Title: A Randomized, Double-Blind, Placebo-Controlled, Ascending Oral Single Dose Trial to Evaluate the Safety, Tolerability, and Pharmacokinetics of TAK-418 in Healthy Subjects

NCT Number: NCT03228433

Protocol Approve Date: 07 July 2017

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 Randomized, Double-Blind, Placebo-Controlled, Ascending Oral Single Dose Trial to Evaluate the Safety, Tolerability, and Pharmacokinetics of TAK-418 in Healthy Subjects

Sponsor: Takeda Development Center Americas, Inc.
One Takeda Parkway
Deerfield, IL 60015

Trial Number: TAK-418-1001

Compound: TAK-418

Date: 07 July 2017 **Version/Amendment Number:** 01

Amendment History:

Date	Amendment Number	Amendment Type (Substantial/Nonsubstantial	Region
06 April 2017	Initial version	Not applicable	Global
07 July 2017	01	Substantial	Global

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF APPENDICES

1.0 STUDY SUMMARY

Name of Sponsor: **Takeda Development Center Americas, Inc.** **One Takeda Parkway** **Deerfield, IL 60015**	**Compound:** **TAK-418**
Trial Number: **TAK-418-1001**	**Phase: 1**

Protocol Title: A Randomized, Double-Blind, Placebo-Controlled, Ascending Oral Single Dose Trial to Evaluate the Safety, Tolerability, and Pharmacokinetics of TAK-418 in Healthy Subjects

Trial Design:

This first-in-human (FIH), randomized, double-blind, placebo-controlled trial is designed to evaluate the safety, tolerability, and pharmacokinetics (PK) of TAK-418 in healthy adult subjects.

TAK-418 and placebo will be administered orally in capsule formulation and will be prepared and dispensed in a blinded fashion by an unblinded pharmacist or qualified trial site personnel; the subject, the investigator, and the sponsor personnel or delegate(s) who are involved in the treatment or clinical evaluation of the subjects will be unaware of the treatment group assignments.

Since the PK, pharmacodynamic, and safety profiles of TAK-418 in humans are still being evaluated, modifications to the dose or dosing regimen may be required to achieve the scientific goals of the trial objectives and/or to ensure appropriate safety monitoring of the trial subjects. Dose escalation and subsequent dose levels will be based on a blinded review of available safety (including neurological assessment), tolerability, and PK data from the previous dose levels and will only occur following agreement between the investigator and the sponsor.

This study will involve 40 subjects, equally divided among 5 sequential cohorts of 8 subjects each, as shown in Table 1. In each cohort, 6 subjects will be randomized to receive TAK-418 and 2 will receive matching placebo. A minimum of 4 male subjects will be enrolled in each cohort. The schedule for dosing and procedures is provided in Table 2.

Table 1. Schematic and Planned Doses for Cohorts 1 Through 5

Dose 5 mg	Dose 15 mg	Dose 45 mg	Dose 90 mg	Dose 180 mg
Cohort 1 (n=8; 6 active: 2 placebo)	Cohort 2 (n=8; 6 active: 2 placebo)	Cohort 3A and 3B (n=8; 6 active: 2 placebo)	Cohort 4 (n=8; 6 active: 2 placebo)	Cohort 5 (n=8; 6 active: 2 placebo)

Additional cohorts may be studied if deemed necessary to fully characterize the pharmacologically active exposure range.

Doses planned to be administered range from 5 to 180 mg, but the actual doses administered after the first dose will be based on emerging safety and tolerability data from the previous doses. If needed, a dose higher than 180 mg but less than 300 mg may be evaluated providing its predicted exposure does not exceed the following exposure levels: the highest dose administered will have a predicted mean area under the plasma concentration-time curve (AUC) that does not exceed the monkey AUC at the no effect level for CCI [redacted] from the 13-week toxicology study or mean maximum observed concentration (C_{max}) that does not exceed one-tenth (CCI [redacted]) of the monkey C_{max} at the NOAEL (CCI [redacted]) from the 4-week toxicology study.

Because this is a FIH trial, a sentinel dosing regimen will be used for Cohort 1 (with the initial 2 subjects receiving either active drug or placebo [1:1]) to ensure adequate safety and tolerability. The remaining 6 subjects will be dosed in 2 groups of 3 subjects each after a review of 72 hours postdose safety and tolerability data of the previous group. A staggered dosing regimen will be used for Cohorts 2 to 5. Each cohort will be divided by 2 groups (3 active:1 placebo), and the second group will be dosed 48 hours after the first group, following assessment of safety and tolerability data.

Subjects in Cohort 3 will receive 2 doses (under fasted state [Cohort 3A] and with food [Cohort 3B]), with at least 7

days of washout between dose administrations. Subjects enrolled in Cohort 3A will return to the site to complete Cohort 3B and will be administered TAK-418/placebo under fed condition with a high fat/high calorie breakfast, which must be consumed within 30 minutes and the dose given within 5 minutes after the end of the meal. All assessments from Day -1 to Day 4 in Cohort 3B will be same as in Cohort 3A and there will be no Day 14 follow-up for Cohort 3A. Post-trial assessments days will be adjusted (including follow-up on Day 14 for all subjects and Days 91, 93, and 182 and 184 postdose, if needed) with respect to Cohort 3B.

Table 2. Trial Schedule

Screening Period (a)	Pretreatment (a)	Treatment		Post-trial (c)
		Dose Administration (b)	Postdose Procedures (b)	
Days -28 to -2	Day -1	Day 1	Days 1 to 4	Day 14 (±2) Days 91, 93, 182, and 184 (±7)

(a) CCI [redacted]
(b) Subjects will remain in the phase 1 unit for a minimum of 48 hours following the dose of trial drug and may be released after 48 hours and complete the 72 hour and later procedures at an outpatient visit. Subject may be kept in clinic for the entire time at the PI's discretion.
(c) CCI [redacted]

Primary Objective:

The primary objective of this trial is to evaluate the safety and tolerability of TAK-418 following single oral doses in healthy subjects.

Secondary Objective:

The secondary objective of this trial is to evaluate the PK of TAK-418 free base (F) following a single oral doses (under fasted and fed states) in healthy subjects.

Subject Population: Healthy adults aged 18 to 55 years, inclusive.

Number of Subjects: 40 subjects (8 subjects in each of 5 cohorts)	**Number of Sites:** 1 site
Dose Levels: 5 mg (Cohort 1), 15 mg (Cohort 2), 45 mg (Cohort 3), 90 mg (Cohort 4), and 180 mg (Cohort 5)	**Route of Administration:** Oral
Duration of Treatment: One single dose in Cohorts 1, 2, 4, and 5 Two single doses in Cohort 3 (under fasted and fed states)	**Period of Evaluation:** Female subjects (Cohorts 1, 2, 4, and 5): approximately 42 days. Female subjects (Cohort 3): approximately 49 days. Male subjects (Cohorts 1, 2, 4, and 5): approximately 121 days (212 days if serum analysis is abnormal on Day 93). Male subjects (Cohort 3): approximately 128 days (219 days if serum analysis is abnormal on Day 93 post Cohort 3B).

Main Criteria for Inclusion:

To be eligible for trial participation, subjects must:

- Be a male subject or female subject (with no childbearing potential) with a body mass index from ≥18.5 to ≤30.0 (kg/m^2) at the Screening Visit.
- Be a nonsmoker who has not used tobacco- or nicotine-containing products (eg, nicotine patch) for at least 6 months before trial drug administration.
- Be judged to be in good health by the investigator, based on clinical evaluations including laboratory safety tests, medical history, physical examination, 12-lead electrocardiogram (ECG), and vital sign measurements performed at the Screening Visit and before administration of the trial drug/invasive procedure.
- Male subjects must have CCI that equal or exceed the World Health Organization reference values.
- Must meet stringent birth control requirements as specified in the protocol.

Main Criteria for Exclusion:

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

- Has a history of cancer (malignancy).
- Is positive for hepatitis B surface antigen, hepatitis C antibodies, or human immunodeficiency virus.
- Male subjects have their serum CCI levels that are clinically abnormal.
- Had major surgery, donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks before the Screening Visit.
- Has a risk of suicide according to the investigator's clinical judgment per the Columbia–Suicide Severity Rating Scale at Screening or has made a suicide attempt in the 6 months before Screening.
- Has a clinically significant history of head injury, trauma, or seizures.

Main Criteria for Evaluation and Analyses:

The primary endpoint of the trial is a composite of safety variables and dose-limiting effects of TAK-418 that will be evaluated after dosing on Day 1 by the number and percentage of subjects who:

- Experience at least 1 treatment-emergent adverse event.
- Discontinue because of an adverse event.
- Meet the markedly abnormal criteria for safety laboratory tests at least once postdose.
- Meet the markedly abnormal criteria for vital sign measurements at least once postdose.
- Meet the markedly abnormal criteria for safety 12-lead ECG parameters at least once postdose.

The secondary endpoints will be as follows:

- Evaluation of the following PK parameters after dosing on Day 1:
  - Area under the concentration-time curve from time 0 to time of the last quantifiable concentration (AUC_{last}).
  - Area under the concentration-time curve from time 0 to infinity (AUC_{∞}).
  - Maximum observed concentration (C_{max}).
  - Time of first occurrence of C_{max} (t_{max}).

Statistical Considerations:

Safety Analysis

Safety parameters will be summarized by pooled placebo, each TAK-418 dose level, and TAK-418 overall (as appropriate). Safety data collected after administration of trial drug under fed conditions will be summarized separately.

PK Analysis

Plasma concentrations of TAK-418F will be summarized by dose over each scheduled sampling time using descriptive statistics.

The amount of TAK-418F excreted in urine will be summarized by dose using descriptive statistics.

Plasma and urine PK parameters of TAK-418F will be summarized by dose using descriptive statistics.

Individual plasma and urine concentration versus time data and PK parameters will be presented in a data listing.

If sufficient data are available, dose proportionality of TAK-418F plasma exposures (C_{max} and AUC) will be assessed statistically using a power model. For evaluation of potential food effect on TAK-418F PK, log-transformed C_{max} and AUC values will be compared between the treatments (Reference=fasting administration; Test=fed administration) using an analysis of variance (ANOVA) with fixed effect for treatment and a random effect for subject. The geometric mean relative bioavailability and 90% confidence intervals (CIs) for C_{max}, AUC_{last}, and AUC_{∞} will be calculated based upon the adjusted means (LS means) from the ANOVA.

Individual results of Bond-Lader Visual Analogue Scale, Columbia–Suicide Severity Rating Scale, and cognitive testing will be provided in the data listings. For cognitive testing, Baseline, postdose and change from Baseline to postdose data will be summarized by dose.

A more detailed analysis will be presented in the statistical analysis plan. Additional analyses will be included, if appropriate.

Sample Size Justification: The sample size of 8 subjects per cohort (6 active: 2 placebo) chosen is based upon precedents from other FIH trials rather than a formal assessment of statistical power.

If a subject discontinues from the trial, a replacement subject may be enrolled, if deemed appropriate by the investigator and the sponsor. The trial site should contact the sponsor for the replacement subject's treatment assignment and randomization number.

1.1 Protocol Amendment No. 01 Summary of Changes

Rationale for Amendment No. 01

This document describes the changes in reference to the protocol incorporating Amendment No. 01. The primary reason for this amendment is to change the study design from a combined single rising dose (SRD) and multiple rising dose (MRD) study to a SRD study, with assessment of CCI and exploratory biomarkers as additional safety parameters. In addition, several clarifications and administrative changes have been made.

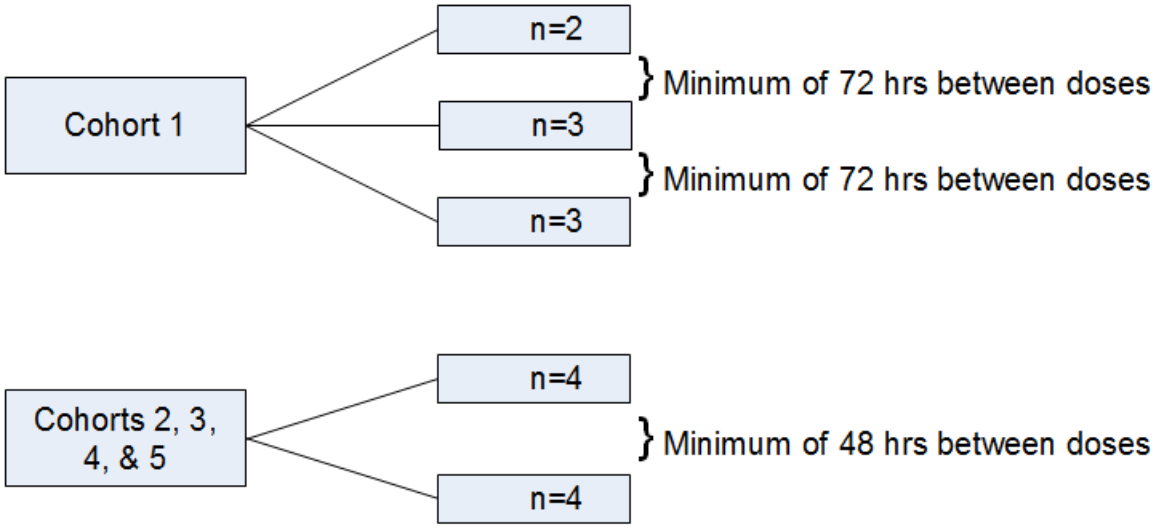
Minor grammatical, editorial, and formatting changes are included for clarification purposes only.

