology Approval	18-Apr-2019 15:47 UTC
PPD	Clinical Approval	18-Apr-2019 16:11 UTC
PPD	Biostatistics Approval	18-Apr-2019 20:19 UTC

Property of Takeda: For non-commercial use only and subject to the applicable Terms of Use