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

Changes in Amendment No. 01:

1. Modified study design to delete the MRD part of the study and associated assessments, and clarified the SRD part.
2. Added objectives relating to CCI .
3. Added inclusion and exclusion criteria based on CCI levels in male subjects.
4. Added biomarkers.
5. Added preliminary data from 13-week toxicology study.

2.0 TRIAL SCHEMATIC



Sentinel dosing for Cohort 1 and staggered dosing for the remaining cohorts. Groups 3A (fasted) and 3B (fed) have 7 days of washout between them.

3.0 SCHEDULE OF TRIAL PROCEDURES

Schedule of Activities

	Day(s) (a)		Scheduled Time (a)														Follow-up/ ET (b)	CCI S
	-28 to -2	-1	Hours											Days				
	Screening		Predose Day 1	0	0.25	0.5	1	1.5	2	3	4	8	12	24	36	48	72	14 (±2)	91, 93, 182, 184 (±7)
Administrative Procedures																			
Informed consent	X																		
Inclusion/exclusion criteria	X	X	X																
Medical history/ demographics	X																		
Prior and concomitant medication review	X----------Continuous Review----------X																		
Clinic Procedures/Assessments																			
Full physical examination	X		X (d)															X	
Neurological examination	X		X (d)											X			X	X	
Height	X																		
Weight	X		X											X				X	
BMI	X																		
Semirecumbent vital signs (HR, SBP, and DBP)	X		X (e)				X		X					X				X	

	Day(s) (a)		Scheduled Time (a)														Follow-up/ ET (b)	CCI [redacted]
	-28 to -2	-1	Hours														Days	
	Screening		Predose Day 1	0	0.25	0.5	1	1.5	2	3	4	8	12	24	36	48	72	14 (±2)	91, 93, 182, 184 (±7)
Vital signs (respiratory rate, oral [at the floor of the mouth]/tympanic temperature)	X		X (e)				X		X					X				X	
12-lead ECG	X	X	X (e)				X		X					X				X	
TAK-418/placebo administration				X															
C-SSRS	X		X											X		X	X	X	
BL-VAS			X				X							X					
CCI [redacted]																			
AE monitoring	X----------Continuous Monitoring----------X																		
Laboratory Procedures/Assessments																			
Hematology	X		X											X				X	
Urinalysis	X		X											X				X	
Serum chemistry	X		X											X				X	
hCG (females)	X	X															X	X	
CCI [redacted]																			

	Day(s) (a)		Scheduled Time (a)														Follow-up/ ET (b)	CCI [redacted]
	-28 to -2	-1	Hours														Days	
	Screening		Predose Day 1	0	0.25	0.5	1	1.5	2	3	4	8	12	24	36	48	72	14 (±2)	91, 93, 182, 184 (±7)
CCI [redacted]																		
CCI [redacted]																		
Urine drug screen	X	X																
Urine/breath alcohol test (j)	X	X																
Hepatitis screen	X																	
HIV	X																	
PK Evaluations																		
Blood for plasma PK			X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Urine for PK (k)			X----------X															
Biomarker Evaluations																		
Company Confidential Information [redacted]																		
Company Confidential Information [redacted]																		
Company Confidential Information [redacted]																		

	Day(s) (a)		Scheduled Time (a)															Follow-up/ ET (b)	CCI S
	-28 to -2	-1	Hours															Days	
	Screening		Predose Day 1	0	0.25	0.5	1	1.5	2	3	4	8	12	24	36	48	72	14 (±2)	91, 93, 182, 184 (±7)
PGx Evaluations																			
Blood sample for DNA PGx (n)			X																
Blood sample for RNA PGx (o)			X											X					
Other																			
CCI																			
Confinement		X----------															----------X		

Footnotes are on the last table page.

AE=adverse event, BL-VAS=Bond-Lader Visual Analogue Scale, BMI=body mass index, C-SSRS=Columbia–Suicide Severity Rating Scale, DBP=diastolic blood pressure, ECG=electrocardiogram, ET=early termination, F-FAD=formyl-flavin adenine dinucleotide, CCI [redacted], hCG=human chorionic gonadotropin, HIV=human immunodeficiency virus, HR=heart rate, CCI [redacted], PBMC=peripheral blood mononuclear cell, PGx=pharmacogenomics, PK=pharmacokinetic, SBP=systolic blood pressure.

(a) For Cohort 3, there will be a 7 day washout between Cohorts 3A and 3B, starting from TAK-418 administration on Day 1 for Cohort 3A. For Cohort 3B, all assessments on Days -1 through Day 4 will be same as Cohort 3A.

(b) For all cohorts, except Cohort 3, all subjects will report back to the trial clinic to return wearable device(s) on Day 14 (±2) and will be re-evaluated per investigator's discretion. Cohort 3A subjects will return wearable devices at on Day 7 (predose Cohort 3B).

(c) CCI [redacted]

(d) Predose physical and neurological examinations may be done within approximately 24 hours predose.

(e) Vital signs and a 12-lead ECG will be performed within approximately 1 hour predose on Day 1.

(f) CCI [redacted]

(g) CCI [redacted]

(h) CCI [redacted]

(i) CCI [redacted]

(j) A urine alcohol test may be performed at the discretion of the investigator.

(k) Urine sample for TAK-418F concentrations may be collected at a dose level projected to produce therapeutic exposure at the following time intervals: Predose (spot collection), 0 to 12 hours, 12 to 24 hours, 24 to 48 hours.

(l) CCI [redacted]

(n) Blood for DNA PGx will be collected within 60 minutes predose.

(o) Blood for RNA PGx will be collected within 60 minutes predose and 24 hours postdose.

(p) For Cohorts 1, 2, 4, and 5, CCI [redacted] at the mandatory follow-up visit on Day 14. For Cohort 3, CCI [redacted] and returned to the site at predose Cohort 3B.

4.0 INTRODUCTION

4.1 Background

Lysine-specific demethylase 1A (LSD1) is involved in a wide variety of cellular processes and pathologies, including signal transduction, transcriptional regulation, viral pathogenesis, cancer proliferation and metastasis, development, differentiation, and chromatin remodeling [1]. As such, LSD1 has emerged as a potential therapeutic target for cancer as well as development disorders involving chromatin remodeling defects, such as autism spectrum disorder (ASD).

An area of focus in ASD research has been on the genetic causes of ASD, since there is a strong heritable component [2]. ASDs are a heterogeneous group of neurodevelopmental disorders that manifest in early childhood, are defined by behavioral observations, and are characterized by impairments in communication and social interaction along with restrictive and repetitive behaviors [3-5]. These dysfunctions hinder the individual's ability to function socially, at school/work, or other areas of life, and require full-time engagement of a one-on-one therapist over many years, often resulting in suboptimal outcomes [4]. There is a clear role for epigenetics, since genes involved in chromatin biology have been identified as risk factors [6]. This is in addition to trials in which chromatin modifications via either gene methylation or histone modification affect gene expression (silencing or activation) and subsequent development of the disorder [7].

One of the modifications that has been extensively studied is methylation of lysine in position 4 of type 3 histone (H3K4) [8], and an important regulator of H3K4 methylation is the LSD1, a member of the lysine-specific demethylase family 1 (KDM1). LSD1 uses a flavin adenine dinucleotide cofactor to oxidize carbon-nitrogen bonds with subsequent production of a demethylated lysine residue and formaldehyde by-product. The first reported specific substrate of LSD1 was histone H3K4me1/2 (LBR1), and subsequently further specific substrates have been identified.

LSD1 operates as a catalytic subunit within specific stable complexes formed with additional biomolecules and enzymes that perform coregulatory or scaffolding functions. Such interactions link the catalytic activity of LSD1 to distinctive biological occupations and have been shown to influence the degree of catalytic activity, substrate specificity, and/or localization of this enzyme within the chromatin [1]. Examples of complexes that contain LSD1 include CoREST, REST, TLX orphan nuclear receptor complex, TAL1 complex, CtBP complex, NuRD complex, androgen receptor nuclear hormone complex, and the Snail/Gfi-1 (SNAG family) of proteins.

Modulation of neuronal histone methylation has been shown to have an impact on both learning and memory processes [5]. This has been further substantiated by the demonstration that LSD1 activity plays an important role in the development of pyramidal cortical neurons and neural stem cell proliferation [5]. Consequently, the development of brain-penetrant LSD1 inhibitors as treatment agents for mood and psychosis disorders has been proposed [7,9].

TAK-418 is a novel small molecule that possesses inhibitory activity against human LSD1, also known as KDM1A. X-ray crystallography and mass spectrometric analysis have demonstrated that TAK-418 reacts on the catalytic flavin adenine dinucleotide (FAD) to form the formylated FAD

(F-FAD) in LSD1. F-FAD can therefore be used as a biomarker of target engagement for TAK-418. Nonclinical data with TAK-418 have demonstrated: (a) effects on social interaction in valproic acid and synthetic double-stranded RNA (polyinosinic:polycytidylic acid) autism rodent models, suggesting utility for treatment of social interaction and cognitive deficits in ASD, and (b) effects on declarative and emotional short-term memory task in rodents.

Please refer to the current TAK-418 Investigator's Brochure for additional background information. Preliminary information from 13-week nonclinical toxicity in monkeys is in Section 6.3.2.

4.2 Rationale for the Proposed Trial

Nonclinical pharmacology, pharmacokinetic (PK), and toxicology trials support the proposed trial in humans to further develop TAK-418 for the treatment of ASD. TAK-418 has shown effects on declarative and emotional short-term memory tasks in rodents and social interaction in autism rodent models that suggest utility for treatment of cognitive deficits in ASD. The nonclinical safety profile of TAK-418 supports clinical development of this compound.

The proposed dose range of TAK-418 to be explored in this first-in-human (FIH) trial is anticipated to achieve a sufficient range of plasma exposures with a margin above the predicted pharmacologically active exposures. The preliminary safety and tolerability data information will facilitate the design and dose selection of a multiple rising dose (MRD) trial.

4.3 Benefit/Risk Profile

This proposed phase 1, randomized, double-blind, placebo-controlled, single-center trial will evaluate the safety, tolerability, and PK of TAK-418 following single oral doses in healthy volunteers aged 18 to 55 years, inclusive. As this is a healthy volunteer trial, there is no expected clinical benefit to the trial participants.

CCI

[redacted]

CCI

[redacted]

5.0 TRIAL OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

The primary objective of this trial is to evaluate the safety and tolerability of TAK-418 following single oral doses in healthy subjects.

5.1.2 Secondary Objective

The secondary objectives of this trial is to evaluate the PK of TAK-418 free base (F) following a single oral dose (under fasted and fed states) in healthy subjects.

5.1.3 Exploratory Objectives

Exploratory objectives of the trial include:

CCI

[redacted]

5.2 Endpoints

5.2.1 Primary Endpoint

The primary endpoint of the trial is a composite of safety variables and dose-limiting effects of TAK-418 that will be evaluated after dosing on Day 1 by the number and percentage of subjects who:

- Experience at least 1 treatment-emergent adverse event (TEAE).

- Discontinue because of an adverse event (AE).
- Meet the markedly abnormal criteria for neurological assessment measurements at least once postdose.
- Meet the markedly abnormal criteria for safety laboratory tests at least once postdose.
- Meet the markedly abnormal criteria for vital sign measurements at least once postdose.
- Meet the markedly abnormal criteria for safety 12-lead ECG parameters at least once postdose.

5.2.2 Secondary Endpoints

The secondary endpoints will be as follows:

Evaluation of the following PK parameters in healthy subjects after dosing on Day 1:

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

5.2.3 Exploratory Endpoints

Exploratory endpoints will be assessed through the following parameters in healthy subjects after dosing on Day 1:

CCI

6.0 TRIAL DESIGN AND DESCRIPTION

6.1 Trial Design

This is an FIH, randomized, double-blind, placebo-controlled trial to evaluate the safety, tolerability, and PK of TAK-418 in healthy adult subjects. The trial will also explore the PD of TAK-418 and its effects on selected biomarkers following single oral doses in healthy adult subjects.

TAK-418 will be administered orally as a capsule formulation. TAK-418 and placebo will be prepared and dispensed in a blinded fashion by an unblinded pharmacist or qualified trial site personnel. The subject, the investigator, and sponsor personnel or delegate(s) who are involved in the treatment or clinical evaluation of the subjects will be unaware of the treatment group assignments.

Because this is a phase 1 assessment of TAK-418 in humans, and the PK, PD, and safety profiles of the compound are still being evaluated, modifications to the dose or dosing regimen may be required to achieve the scientific goals of the trial objectives and/or to ensure appropriate safety monitoring of the trial subjects. Details of allowed modifications are provided in Section 6.4.

This study consists of 5 cohorts of subjects, sequentially paneled, with a double-blind design. Each cohort will consist of 8 subjects, where 6 subjects will be randomized to receive TAK-418 and 2 subjects will be assigned to receive matching placebo. A minimum of 4 male subjects will be enrolled in each cohort. The trial population will be approximately 40 healthy subjects. Additional cohorts may be studied if deemed necessary to fully characterize the pharmacologically active exposure range. For Cohort 3, there will be at least 7 days of washout between dose administration in the fasted and fed states.

The planned dose levels of TAK-418 to be evaluated in Cohorts 1 to 5 are outlined in Table 6.a.

Table 6.a Schematic and Planned Doses of Trial Design—Cohorts 1 to 5

Dose 5 mg	Dose 15 mg	Dose 45 mg	Dose 90 mg	Dose 180 mg
Cohort 1 (n=8; 6 active: 2 placebo)	Cohort 2 (n=8; 6 active: 2 placebo)	Cohort 3A and 3B (n=8; 6 active: 2 placebo)	Cohort 4 (n=8; 6 active: 2 placebo)	Cohort 5 (n=8; 6 active: 2 placebo)

Additional cohorts may be studied if deemed necessary to fully characterize the pharmacologically active exposure range.

Doses planned to be administered range from 5 to 180 mg, but the actual doses administered after the first dose will be based on emerging safety and tolerability data from the previous doses. If needed, a dose higher than 180 mg but less than 300 mg may be evaluated providing its predicted exposure does not exceed the following exposure levels. The highest dose administered will have a predicted mean area under the plasma concentration-time curve (AUC) that does not exceed the monkey AUC at the no-observed-adverse-effect level (NOAEL; males) from the 13-week

toxicology study or mean maximum observed concentration (C_{max}) that does not exceed one-tenth of the monkey C_{max} from the 4-week toxicology study.

Subjects in Cohort 3 will receive 2 doses (under fasted state [Cohort 3A] and with food [Cohort 3B]), with at least 7 days of washout between dose administrations. Subjects enrolled in Cohort 3A will return to the site to complete Cohort 3B and will be administered TAK-418/placebo under fed condition with a high fat/high calorie breakfast, which must start 30 minutes before the dose is administered. All assessments from Day -1 to Day 4 in Cohort 3B will be same as in Cohort 3A; however, there will be no follow-up for CCI after Cohort 3A and the Day 14 follow-up assessment for Cohort 3B. For male subjects, CCI days will be adjusted based on dosing in Cohort 3B.

CCI

A sentinel dosing regimen will be used for Cohort 1 (with the initial 2 subjects [1a] receiving either active drug or placebo in a 1:1 ratio) to ensure adequate safety and tolerability. After a minimum of 72 hours after the dosing of Cohort 1a, 3 subjects (Cohort 1b) will be dosed after review of the postdose safety and tolerability of the initial 2 subjects (Cohort 1a). After a minimum of 72 hours after dosing Cohort1b, the last 3 subjects of Cohort 1(1c), will be dosed after review of the postdose safety and tolerability.

A staggered dosing regimen will be used for Cohorts 2 to 5. Each cohort will be divided by 2 groups (3 active: 1 placebo), and the second group will be dosed after a minimum of 48 hours after the first group, following assessment of safety and tolerability data. Subjects in Cohort 3 receive 2 doses (fasted and fed state). There will be at least 7 days of washout between dose administrations.

CCI

The trial schedule is detailed in Table 6.b.

Table 6.b Trial Schedule

Screening Period	Pretreatment (a)	Treatment		Posttrial (c)
		Dose Administration (b)	Postdose Procedures (b)	
Days -28 to -2	Day -1	Day 1	Days 1 to 4	Day 14 (±2) (c) Days 91, 93, 182, and 184 (±7)

(a) CCI [redacted]
(b) Subjects will remain in the phase 1 unit for a minimum of 48 hours following the dose of trial drug and may be released after 48 hours and complete the 72 hour and later procedures at an outpatient visit. Subjects may be kept in the clinic for longer time at PI's discretion.
(c) CCI [redacted]

6.2 Dose Escalation

Dose escalation and subsequent dose levels will be based on a blinded review of available safety (including neurological assessment) and tolerability data from the previous dose levels and will only occur following agreement between the investigator and the sponsor. PK data will be used to guide dose selection after each cohort.

Following Cohort 1, subsequent dose levels may be higher, may be lower, or may remain the same as the preceding dose level. After Cohort 2, dose escalations will be limited to an escalated dose that is predicted to give no greater than a 3-fold increase in either C_{max} or AUC of the immediate prior dose level. Dosing will continue as long as the mean AUC of the highest dose level is predicted not to exceed the mean area under the serum concentration-time curve from time 0 to 24 hours (AUC_{24}) at the no effect level for CCI [redacted] findings in male monkeys (the more sensitive species) from the 13-week toxicology study (CCI [redacted]) or the mean C_{max} of the highest dose is predicted not to exceed one-tenth of the mean C_{max} of the NOAEL from the 4 weeks toxicology study in monkeys (CCI [redacted]). If needed, a higher dose than the planned dose of 180 mg but less than 300 mg will be evaluated providing that the predicted exposure of this dose does not exceed the exposure levels mentioned above. If the majority of plasma concentrations of TAK-418F are below the limit of detection, the dose will be escalated to the next planned dose level provided safety and tolerability at the preceding dose level are considered acceptable.

6.3 Justification for Trial Design, Dose, and Endpoints

6.3.1 Justification of Trial Design and Regimen

Because this is an FIH trial, a sentinel dosing regimen will be used for Cohort 1 (with the initial 2 subjects receiving either active drug or placebo [1:1]) to ensure adequate safety and tolerability. The remaining 6 subjects will be dosed in 2 groups of 3 subjects each after a review of 72 hours postdose safety and tolerability data of the previous group. A staggered dosing regimen will be used for Cohorts 2 to 5. Each cohort will be divided by 2 groups (3 active: 1 placebo), and the

second group will be dosed 48 hours after the first group, following assessment of safety and tolerability data. Subjects in Cohort 3 receive 2 doses (fasted and fed state) with food, with at least 7 days of washout between dose administrations.

The planned initial dose of TAK-418 for Cohort 1 is 5 mg. Doses for subsequent periods/cohorts will be determined based on the available safety, tolerability, and PK data from the preceding period/cohort. The doses will be administered to the subjects by the investigator or the investigator's designee. TAK-418 will be administered orally in a capsule formulation.

6.3.2 Dose

The proposed starting dose for this study was determined by calculating the human equivalent dose (HED) (Food and Drug Administration [FDA] Guidance for Industry Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers, July 2005) from nonclinical toxicity studies and by taking into consideration the estimated pharmacologically active dose (PAD)/exposures in human subjects. Converting the NOAEL of CCI for male monkeys from the 13-week toxicity study, which is the more sensitive species, results in a HED value of CCI based on body surface area. Multiplying this HED of CCI, a conservative estimate of human body weight, achieves a total daily dose of 77 mg/day. By adding a 10-fold safety factor as per FDA guidance, the maximum recommended starting dose is CCI. The pharmacologically active exposure based on the nonclinical pharmacology models was CCI. Using the most conservative exposure for allometry and physiologically based PK modeling, this exposure would be achieved at a dose of approximately 13 to 35 mg in humans. Therefore, the proposed starting dose is 5 mg, which is below the maximum safe starting dose and projected PAD. In the event that the majority of individual plasma concentrations of TAK-418F in human volunteers are below the limit of detection, the dose will be escalated to the next planned dose level, provided that safety and tolerability at the preceding dose level are considered acceptable.

Convulsions were observed in 3 monkeys at dose levels ≥75 mg/kg/day in the 13-week toxicology study currently in the reporting phase, but were not observed when the dose was lowered to C CI Based on allometric scaling from rat and monkey PK, the projected human TAK-418F C_{max} and AUC following a single dose of TAK-418 CCI range from CCI and CCI, respectively. The projected human TAK-418F C_{max} and AUC following a single dose of TAK-418 180 mg range from CCI L and CCI, respectively.

TAK-418 demonstrated good absorption with bioavailability of CCI after oral administration. The terminal disposition phase half-life ($t_{1/2z}$) value after intravenous (IV) administration was CCI in mice, rats, monkeys, and humans CCI

CCI [redacted] The in vitro metabolism of [C]TAK-418 was evaluated using hepatic microsomes and hepatic cytosol from mice, rats, dogs, monkeys, and humans. TAK-418 was mainly metabolized to unidentified metabolites via cytochrome P450 (CYP) 2D6 and to a lesser extent via CYP1A2, CYP2C8, CYP2C19, and CYP3A4. In addition, TAK-418 was eliminated via non-CYP pathways (including degradation). TAK-418 has no substantial inhibition of any CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5) at concentrations up to100 µmol/L. An in vitro induction study indicated that TAK-418 has no substantial induction potential for CYP1A2, CYP2B6, or CYP3A4 at concentrations up to 100 µmol/L.

A comprehensive series of nonclinical safety studies (Good Laboratory Practice [GLP] compliant) have been conducted with TAK-418 to support early human studies. No safety concerns were identified in standard safety pharmacology assessment of the central nervous system in rats up to oral doses of 300 mg/kg. An effect on human ether-à-go-go-related gene potassium currents was observed at ≥5 µg/mL free concentration of TAK-418 CCI [redacted] total plasma concentration of TAK-418 in humans); however, no effect on ECG parameters in telemetrized monkeys was observed through 100 mg/kg although an increase in mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) and an increase in HR were observed at 100 mg/kg; all parameters were normal at 20 mg/kg. A decrease in respiration rate and minute volume at 300 mg/kg but not 100 mg/kg was observed in a rat respiration study using plethysmography.

In GLP-compliant toxicity studies, no safety concerns for genotoxicity were identified in an Ames test or in vivo assessment of DNA damage or micronucleus formation in rats through a 300 mg/kg/day dose. Ultraviolet-visible absorption of light by TAK-418 did not indicate a potential for phototoxicity. In 4-week repeated-dosing toxicity studies in rats, changes that were seen included excessive salivation, decreases in red blood cell parameters, plasma potassium and chloride, increases in urea nitrogen and urine volume, and gastric erosion at 300 mg/kg/day; the NOAEL was CCI [redacted] for both sexes. The mean C_{max} and AUC_{24} values at CCI [redacted] after the 30th dose were CCI [redacted] and CCI [redacted] (females), respectively. In a 4-week monkey toxicity study, decreased food intake, weight loss, and emesis at 100 mg/kg/day were the basis for a NOAEL of CCI [redacted]. The mean C_{max} and AUC_{24} values at CCI [redacted] after the 28th dose were CCI [redacted] and CCI [redacted] (females), respectively. Recovery groups were not included in the 4-week repeat-dose studies. In the 13-week study, currently in the reporting phase, clinical observations associated with administration of TAK-418 included convulsions, emesis, decreased activity, hunched posture, lying on side in cage, and reduced appetite predominantly at 100/75/60 mg/kg/day. CCI [redacted] degeneration in mature male monkeys was observed in 1 monkey at 20 mg/kg/day and 2 monkeys at 100 mg/kg/day, one of which was recovery. Though severity of finding was less in the one recovery animal, the recovery period was of insufficient duration to assess reversibility. The NOAEL for CCI [redacted] finding in male monkeys was CCI [redacted]. Convulsions were observed at CCI [redacted] and were observed within 1-hour postdose, lasted less than 2 minutes, and reversed without therapeutic intervention. No convulsions occurred at CCI [redacted]. Liquid feces occurred

at CCI but did not increase in frequency with dose. Minimal decrease in red blood cell (RBC) mass was observed at 100/75/60 mg/kg/day. Minimal increase in fibrinogen, decrease in albumin, and increase alkaline phosphatase of uncertain relationship to TAK-418 was observed in individual animals across dose groups. At CCI, the mean C_{max} and AUC_{24} values after the 91st dose were CCI (males) and CCI and CCI (females). At CCI, the mean C_{max} and AUC_{24} values after the 91st dose were CCI for male monkeys.

6.3.3 Justification for Endpoints

6.3.3.1 Safety and PK

The primary endpoint for this trial is the composite of safety variables to determine the safety and tolerability of single oral doses of TAK-418, and dose-limiting effects of TAK-418. The secondary endpoints consist of standard PK variables to determine drug exposure at each dose to facilitate dose escalation.

6.3.3.2 Exploratory Endpoints

CCI

6.3.3.3 Biomarkers

CCI

6.3.3.4 Pharmacogenomics (PGx)

DNA and RNA from blood samples will be used to evaluate drug metabolizing enzymes and transporter polymorphisms that may contribute to the variability in the PK of TAK-418.

6.3.3.5 Wearable Devices

CCI

CCI

[redacted]

6.3.4 Critical Procedures Based on Trial Objectives: Timing of Procedures

For this trial, the collecting blood samples for TAK-418F (PK) is the critical procedure.

- At any postdose time point, the blood sample for TAK-418F (PK) needs to be collected as close to the exact time point as possible.
- All other procedures should be completed as close as possible, either before or after the prescribed/scheduled time.
- The order of priority can be changed during the trial with joint agreement of the investigator and the sponsor.

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

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

This is a phase 1 assessment of TAK-418 in humans, and the PK, PD, and safety profiles of the compound are still being elucidated. This protocol is written with some flexibility to accommodate the inherent dynamic nature of phase 1 clinical trials. Modifications to the dose, dosing regimen, and/or clinical or laboratory procedures currently outlined below may be required to achieve the scientific goals of the trial objectives and/or to ensure appropriate safety monitoring of the trial subjects.

Some alterations from the currently outlined dose and/or dosing regimen may be permitted based on newly available data, but the maximum daily dose/exposure detailed in Section 6.3.2, may not exceed those currently outlined.

- Additional cohorts may be added.
- Repeat of or decrease in the dose of the trial drug administered.
- Entire cohorts may be omitted.
- Lengthening of the washout period between doses if supported by safety and PK evidence.

- Decrease of the washout period between doses if supported by safety and PK evidence.
- A planned PK data review may be eliminated if agreed to by the sponsor and investigator and if no further increases in total daily dose occur.
- Addition of a PK data review.
- Instructions to take trial drug with or without food or drink may also be modified based on newly available data, that is, food effect is known.
- Modification of the fed cohort to another cohort.

The PK/PD sampling scheme currently outlined in the protocol may be modified during the trial based on newly available PK or PD data (eg, to obtain data closer to the time of peak plasma concentrations). If indicated, these collected samples may also be assayed in an exploratory manner for metabolites and/or additional PD markers.

Up to an additional 50 mL of blood may be drawn over the course of the study for PK and/or biomarker analyses. This may include repeat samples or modified PK/biomarker time points based on emerging data. The total blood volume withdrawn from any single subject will not exceed the maximum allowable volume during his/her participation in the entire trial.

The timing of planned procedures for assessment of safety procedures (eg, vital signs, ECG, safety laboratory tests) currently outlined in the protocol may be modified during the trial based on newly available safety, tolerability, PK, or PD/biomarker data (eg, to obtain data closer to the time of peak plasma concentrations). These changes will not increase the number of trial procedures for a given subject during his/her participation in the entire trial.

Additional laboratory safety tests may be added to blood samples previously drawn to obtain additional safety information (eg, adding creatine kinase to serum chemistry panel that was already drawn).

It is understood that the current trial may employ some or none of the alterations described above. Any alteration made to this protocol to meet the trial objectives must be detailed by the sponsor in a letter to the Trial File and forwarded to the investigator for retention. The letter may be forwarded to the institutional review board (IRB)/independent ethics committee (IEC) at the discretion of the investigator.

6.5 Trial Beginning and End/Completion

6.5.1 Definition of Beginning of the Trial

The overall trial begins when the first subject signs the trial informed consent form.

6.5.2 Definition of End of the Trial

The overall trial ends when the last subject completes the last planned or Follow-up Visit/interaction associated with a planned visit (this can be a phone contact), discontinues from the trial, or is lost to follow-up (ie, the investigator is unable to contact the subject).

6.5.3 Definition of Trial Completion

The primary objective of this early phase 1 trial is to evaluate safety and tolerability of TAK-418 when administered as single oral doses in healthy subjects. It is possible that trial subjects may not receive all doses specified in the protocol if this objective is achieved at lower dose levels in this trial. This is not considered an early termination of the trial, but rather an earlier than anticipated achievement of the trial objective(s) or trial completion. Therefore, the definition of trial completion follows the same rules as definition of end of trial (Section 6.5.2) for the dosing group achieving the primary objective.

6.5.4 Definition of Trial Discontinuation

Trial discontinuation because of nonsafety reasons, such as:

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

Trial discontinuation because of safety reasons:

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

6.5.5 Criteria for Premature Termination or Suspension of the Trial

6.5.5.1 Criteria for Premature Termination or Suspension of Trial Sites

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

6.5.5.2 Procedures for Premature Termination or Suspension of the Trial or the Participation of Trial Site(s)

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

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

7.1 Inclusion Criteria

To be eligible for participation in this trial, the subject must:

1. Understand the trial procedures and agree to participate by providing written informed consent.
2. Be willing and able to comply with all trial procedures and restrictions.
3. Be male subject or a female subject (with no childbearing potential) aged 18 to 55 years, inclusive, at the Screening Visit.
4. Have a body mass index (BMI) ≥18.5 and ≤30.0 (kg/m^2) at the Screening Visit.
5. Be a nonsmoker who has not used tobacco- or nicotine-containing products (eg, nicotine patch) for at least 6 months before administration of the initial dose of trial drug or invasive procedure.
6. Be judged to be in good health by the investigator, based on clinical evaluations including laboratory safety tests, medical history, physical examination, 12-lead ECG, and vital sign measurements performed at the Screening Visit and before administration of the initial dose of trial drug or invasive procedure as per principal investigator's judgment.
7. Female subjects with no childbearing potential, defined by at least 1 of the following criteria:
    a) Postmenopausal (defined as 12 months of spontaneous amenorrhea in women aged >45 years, 6 months of spontaneous amenorrhea in women aged >45 years with CCI [redacted] levels >40 mIU/mL). Appropriate documentation of CCI levels is required.
    b) Surgically sterile by hysterectomy and/or bilateral oophorectomy with appropriate documentation of surgical procedure.
    c) Had a tubal ligation with appropriate documentation of surgical procedure.
    d) Has a congenital condition resulting in no uterus.
8. Male subjects must have CCI [redacted]
9. Male subjects must use adequate contraception (as defined in the informed consent) from Screening, throughout the duration of the trial, and for 5 half-lives plus 90 days after last dose of trial medication and follow necessary precautions listed in Appendix D

7.2 Exclusion Criteria

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

1. Has participated in another investigational trial within 4 weeks before the pretrial (Screening) visit. The 4-week window will be derived from the date of the last trial procedure and/or AE

related to the trial procedure in the previous trial to the pretrial/Screening Visit of the current trial.

2. Is an employee or immediate family member (eg, spouse, parent, child, sibling) of clinical research unit (CRU) or of the sponsor.
3. Has a history of cancer (malignancy).
4. Has a history of significant multiple and/or severe allergies (eg, food, drug, latex allergy) or has had an anaphylactic reaction or significant intolerability to prescription or nonprescription drugs or food.
5. Has a positive alcohol or drug screen.
6. Has a positive pregnancy test.
7. Is breastfeeding.
8. Is positive for hepatitis B surface antigen (HBsAg), hepatitis C antibodies, or human immunodeficiency virus (HIV), confirmatory testing is allowed; most sensitive test should take precedence.
9. Had major surgery, donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks before the pretrial Screening Visit.
10. Male subjects who have serum CCI [redacted] that are clinically abnormal.
11. Is unable to refrain from or anticipates the use of any medication, including prescription and nonprescription drugs or herbal remedies beginning approximately 7 days before administration of the initial dose of trial drug, throughout the trial (including washout intervals between treatment periods), until the posttrial visit. There may be certain medications that are permitted, see Section 7.3.
12. Has a history of alcohol consumption exceeding 3 standard drinks per day on average (1 glass is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce] per day).
13. Consumes excessive amounts, defined as greater than 6 servings (1 serving is approximately equivalent to 120 mg of caffeine) of coffee, tea, cola, energy drinks, or other caffeinated beverages per day.
14. Is currently a regular user (including “recreational use”) of any illicit drugs or has a history of drug (including alcohol) abuse within approximately 6 months.
15. Has a risk of suicide according to the investigator’s clinical judgment per C-SSRS at Screening or has made a suicide attempt in the 6 months before Screening.
16. Has a clinically significant history of head injury, trauma, or seizures.
17. Has a lifetime history of major psychiatric disorder, such as major depressive disorder, bipolar disorder, or schizophrenia.

18. Is of any concern to the investigator regarding the safe participation of the subject in the trial or for any other reason the investigator considers the subject inappropriate for participation in the trial.
19. Screening ECG reveals a QT interval with Fridericia correction method (QTcF) >450 ms (men) or >470 ms (women).
20. Has a resting HR outside of the range of 50 to 100 beats per minute, confirmed on repeat testing within a maximum of 30 minutes, at Screening Visit or Check-in (Day -1).
21. Has a history of serious skin reactions (hypersensitivity) to adhesives, metals, or plastic; this criterion applies only to subjects participating in the trial of the 2 wearable digital devices.

7.3 Excluded Medications, Supplements, Dietary Products

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

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

Category	Between Screening and Randomization (Days -28 to Predose [Day 1])	Postrandomization (Day 1) to Follow-up
Tobacco- and nicotine-containing products	Completely restricted	Completely restricted
Cannabis products	Completely restricted	Completely restricted
Alcohol	Completely restricted 7 days before dosing	Completely restricted 7 days before dosing At all other times no more than 3 drinks/day
Xanthine and/or caffeine	Completely restricted 24 hours before dosing	Completely restricted 24 hours before dosing At all other times no more than 6 units/day
Medications	Completely restricted 7 days before dosing	Completely restricted (a)
Food substance		
Grapefruit/grapefruit juice	Completely restricted 7 days before dosing	Completely restricted
Fruit juice	No restriction	Dosing will occur without consumption of fruit juice. Fruit juice is restricted up to 4 hours postdose.
Mustard green (b)	Completely restricted 7 days before dosing	Completely restricted
Charbroiled meat	Completely restricted 7 days before dosing	Completely restricted

(a) If medications are required to treat an AE, certain medications may be allowed after discussion and agreement between the sponsor and principal investigator.
(b) Mustard green family includes kale, broccoli, watercress, collard greens, kohlrabi, Brussel sprouts, and mustard.

7.4 Diet, Fluid, Activity

7.4.1 Diet and Fluid

During confinement, subjects will be given 3 meals (with the exception of breakfast on Day 1 of the fasting regimens [all cohorts except Cohort 3B]) and an evening snack. Each meal will contain approximately 30% fat (relative to the total calories) except for the high fat meal on Day 1 during the fed regimen (Cohort 3B).

On Day 1 of the fasting regimens, subjects will be administered TAK-418 by mouth with 240 mL of water after an overnight fast of at least 10 hours. Subjects will continue to fast for an additional 4 hours after dosing. Lunch will be served following the 4-hour postdose PK blood collection. Subjects may consume water ad libitum with the exception of 1 hour before and 1 hour after trial drug administration.

On Day 1 of the fed regimen (Cohort 3B), after an overnight fast of at least 10 hours, subjects will receive a high-fat (approximately 50% of total caloric content of the meal) and high-calorie (approximately 800 to 1000 calories) meal (eg, 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 ounces of hash brown potatoes, and 8 ounces of whole milk). This test meal should derive approximately 150, 250, and 500 to 600 calories from protein, carbohydrate, and fat, respectively. The caloric breakdown of the test meal should be provided in the trial report. The meal must be consumed within 30 minutes. Within 5 minutes after the end of the meal, subjects will be administered TAK-418 by mouth with 240 mL of water. Lunch will be served following the 4-hour postdose PK blood collection. Subjects may consume water ad libitum with the exception of 1 hour before and 1 hour after trial drug administration.

Subjects will remain semirecumbent for 4 hours following trial drug administration, except as necessitated by the occurrence of an AE/or trial procedures (eg, obtaining 12-lead ECG).

7.4.2 Activity

Subjects will avoid unaccustomed strenuous physical activity (eg, weight lifting, running, bicycling) from the Screening Visit until the posttrial visit.

7.5 Criteria for Discontinuation or Withdrawal of a Subject

1. The subject experiences an AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the AE.
2. Liver Function Test (LFT) Abnormalities

   In multidose trials, trial drug should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a subject's laboratory profile has returned to normal/baseline status, see Section 10.2.9.5), if the following circumstances occur at any time during trial drug treatment:

- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >8 times the upper limit of normal (ULN), or
- ALT or AST >5×ULN and persists for more than 2 weeks, or
- ALT or AST >3×ULN in conjunction with elevated total bilirubin >2×ULN or international normalized ratio >1.5, or
- ALT or AST >3×ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

3. Significant protocol deviation. The discovery that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.
4. Lost to follow-up. The subject did not return to the clinic, and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented in the subject's source documentation.
5. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from the trial. The reason for withdrawal, if provided, should be recorded in the electronic case report form (eCRF).
   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category).
6. Trial termination. The sponsor, IRB, or regulatory agency terminates the trial.

Note: Skin reactions (cutaneous hypersensitivity) to one of the wearable digital devices will lead to removal of that device for the remainder of the trial. The subject would not be required to discontinue the other device or the trial as a whole.

7.6 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may discontinue a subject's trial participation at any time during the trial when the subject meets the trial termination criteria described in Section 7.5. In addition, a subject may discontinue his or her participation without giving a reason at any time during the trial. 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 Early Termination Visit.

7.7 Subject Replacement

If a subject discontinues from the trial, a replacement subject may be enrolled, if deemed appropriate by the investigator and sponsor. The trial site should contact the sponsor for the replacement subject's treatment assignment and randomization number.

8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

8.1 Clinical Trial Drug

Details regarding the composition and extemporaneous preparation of the active and placebo are found in the Pharmacy Manual, Compounding Instructions, and/or similar documents. Clinical trial drug will be packaged to support enrollment and replacement of subjects as required. When a replacement subject is required, the sponsor needs to be contacted before dosing.

8.1.1 Clinical Trial Drug Labeling

Clinical trial drug will be affixed with a clinical label in accordance with regulatory requirements.

8.1.2 Clinical Trial Drug Inventory and Storage

Clinical trial drug must be stored in a secure, limited-access location under the storage conditions specified on the label. Inventory (receipt and dispensing) of trial drug must be recorded by an authorized unblinded person at the trial site.

8.1.3 Clinical Trial Drug Blinding

This trial is blinded but provided open-label; therefore, an unblinded pharmacist or qualified trial site personnel will be used to blind supplies. Treatment identity (name, strength, or potency) is included in the label text; randomization code/disclosure envelopes or lists are provided.

8.1.4 Accountability and Destruction of Sponsor-Supplied Drugs

The investigator is responsible for keeping accurate records of the clinical trial drug received from the sponsor or designee, the amount dispensed to and returned by the subjects, and the amount remaining at the conclusion of the trial. For all trial sites, the local country sponsor personnel or designee will provide appropriate documentation that must be completed for clinical trial drug accountability, return, and destruction (or sponsor or designee-approved site equivalent forms).

8.1.5 Ancillary Supplies

All ancillary supplies will be provided by either the site or Takeda, based upon availability. If provided by Takeda, unused ancillary supplies will be accounted for and disposed of as directed by Takeda or a Takeda designee.

8.1.6 Randomization Code Creation and Storage

Randomization personnel of the sponsor or designee of the sponsor will generate the randomization schedule. All randomization information will be stored in a secured area, accessible only by authorized personnel.

8.1.7 Clinical Trial Blind Maintenance/Unblinding Procedure

Clinical trial drug blind is maintained through a randomization schedule held by the site unblinded pharmacist. The clinical trial drug blind shall not be broken by the investigator unless information

concerning the clinical trial drug is necessary for the medical treatment of the subject. If possible, the medical monitor should be contacted before the trial drug blind is broken. Unblinding is performed per the standard operating procedures of the sponsor or contract research organization (CRO).

9.0 STUDY PROCEDURES

The following sections describe the trial procedures and data to be collected as indicated in the Schedule of Trial Procedures (Section 3.0). For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. Please note that it may become necessary to perform the following procedures at unscheduled time periods, per the discretion of the investigator.

9.1 Administrative Procedures

9.1.1 Informed Consent Procedure

Informed consent must be obtained before the subject entering into the trial and before any protocol-directed procedures are performed. The requirements of informed consent are described in Section 13.2. A separate optional informed consent is required for the digital device component of the trial. Subject participation in the wearable device component of the trial is optional.

9.1.2 Assignment of Screening and Randomization Numbers

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur before randomization or allocation. Each subject will be assigned only 1 screening number. Screening numbers must not be re-used for different subjects. Any subject who is screened multiple times will be assigned a new screening number for each screening event.

All eligible subjects will be randomly allocated and will receive a randomization number. The randomization number identifies the subject for all procedures occurring after randomization. Once a randomization number is assigned to a subject, it can never be reassigned to another subject. A single subject cannot be assigned more than 1 randomization number.

9.1.3 Clinical Trial Drug Assignment

On Day 1, subjects will be assigned a randomization number in ascending numerical order at each trial site. The randomization number encodes the subject assignment to either the TAK-418 or the placebo arm of the trial, according to the randomization schedule generated before the trial by the sponsor's Statistics Department. Each participant will be dispensed blinded trial treatment, labeled with his/her unique randomization number, throughout the trial.

9.1.4 Inclusion and Exclusion Criteria

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

9.1.5 Medical History, Medication History, and Demographics

Qualified site personnel are to collect subject significant medical history (past and concurrent) per the site's standard of care and appropriate clinical judgment and subject demographics.

Qualified site personnel are to review subject prior and concomitant medication use. Medications are defined as prescription and over-the-counter drugs, vitamin supplements, nutraceuticals, and oral herbal preparations.

9.2 Clinical Procedures and Assessments

9.2.1 Full Physical Examination

Qualified site personnel will conduct full physical examinations.

9.2.2 Neurological Examination

Qualified site personnel will conduct full neurological examinations.

9.2.3 Height and Weight

Body weight and height will be obtained with the subject's shoes off, and jacket or coat removed.

9.2.4 BMI

BMI equals a person's weight in kilograms divided by height in meters squared (BMI=kg/m^2). Body weight and height will be obtained with the subject's shoes off and jacket or coat removed.

BMI will be rounded to the nearest whole number according to the standard convention of 0.1 to 0.4 round down and 0.5 to 0.9 round up.

9.2.5 Vital Signs

Body temperature will be measured with an oral (temperature taken at floor of the mouth) or tympanic thermometer. The same method (eg, oral or tympanic) must be used for all subsequent measurements for each individual subject and should be the same for all subjects.

Subjects should rest in a semirecumbent position for at least 5 minutes before having vital sign measurements obtained. Vital signs will include HR, SBP, and DBP. The same method (eg, same size cuff, manual or automated) must be used for all measurements for each individual subject and should be the same for all subjects.

Subjects will continue to rest in a semirecumbent position from the time of dosing until 4 hours postdose except to stand for the measurement of standing vital signs (if needed) or other trial-related procedure.

9.2.6 12-Lead ECG

Special care must be taken for proper lead placement by qualified personnel. Skin should be clean and dry before lead placement. Subjects may need to be shaved to ensure proper lead placement. Female subjects may need to remove their bra.

Subjects should be resting in a semirecumbent position for at least 5 minutes before each ECG measurement.

QT intervals with QTcF will be used to calculate QT intervals in this trial.

Before each treatment period/cohort, a predose ECG will be obtained within approximately 1 hour before dosing of TAK-418. This measurement will be used as the baseline. The principal investigator should arrange to have a trial cardiologist available as needed to review ECG tracings with abnormalities.

During each treatment period, if a subject demonstrates an increase in QTcF interval ≥40 msec compared with a predose baseline measurement, the ECG will be repeated within 5 minutes. The average value of the QTcF interval from the 2 ECGs will represent the value at that time point. If the average QTcF interval increase from Baseline for any postdose time point is ≥40 msec, the subject will continue to be monitored by repeat 12-lead ECGs every 60 minutes for at least 4 hours or until the QTcF is within 40 msec of the baseline value. If prolongation of the QTcF interval ≥40 msec persists, a consultation with a trial cardiologist may be appropriate and the sponsor should be notified.

If the QTcF interval is ≥500 msec, the sponsor should be notified and the ECGs should be reviewed by a cardiologist. The subject should be telemetry-monitored (until the QTcF is <500 msec) or should be considered for transfer to a location where closer monitoring is available.

If the subject has unstable hemodynamics, or has any clinically significant dysrhythmias noted on telemetry, the subject should be immediately transferred to an acute care setting for definitive therapy.

If repeat ECGs are required, the clinical site will decide whether to leave the electrodes in place or mark the position of the electrodes for subsequent ECGs. To mark the position of the electrodes, 12-lead electrode sites will be marked on the skin of each subject with an ECG skin marker pen to ensure reproducible electrode placement.

The following ECG parameters will be recorded: HR, PR-interval, QRS-duration, QT-interval, QTcF-interval, and the interpretation of the ECG profile by the principal investigator.

9.2.7 Trial Drug Administration

For the trial, trial drug (or placebo) will be administered in the manner described in Section 7.4.1.

9.2.8 BL-VAS

The Bond-Lader Visual Analogue Scale (BL-VAS) of Mood and Alertness consists of a questionnaire of 16 analogue scales that derive 3 factors that assess change in Self-Rated Alertness, Self-Rated Calmness, and Self-Rated Contentment. It has proven sensitivity to a wide range of compounds. In the original versions, ratings were performed by the subject by marking a point on a 10 cm line that is meant to represent the full range of the particular dimension (for example, alert—drowsy). Nine items assess alertness, 5 items assess contentedness, and 2 items assess calmness. A mark on the far left side or far right side of the scale represents extremes with regard to the adjectives on each side of the line (eg, a higher or more rightward score on a scale marked awake—drowsy indicates that the subject feels drowsier).

9.2.9 CCI

CCI

[redacted]

9.2.10 AE Monitoring

AE monitoring begins following signing of informed consent. Changes in subject health status from baseline assessment to trial drug administration should be captured in the subject's medical history. A complete description of AE collections and procedures is provided in Section 10.0.

9.2.11 Laboratory Procedures and Assessments

Laboratory samples will be collected in accordance with acceptable laboratory procedures. Samples will be taken following a minimum 8-hour overnight fast on the days stipulated in the Schedule of Trial Procedures (Section 3.0).

9.2.11.1 Clinical Laboratory Tests

Hematology

Hematology will consist of the following tests:

Erythrocytes (RBCs)	Hemoglobin
Hematocrit	Platelets
Leukocytes (white blood cells [WBCs]) with absolute differential	

Urinalysis

Urinalysis will consist of the following tests:

Protein	Glucose
Blood	Nitrite

Urine microscopy will be performed if urinalysis is abnormal. Microscopy consists of RBC/high-power field, WBC/high-power field, and casts.

Chemistry

Chemistry evaluations will consist of the following standard chemistry panel:

Albumin	Alkaline phosphatase
ALT	AST
Blood urea nitrogen	Calcium
Carbon dioxide	Chloride
Creatinine	Glucose
Gamma-glutamyl transferase	Sodium
Potassium	Bilirubin (total), if above ULN total bilirubin will be fractionated
Protein (total)	

9.2.11.2 Diagnostic Screening

Serum

Serum diagnostic evaluations will include the following tests:

HIV	Hepatitis Screen (HBsAg, hepatitis C virus antibody)
β–human chorionic gonadotropin (females only)	CCI [redacted]
CCI [redacted]	[redacted]
CCI [redacted]	[redacted]

Alcohol Screen

Subjects will undergo an alcohol breath test. A urine alcohol test may be performed at the discretion of the investigator.

Urine

A urine drug screen will include the following tests:

Amphetamines	Cotinine
Barbiturates	3,4-methylenedioxy-methamphetamine (MDMA)
Benzodiazepines	Methadone/metabolite
Buprenorphine/metabolite	Opiates
Cannabinoids	Oxycodone/oxymorphone
Cocaine/metabolites	Phencyclidine

CCI [redacted]

9.2.12 C-SSRS

Suicidal ideation will be assessed using the C-SSRS at the times stipulated in the Schedule of Study Procedures (Section 3.0).

Two versions of the C-SSRS will be used in this trial: the Screening/Baseline C-SSRS Lifetime and the Since-Last-Visit C-SSRS.

9.3 Biomarker, PK, PD, and PGx, Samples

Samples for PK, PD, and or other biomarker analysis will be collected as specified in the Schedule of Trial Procedures (Section 3.0). Please refer to the Laboratory Manual for information on the collection, processing, and shipment of samples to the Central Laboratory. CCI [redacted]

CCI [redacted]

It is anticipated that the total blood volume drawn will be approximately 250 mL for all cohorts except cohort 3 (fasted and fed), where it will be approximately 415 mL.

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

Table 9.a Primary Specimen Collections

CCI

9.3.1 PK Measurements

The PK parameters of TAK-418F will be derived using noncompartmental analysis methods and will be determined from the concentration-time data for all evaluable subjects. Actual sampling times, rather than scheduled sampling times, will be used in all PK computations involving sampling times for plasma PK parameters. Nominal time intervals will be used for computations of urine PK parameters.

The following PK parameters will be calculated as appropriate:

- t_{max}.
- C_{max}.
- AUC_{last}.
- AUC_{∞}.
- CCI
-
-

- CCI [redacted]

Additional PK parameters may be calculated as appropriate. A detailed PK analysis plan will be prepared before PK parameter computation.

9.3.1.1 Plasma for PK Measurements

PK blood samples for plasma TAK-418F concentrations will be collected as specified in the Schedule of Trial Procedures (See Section 3.0).

Plasma TAK-418F concentration will be measured by liquid chromatography with tandem mass spectrometry method.

9.3.1.2 Urine for PK Measurements

PK urine samples for urine TAK-418F concentrations will be collected as specified in the Schedule of Trial Procedures (See Section 3.0).

Urine TAK-418F concentration will be measured by liquid chromatography with tandem mass spectrometry method.

9.3.2 Biomarker Measurements

9.3.2.1 CCI [redacted]

CCI [redacted]

9.3.2.2 CCI [redacted]

CCI [redacted]

9.3.2.3 CCI [redacted]

CCI [redacted]

9.3.3 PGx Measurements

9.3.3.1 Blood Sample for DNA and RNA PGx Measurements

Blood samples for DNA and RNA PGx measurement will be taken.

When sampling of whole blood for PGx analysis occurs, every subject must sign an informed consent/be consented to participate in the trial. PGx is a component of the trial, and participation is mandatory.

PGx is the study of variations of DNA and RNA characteristics as related to drug response. There is increasing evidence that an individual's genetic background may affect the PK (absorption, distribution, metabolism, and excretion), PD (pharmacologic effects) and/or the clinical outcome (efficacy and/or safety).

PGx research in this trial may be conducted to understand how individual genetic variation in subjects affects their trial drug treatment response. This information may also be used, for example, to develop a better understanding of the safety and efficacy of TAK-418 and other trial drugs, to interpret changes in biomarkers, to increase understanding of the disease/condition being studied and other related conditions, to gain a better understanding of the drug pharmacology and for generating information needed for research, development, and regulatory approval of tests to predict response to TAK-418 or to monitor the response to TAK-418.

Whole blood samples for DNA and RNA isolation will be collected from each consented subject in the trial. If necessary and feasible, a second aliquot of blood may be taken at a later time point if isolation of DNA from the first sample was not successful or possible.

Since PGx is an evolving science, many genes and their functions are not yet fully understood. Future data may suggest a role of these genes in drug response, which may lead to additional hypothesis-generating exploratory research and diagnostic development on stored samples.

Detailed instructions for the handling and shipping of samples are provided in the Laboratory Manual.

9.3.3.2 Biological Sample Retention and Destruction

In this study, blood, CCI and urine samples for biomarker measurement will be collected as described in Section 9.3.3.1. Any leftover biomarker samples if not used will be preserved and retained at sponsor selected for long term storage facility for up to 15 years from the end of study. After that time the samples will be destroyed.

The PGx samples will be initially stored at a vendor/comparable laboratory, under contract to Takeda, with validated procedures in place, and then preserved and retained at a sponsor selected long-term storage facility, for up to but not longer than 15 years from the end of the study when the study report is signed, or if less, the maximum period permitted under applicable law or until consent is withdrawn.

The sponsor and vendors working with the sponsor will have access to the samples collected and any test results. All samples collected during the trial will be stored securely with limited access and the sponsor will require anyone who works with the samples to agree to hold the research information and any results in confidence.

The sample will be labeled with a unique sample identifier as in the main trial but using a code that is different from the code attached to the health information and other clinical test results collected

in the trial. The sample and data are linked to personal health information with code numbers; the samples are stripped of all personal identifying information but a key linking the samples to clinical analysis data exists. This link means that the subject may be identified but only indirectly. The sample identifier will be kept secure by or on behalf of the sponsor.

Subjects who consented and provided a PGx sample for DNA and RNA analysis can withdraw their consent at any time and request disposal of a stored sample. Any remaining sample that can be identified as coming from the subject will be destroyed. The trial doctor and sponsor may continue to use and distribute any information and test results gathered before the request to withdraw.

9.3.4 CCI

CCI

9.3.5 Confinement

Subjects will report to the clinical site on the evening before (Day -1) the scheduled day of administration of the trial drug. Subjects will remain in the unit until 48 hours postdose. At the discretion of the investigator, subjects may be requested to remain in house longer.

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 trial; 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 underlying disease should not be considered AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of trial 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 to be AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory re-test and/or continued monitoring of an abnormal value are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.
- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), the diagnosis only should be reported appropriately as an AE.

Pre-existing conditions:

- A pre-existing condition (present at the time of signing of informed consent) is considered a concurrent medical history condition and should NOT be recorded as an AE. A baseline evaluation (eg, laboratory test, ECG, x-ray) should NOT be recorded as an AE unless related to a trial 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 trial medication or after any change in trial 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 trial medication, the event should be captured once with the maximum severity recorded.

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled before signing of informed consent are not considered AEs. However, if a preplanned procedure is performed early (eg, as an emergency) because of 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 trial subject, at a dose above that which is assigned to that individual subject according to the trial 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 eCRF, 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 10.2.9.
- 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.
    - Includes any event or synonym described in the Takeda Medically Significant AE List (Table 10.a).

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 Section 10.2.9.3).

10.1.2 Special Interest AEs

No AEs of special interest have been identified for this compound.

10.2 AE Procedures

10.2.1 Assigning Severity/Intensity of AEs

The different categories of severity/intensity are:

Mild:	The event is transient and easily tolerated by the subject.
Moderate:	The event causes the subject discomfort and interrupts the subject's usual activities.
Severe:	The event causes considerable interference with the subject's usual activities.

10.2.2 Assigning Causality of AEs

The relationship of each AE to trial 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 possible involvement of the drug can be argued, 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 drugs and concurrent treatments.

10.2.3 Assigning Relationship to Trial Procedures

Relationship (causality) to trial procedures should be determined for all AEs.

The relationship should be assessed as "Related" if the investigator considers that there is reasonable possibility that an event is due to a trial procedure. Otherwise, the relationship should be assessed as "Not Related".

10.2.4 Start Date

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

10.2.5 Stop Date

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

10.2.6 Frequency

Episodic AEs (eg, headache) or those that occur repeatedly over a period of consecutive days are intermittent. All other events are continuous.

10.2.7 Action Concerning Trial Drug

- Drug withdrawn: a trial medication is stopped because of the particular AE.
- Dose not changed: the particular AE did not require stopping a trial medication.
- Unknown: only to be used if it has not been possible to determine what action has been taken.
- Not applicable: a trial medication was stopped for a reason other than the particular AE, for example, the trial has been terminated, the subject died, dosing with trial medication was already stopped before the onset of the AE.

10.2.8 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 trial 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."
- 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 because of hospital change or residence change at the end of the subject's participation in the trial.

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

10.2.9.1 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. For female subjects, routine collection of AEs will continue until the follow-up on Day 14 (±2 days). In addition, for male subjects, routine collection of AEs will continue until Days 93 and/or 184 (±7 days). For subjects who discontinue before the administration of trial medication, AEs will be followed until the subject discontinues trial participation.

10.2.9.2 Reporting AEs

At each trial 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 trial. Subjects experiencing an SAE before 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. Nonserious AEs that begin before the first exposure to investigational product, related or unrelated to the trial procedure, need not be followed-up for the purposes of the protocol.

All subjects experiencing AEs, whether considered associated with the use of the trial 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 eCRF, 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 stop date and time.
- Severity.
- Investigator's opinion of the causal relationship between the event and administration of trial medication(s) (related or not related).
- Investigator's opinion of the causal relationship to trial procedure(s), including the details of the suspected procedure.
- Action concerning trial medication.
- Outcome of event.

- Seriousness.

10.2.9.3 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 trial 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 trial 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.

10.2.9.4 Reporting Special Interest AEs

No AEs of special interest have been identified for TAK-418.

10.2.9.5 Reporting of Abnormal LFTs

If a subject is noted to have ALT or AST elevated >3×ULN on 2 consecutive occasions, the abnormality should be recorded as an AE. In addition, an LFT Increases eCRF must be completed providing additional information on relevant recent history, risk factors, clinical signs and symptoms and results of any additional diagnostic tests performed.

If a subject is noted to have ALT or AST >3×ULN and total bilirubin >2×ULN for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported per Section 10.2.9.3. The investigator must contact the Medical Monitor for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease. Follow-up laboratory tests as described in Section 9.2.11 must also be performed. In addition, an LFT Increases eCRF must be completed and transmitted with the Takeda SAE form (per Section 10.2.10).

10.2.9.6 Exploratory Biomarkers and Data From Wearable Devices

- Changes from Baseline in exploratory biomarkers will not be considered as adverse events and will not be used to guide the subject's medical care during the study.
- The vital sign and cardiac rhythm data derived from the Body Guardian device will be analyzed at the end of the trial. These data are exploratory in nature. Abnormalities detected solely by the digital devices will not be considered AEs and will not be used to guide a subject's medical care during this trial.

10.2.10 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 trial 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 trial. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

11.0 STATISTICAL METHODS

11.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized before unblinding of subject's treatment assignment. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all trial objectives.

A targeted data review will be conducted before unblinding of subject's treatment assignment.

This review will assess the accuracy and completeness of the trial database, subject evaluability, or appropriateness of the planned statistical methods.

11.1.1 Analysis Sets

Safety Set

The safety set will consist of all subjects who receive at least 1 dose of trial drug. Subjects in this analysis set will be used for demographic, baseline characteristics, and safety summaries.

PK Set

The PK set will consist of all subjects who receive at least 1 dose of trial drug and have at least 1 measurable plasma concentration or amount of drug in the urine for TAK-418. All subjects with valid PK parameter estimates will be included in the summaries and analyses for that parameter.

PD/Biomarker Set

The PD/biomarker set will consist of all subjects who receive at least 1 dose of trial drug and have at least 1 postdose value for PD/biomarker parameter.

If any subject is found to be noncompliant with the dosing schedule or has incomplete data, a decision will be made on a case-by-case basis as to whether that subject should be included in the PK and PD analyses; however, data for all subjects will be presented in the data listings.

11.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized for the pooled placebo group, each TAK-418 dose level, TAK-418 overall, and overall including placebo group. Summary statistics (number of subjects, mean, SD, median, minimum, and maximum) will be presented for continuous variables (eg, age, weight, and BMI), and the number and percentage of subjects within each category will be presented for categorical variables (eg, sex, ethnicity, and race). Individual subject demographic and baseline characteristic data will be provided in the data listings.

11.1.3 PK Analysis

Plasma concentrations of TAK-418F will be summarized by dose over each scheduled sampling time using descriptive statistics.

The amount of TAK-418F excreted in urine will be summarized by dose using descriptive statistics.

Individual plasma and urine concentration versus time and PK parameter data will be presented in a data listing.

Plasma and urine PK parameters of TAK-418F will be summarized by dose using descriptive statistics.

If sufficient data are available, dose proportionality of TAK-418F plasma exposures (C_{max} and AUC) will be assessed statistically using a power model. For evaluation of potential food effect on TAK-418F PK, log-transformed C_{max} and AUC values will be compared between the treatments (Reference=fasting administration; Test=fed administration) using an analysis of variance (ANOVA) with fixed effect for treatment and a random effect for subject. The geometric mean relative bioavailability and 90% CIs for C_{max}, AUC_{last}, and AUC_{∞} will be calculated based upon the adjusted means (LS means) from the ANOVA.

A more detailed analysis will be presented in the SAP. Additional analyses will be included, if appropriate.

11.1.4 CCI

CCI [redacted]

11.1.5 CCI

CCI [redacted]

11.1.6 Safety Analysis

The safety set will be used for all summaries of safety parameters. These summaries will be presented by pooled placebo, each TAK-418 dose level, and TAK-418 overall (as appropriate). Safety data collected after administration of trial drug under fed conditions will be summarized separately.

11.1.6.1 AEs

All AEs will be coded by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA). TEAEs with onset occurring within 30 days (onset date – last date of dose +1≤30) after trial drug administration will be included in the

summary tables. All AEs will be in the listings. TEAEs will be summarized by SOC and PT. The following summary tables will be included in the report: summary of TEAEs and drug-related AEs, relationship of AEs to trial drug (related vs not related), severity of AEs, and related AEs. Data listings will be provided for all AEs including TEAEs, AEs leading to trial drug discontinuation, and SAEs.

11.1.6.2 Clinical Laboratory Evaluation

Individual results of laboratory tests from hematology, chemistry, and urinalysis that meet Takeda's markedly abnormal criteria will be summarized and provided in the data listings. Baseline, postdose, and change from Baseline to postdose laboratory data will be summarized. All clinical laboratory data will be provided in the data listings.

11.1.6.3 Vital Signs

Individual results of vital signs that meet Takeda's markedly abnormal criteria will be summarized and provided in the data listings. Baseline, postdose, and changes from Baseline in vital sign measurements will be summarized. All vital sign data will be provided in the data listings.

11.1.6.4 ECGs

Individual results of quantitative ECG parameters from the 12-lead safety ECGs that meet Takeda's markedly abnormal criteria will be summarized and provided in the data listings. Baseline, postdose, and changes from Baseline in quantitative ECG parameters will be summarized. Shift tables will be generated to show the investigator's ECG interpretations at each postdose collection by the interpretation at Baseline.

All ECG data will be provided in the data listings.

11.1.6.5 Other Safety Parameters

Physical examination findings will be presented in the data listings.

11.2 Interim Analysis and Criteria for Early Termination

No formal interim analyses will be conducted. Safety and PK data (at least up to 24 hours postdose) will be reviewed after each dose before escalation to the next dose.

11.3 Determination of Sample Size

The sample size of 8 subjects per cohort (6 active: 2 placebo) chosen is based upon precedents from other FIH trials rather than a formal assessment of statistical power.

Subjects who drop out for nonsafety reasons may be replaced on a case-by-case basis at the discretion of the sponsor in consultation with the investigator. Subjects who replace dropouts will be allocated to the same dose as the subject they replace. Subjects who drop out for safety reasons will not be replaced.

12.0 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Trial-Site Monitoring Visits

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

All aspects of the trial 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, trial drug, subject medical records, informed consent documentation, and review of eCRFs and associated source documents. It is important that the investigator and other trial 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 trial subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

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

12.2.1 CCI

CCI [redacted]

12.3 Quality Assurance Audits and Regulatory Agency Inspections

The trial 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 trial. In addition, there is the possibility that this trial 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

trial 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 trial documents as described in Section 12.1.

13.0 ETHICAL ASPECTS OF THE STUDY

This trial will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the International Council for Harmonisation (ICH) Harmonised Tripartite Guideline for GCP. Each investigator will conduct the trial 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 trial, 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 because of 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 trial (ie, before shipment of the sponsor-supplied drug or trial specific screening activity). The IRB or IEC approval must refer to the trial 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 trial. 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 trial 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 trial. The informed consent form and the subject information sheet (if applicable) further explain the nature of the trial, its objectives, and potential risks and benefits, in addition to 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 before 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 trial, and (2) decide whether or not to participate in the trial. If the subject, or the subject's legally acceptable representative, determines he or she will participate in the trial, 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 before the subject entering into the trial. 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 before subject entering into the trial; 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.

Subjects who consented and provided a blood and/or CCI samples for DNA and/or RNA analysis can withdraw their consent and request disposal of a stored sample at any time before analysis. Notify sponsor of consent withdrawal.

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 trial, a subject's source data will only be linked to the sponsor's clinical trial 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 trial 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 (ie, subject name, address, and other identifier fields not collected on the subject's eCRF).

13.4 Publication, Disclosure, and Clinical Trial 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 trial. During and after the trial, only the sponsor may make trial information available to other trial investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical trial site agreement, any public disclosure (including publicly accessible websites) related to the protocol or trial results, other than trial recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the trial (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 Trial Registration

To ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum register all interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov and/or other publicly accessible websites before start of trial, 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 trial sites closest to their homes by providing the investigator name, address, and phone number to the callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

Any investigator who objects to 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 Trial Results Disclosure

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

13.5 Insurance and Compensation for Injury

Each subject in the trial 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 trial insurance against the risk of injury to trial subjects. Refer to the trial 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 Trial Contact Information

Contact Type/Role	Contact
SAE and pregnancy reporting	Pharmacovigilance Takeda Development Center Americas, Inc. Fax: 224-554-1052

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 trial in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of trial subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting SAEs defined in Section 10.2.10 of this protocol.
- Terms outlined in the trial site agreement.
- Responsibilities of the Investigator (Appendix A).

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

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Provence)

Location of Facility (Country)

14.1.3 Trial-Related Responsibilities

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

14.1.4 List of Abbreviations

AE	adverse event
ALT	alanine aminotransferase
ANOVA	analysis of variance
ASD	autism spectrum disorder
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{24}	area under the serum concentration-time curve from time 0 to 24 hours
AUC_{∞}	area under the concentration-time curve from time 0 to infinity, calculated using the observed value of the last quantifiable concentration
AUC_{last}	area under the concentration-time curve from time 0 to time of the last quantifiable concentration
BDNF	brain-derived neurotrophic factor
BL-VAS	Bond-Lader Visual Analogue Scale
BMI	body mass index
CFR	Code of Federal Regulations
Clu	clusterin
C_{max}	maximum observed concentration
CoREST	REST corepressor 1
CRO	contract research organization
CRU	clinical research unit
C-SSRS	Columbia Suicide Severity Rating Scale
CtBP	C-terminal-binding protein
CYP	cytochrome P-450
DBP	diastolic blood pressure
DSST	Digital Symbol Substitution Test
ECG	Electrocardiogram
eCRF	electronic case report form
F	free base
FAD	flavin adenine dinucleotide
FDA	Food and Drug Administration
F-FAD	formyl-flavin adenine dinucleotide
FIH	first-in-human
CCI	[redacted]
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GTPase	guanosine triphosphatase
H3K4	position 4 of type 3 histone
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HED	human equivalent dose

HIV	human immunodeficiency virus
HR	heart rate
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IRB	institutional review board
KDM1	lysine-specific demethylase family 1
KDM1A	LSD1
LFT	liver function test
[redacted]	[redacted]
LSD1	lysine-specific demethylase 1A
MedDRA	Medical Dictionary for Regulatory Activities
MRD	multiple rising dose
mRNA	messenger RNA
miRNA	micro RNA
NOAEL	no-observed-adverse-effect level
NuRD	nucleosome Remodeling Deacetylase
PAD	pharmacologically active dose
PBMC	peripheral blood mononuclear cells
PD	pharmacodynamic(s)
PGx	pharmacogenomics
PK	pharmacokinetic(s)
PT	preferred term
Ptgds	prostaglandin D2 synthase
QTcF	QT interval with Fridericia correction method
RBC	red blood cell
REST	repressor element-1 silencing transcription factor
RNA-Seq	RNA-sequencing
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SNAG	SNAIL (Zinc finger protein SNAI1)/Gfi-1 (Zinc finger protein encoded by the GFI1 gene)
SOC	system organ class
SRD	single rising dose
SUSAR	suspected unexpected serious adverse reactions
$t_{1/2z}$	terminal disposition phase half-life
TAL1	T-cell acute lymphocytic leukemia protein 1
TEAE	treatment-emergent adverse event
TLX	Nuclear receptor encoded by the *NR2E1* gene
t_{max}	time of first occurrence of C_{max}
Tmeff1	follistatin like domains 1
ULN	upper limit of normal

WBC	white blood cell

14.1.5 Corporate Identification

TDC Japan	Takeda Development Center Japan
TDC Asia	Takeda Development Center Asia, Pte Ltd
TDC Europe	Takeda Development Centre Europe Ltd.
TDC Americas	Takeda Development Center Americas, Inc.
TDC	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable
Takeda	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable

15.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, medical history, and concurrent conditions will be coded using the MedDRA. Drugs will be coded using the World Health Organization Drug Dictionary.

15.1 CRFs (Electronic and Paper)

Completed eCRFs are required for each subject who signs an informed consent.

The sponsor or its designee will supply investigative sites with access to eCRFs. The sponsor will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this trial to the sponsor and regulatory authorities. eCRFs must be completed in English. Data are transcribed directly onto eCRFs.

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

After the lock of the clinical trial database, any change of, modification of, or addition to the data on the eCRFs should be made by the investigator with use of change and modification records of the eCRFs. The principal investigator must review the data change for completeness and accuracy, and must sign and date.

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

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 trial-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 eCRFs, 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 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the trial 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.

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17.0 APPENDICES

Appendix A Responsibilities of the Investigator

Clinical research trials 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 trial.

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

1. Conduct the trial 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 trial-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.
4. Ensure that trial related procedures, including trial specific (nonroutine/nonstandard panel) screening assessments are NOT performed on potential subjects, before the receipt of written approval from relevant governing bodies/authorities.
5. Ensure that all colleagues and employees assisting in the conduct of the trial are informed of these obligations.
6. Secure prior approval of the trial and any changes by an appropriate IRB/IEC that conform to 21 Code of Federal Regulations (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 trial to the IRB/IEC, and issue a final report within 3 months of trial 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 trial, 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 trial. 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 trial, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of

2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

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 trial 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 trial.
7. A description of the subject's responsibilities.
8. A description of the conduct of the trial.
9. A statement describing the treatment(s) and the probability for random assignment to each treatment.
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 trial.
17. The anticipated expenses, if any, to the subject for participating in the trial.
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 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 trial.
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 trial 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 trial. 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 trial medication(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical trials;
    d) that subjects agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the trial 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 trial results are published.

25. Male subjects must use adequate contraception (as defined in the informed consent) from Screening, throughout the duration of the trial, and for 5 half-lives plus 90 days after last dose of trial medication. If the partner or wife of the subject is found to be pregnant during the trial, the investigator will offer the subject the choice to receive unblinded treatment information.
26. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix C Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of investigator, including his or her name, address, and other personally identifiable information. In addition, investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the 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 trial and/or other clinical trials.
- Management, monitoring, inspection, and audit of the trial.
- Analysis, review, and verification of the trial results.
- Safety reporting and pharmacovigilance relating to the trial.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the trial.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical trials that may contain the same chemical compound present in the trial medication.
- Inspections and investigations by regulatory authorities relating to the trial.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of trial records.
- Posting investigator site contact information, trial details and results on publicly accessible clinical trial registries, databases, and websites.

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

Female Subjects and Their Male Partners

Female subjects of childbearing potential are excluded from this trial; there are no requirements for contraception or pregnancy avoidance.

Male Subjects and Their Female Partners

From signing of informed consent, throughout the duration of the trial, and for 5 half-lives PLUS 90 days after the last dose of trial drug, male subjects who are sexually active with a female partner of childbearing potential must use barrier contraception (eg, condom with or without spermicidal cream or jelly). In addition, they must be advised not to donate sperm during this period. Females of childbearing potential who are partners of male subjects are also advised to use additional contraception as shown in the list containing highly effective/effective contraception below.

1. Highly effective methods of contraception are defined as "those, alone or in combination, that result in a low failure rate (ie, less than 1% failure rate per year when used consistently and correctly). In this trial, where medications and devices containing hormones are included, females of childbearing potential who are partners of male subjects are advised to use additional contraception chosen from the list below:
    - Nonhormonal methods:
        - Intrauterine device.
        - Bilateral tubal occlusion.
    - Hormonal methods:
        - Combined (estrogen and progestogen) hormonal contraception associated with inhibition of ovulation initiated at least 3 months before the first dose of trial drug.
            - Oral.
            - Intravaginal (eg, ring).
            - Transdermal.
        - Progestogen-only hormonal contraception associated with inhibition of ovulation initiated at least 3 months before the first dose of trial drug.
            - Oral.
            - Injectable.
            - Implantable.
2. Since genotoxicity/teratogenicity/embryotoxicity is unlikely to be caused by the investigational drug, additional effective methods of contraception (there may be a higher than 1% failure rate) that may be chosen by the female partner of a male subject are:

- Double-barrier method (contraceptive sponge, diaphragm or cervical cap with spermicidal jellies or creams).
- Progestogen only hormonal contraception, where inhibition of ovulation is not the primary mode of action.

3. Unacceptable methods of contraception are:
   - Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods).
   - Spermicides only.
   - Withdrawal.
   - No method at all.
   - Use of female and male condoms together.
   - Cap/diaphragm/sponge without spermicide and without condom.
4. Male subjects will be provided with information on highly effective/effective methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy and sperm donation during the course of the trial.
5. Male subjects will receive continued guidance with respect to the avoidance of pregnancy and sperm donation as part of the trial procedures. Such guidance should include a reminder of the following:
   - Contraceptive requirements of the trial.
   - Reasons for use of barrier methods (ie, condom) in males with pregnant partners.
   - Assessment of subject compliance through questions such as
     – Have you used the contraception consistently and correctly since the last visit?
     – Have you forgotten to use contraception since the last visit?

Appendix E Detailed Description of Amendments to Text

The primary section(s) of the protocol affected by the changes in Amendment No. 01 are indicated. The corresponding text has been revised throughout the protocol.

Change 1: Modified study design to delete the MRD part of the study and associated assessments, and clarified the SRD part.

Initial wording:

This is an FIH, randomized, double-blind, placebo-controlled trial to evaluate the safety, tolerability, and PK of TAK-418. The trial will also explore the PD of TAK-418 and its effects on selected biomarkers following single and multiple doses in healthy adult subjects.

The trial is composed of 2 parts: Part 1 (SRD) and Part 2 (MRD). Both Parts 1 and 2 are sequential panel design in healthy subjects.

Part 1: SRD in Healthy Subjects

Part 1 consists of 5 cohorts of subjects, sequentially paneled, with a double-blind design. Each cohort will consist of 8 subjects, where 6 subjects will be randomized to receive TAK-418 and 2 subjects will be assigned to receive matching placebo. The trial population for Part 1 will be approximately 40 healthy subjects. Additional cohorts may be studied if deemed necessary to fully characterize the pharmacologically active exposure range. For Cohort 3, there will be at least 7 days of washout between dose administration in the fasted and fed states.

The planned dose levels of TAK-418 to be evaluated in Cohorts 1 to 5 are outlined in Table 6.a.

[Table 6.a Part 1: Schematic and Planned Doses of Trial Design—Cohorts 1 to 5]

(a) An additional cohort may be studied if deemed necessary to fully characterize the pharmacologically active exposure range.
(b) Doses planned to be administered range from 5 to 180 mg, but the actual doses administered after the first dose will be based on emerging safety and tolerability data from the previous doses. The highest dose administered will have a predicted mean area under the concentration-time curve (AUC) that does not exceed the monkey AUC at the no-observed-adverse-effect level (NOAEL) or mean C_{max} that does not exceed one-tenth of the monkey C_{max} at the NOAEL.
(c) Cohorts 3A and 3B will be evaluated with the same subjects for the assessment of food effect on TAK-418. Only Cohort 3B will be administered TAK-418 under fed condition with a high fat/high calorie breakfast.

Part 2: MRD in Healthy Subjects

Part 2 will consist of 3 cohorts of subjects, sequential multiple-dose panels, with a double-blind design. Three dose cohorts, Cohorts 6, 7, and 8, are considered adequate to explore the pharmacologically active exposure range. Each cohort will be comprised of 8 subjects, where 6 subjects will be randomized to receive TAK-418 and 2 subjects will be assigned to receive matched placebo. The trial population for Part 2

will be comprised of approximately 24 healthy subjects. Part 2 may commence after completion of SRD Cohort 3A in Part 1, in which the starting dose will not exceed the dose tested in Cohort 3A from Part 1.

It is planned that subjects will receive once-daily (QD) dosing of TAK-418 or matching placebo for 7 days to achieve steady-state. The mean terminal disposition phase half-life ($t_{1/2z}$) of TAK-418 from Part 1 will inform the duration of dosing required in Part 2 to achieve steady-state.

Two wearable digital devices, an actigraphy device and an ECG device, will be applied from Day -1 in subjects who consent to be in this additional exploratory part of the trial. Both devices will be used continuously through the dosing procedures, the postdosing period while subjects are in the unit, and for approximately 6 days after the subjects' discharge from the unit. Subjects will return the devices to the unit at the follow-up visit.

The trial schedule is detailed in Table 6.c.

[Table 6.c Part 2: Trial Schedule]

Amended or new wording:

This is an FIH, randomized, double-blind, placebo-controlled trial to evaluate the safety, tolerability, and PK of TAK-418 **in healthy adult subjects.** The trial will also explore the PD of TAK-418 and its effects on selected biomarkers following single ~~and multiple~~ **oral** doses in healthy adult subjects.

~~The trial is composed of 2 parts: Part 1 (SRD) and Part 2 (MRD). Both Parts 1 and 2 are sequential panel design in healthy subjects.~~

~~**Part 1: SRD in Healthy Subjects**~~

~~Part 1~~ **This study** consists of 5 cohorts of subjects, sequentially paneled, with a double-blind design. Each cohort will consist of 8 subjects, where 6 subjects will be randomized to receive TAK-418 and 2 subjects will be assigned to receive matching placebo. **A minimum of 4 male subjects will be enrolled in each cohort.** The trial population will be approximately 40 healthy subjects. Additional cohorts may be studied if deemed necessary to fully characterize the pharmacologically active exposure range. For Cohort 3, there will be at least 7 days of washout between dose administration in the fasted and fed states.

The planned dose levels of TAK-418 to be evaluated in Cohorts 1 to 5 are outlined in Table 6.a.

[Table 6.a Schematic and Planned Doses of Trial Design—Cohorts 1 to 5]

~~(a) An~~ **Additional** cohort**s** may be studied if deemed necessary to fully characterize the pharmacologically active exposure range.

~~(b)~~ Doses planned to be administered range from 5 to 180 mg, but the actual doses

administered after the first dose will be based on emerging safety and tolerability data from the previous doses. **If needed, a dose higher than 180 mg but less than 300 mg may be evaluated providing its predicted exposure does not exceed the following exposure levels.** The highest dose administered will have a predicted mean area under the **plasma** concentration-time curve (AUC) that does not exceed the monkey AUC at the no-observed-adverse-effect level (NOAEL; **males) from the 13-week toxicology study or mean maximum observed concentration** (C_{max}) that does not exceed one-tenth of the monkey C_{max} from the **4-week toxicology study.**

~~(c) Cohorts 3A and 3B will be evaluated with the same subjects for the assessment of food effect on TAK-418. Only Cohort 3B will be administered TAK-418 under fed condition with a high fat/high calorie breakfast.~~

Subjects in Cohort 3 will receive 2 doses (under fasted state [Cohort 3A] and with food [Cohort 3B]), with at least 7 days of washout between dose administrations. Subjects enrolled in Cohort 3A will return to the site to complete Cohort 3B and will be administered TAK-418/placebo under fed condition with a high fat/high calorie breakfast, which must start 30 minutes before the dose is administered. All assessments from Day -1 to Day 4 in Cohort 3B will be same as in Cohort 3A; however, there will be no follow-up for CCI [redacted] **after Cohort 3A and the Day 14 follow-up assessment for Cohort 3B. For male subjects,** CCI [redacted] **days will be adjusted based on dosing in Cohort 3B.**

~~**Part 2: MRD in Healthy Subjects**~~

~~Part 2 will consist of 3 cohorts of subjects, sequential multiple-dose panels, with a double-blind design. Three dose cohorts, Cohorts 6, 7, and 8, are considered adequate to explore the pharmacologically active exposure range. Each cohort will be comprised of 8 subjects, where 6 subjects will be randomized to receive TAK-418 and 2 subjects will be assigned to receive matched placebo. The trial population for Part 2 will be comprised of approximately 24 healthy subjects. Part 2 may commence after completion of SRD Cohort 3A in Part 1, in which the starting dose will not exceed the dose tested in Cohort 3A from Part 1.~~

~~It is planned that subjects will receive once-daily (QD) dosing of TAK-418 or matching placebo for 7 days to achieve steady-state. The mean terminal disposition phase half-life ($t_{1/2z}$) of TAK-418 from Part 1 will inform the duration of dosing required in Part 2 to achieve steady-state.~~

~~Two wearable digital devices, an actigraphy device and an ECG device, will be applied from Day -1 in subjects who consent to be in this additional exploratory part of the trial. Both devices will be used continuously through the dosing procedures, the postdosing period while subjects are in the unit, and for approximately 6 days after the subjects' discharge from the unit. Subjects will return the devices to the unit at the follow-up visit.~~

~~The trial schedule is detailed in Table 6.c.~~

~~[Table 6.c Part 2: Trial Schedule]~~

Rationale for Change:

Change in study design to exclude MRD part of the study, include male subjects with normal [redacted], and to provide additional clarification.

The following sections also contain this change:

- Title Page
- Section 1.0 STUDY SUMMARY
- Section 2.0 Trial Schematic
- Section 3.0 Schedule of Trial Procedures
- Section 5.1.1 Primary Objective
- Section 5.1.2 Secondary Objective
- Section 5.1.3 Exploratory Objectives
- Section 6.2 Dose Escalation
- Section 6.3 Justification for Trial Design, Dose, and Endpoints
- Section 6.3.3.1 Safety and PK
- Section 6.3.3.2 Exploratory Endpoints
- Section 6.4 Trial Design/Dosing/Procedures Modifications Permitted Within Protocol Parameters
- Section 6.5.3 Definition of Trial Completion
- Section 9.2.7 Trial Drug Administration
- Section 9.3 Biomarker, PK, PD, and PGx, Samples
- Section 9.3.1 PK Measurements
- Section 9.3.5 Confinement
- Section 11.1.3 PK Analysis
- Section 11.1.6 Safety Analysis
- Section 11.3 Determination of Sample Size

Change 2: Added objectives relating to CCI .

The primary change occurs in 5.1 Objectives

Added text: 5.1.3 Exploratory Objectives

CCI

Rationale for Change:

CCI

The following sections also contain this change:

- Section 1.0 STUDY SUMMARY
- Section 4.3 Benefit/Risk Profile
- Table 6.b Trial Schedule
- Section 6.2 Dose Escalation
- Section 6.3.2 Dose
- Section 9.3 Biomarker, PK, PD, and PGx, Samples
- Section 9.3.2.3 CCI
- Section 9.3.3.2 Biological Sample Retention and Destruction
- Section 10.2.9.1 Collection Period

Change 3: Added inclusion and exclusion criteria based on CCI [redacted] in male subjects.

This primary change occurs in 7.1 Inclusion Criteria and 7.2 Exclusion Criteria

Added text 7.1 Inclusion Criteria

8. Male subjects must have CCI [redacted]

7.2 Exclusion Criteria

10. Male subjects who have serum CCI [redacted] **levels that are clinically abnormal.**

Rationale for Change:

To ensure that male subjects with normal CCI [redacted] function are enrolled.

The following sections also contain this change:

- Section 1.0 STUDY SUMMARY
- Section 3.0 Schedule of Trial Procedures
- Table 6.b Trial Schedule
- Section 9.2.11.2 Diagnostic Screening

Change 4: Added biomarkers.

This primary change occurs in Section 5.1.3 Exploratory Objectives

Added text:

- **To collect plasma samples for possible exploratory biomarker analysis including but not limited to brain-derived neurotrophic factor (BDNF).**
- CCI [redacted]

Rationale for Change:

CCI [redacted]

The following sections also contains this change:

- Section 5.2.3 Exploratory Endpoints
- Section 6.3.3.3 Biomarkers
- Section 9.3.2.2 Plasma Samples for Circulating Biomarkers
- Section 10.2.9.6 Exploratory Biomarkers and Data From Wearable Devices
- Section 11.1.5 Biomarker Analysis

Change 5: Added preliminary data from 13-week toxicology study.

This primary change occurs in Section 4.3 Benefit/Risk Profile

Initial wording:	CCI [redacted]
Amended or new wording:	CCI [redacted]

CCI

Rationale for Change:

To provide observed CCI toxicity in nonclinical study and management of potential risk.

The following sections also contains this change.

- Section 1.0 STUDY SUMMARY
- Section 6.1 Trial Design
- Section 6.2 Dose Escalation

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical VP Approval	11-Jul-2017 11:39 UTC
	Clinical Pharmacology Approval	11-Jul-2017 12:36 UTC
	Statistical Approval	11-Jul-2017 12:52 UTC