Title: A Randomized, Double-Blind, Placebo-Controlled, Single and Multiple Oral Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of TAK-418 in Healthy Female Subjects.

NCT Number: NCT03501069

Protocol Approve Date: 20 March 2018

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

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

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

TAKEDA PHARMACEUTICALS

PROTOCOL

A Randomized, Double-Blind, Placebo-Controlled, Single and Multiple Oral Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of TAK-418 in Healthy Female Subjects.

Study Identifier:	TAK-418-1003
Compound:	TAK-418
Date:	20 March 2018
Version/Amendment Number:	Original Protocol

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1.0 STUDY SUMMARY

Name of Sponsor:	**Compound:**
Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company, Ltd 40 Landsdowne Street Cambridge MA 02139 USA	TAK-418
Study Identifier: TAK-418-1003	**Phase:** 1
Protocol Title: A Randomized, Double-Blind, Placebo-Controlled, Single and Multiple Oral Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of TAK-418 in Healthy Female Subjects.	

Trial Design:

This phase 1, randomized, double-blind, placebo-controlled trial is designed to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of single and multiple (once-daily [QD]) rising oral doses of TAK-418 (capsule formulation) in healthy adult female subjects.

Approximately 48 subjects are planned for enrollment in 6 cohorts (n=8 per cohort). In single-rising dose (SRD) cohort 1, subjects will receive a single oral dose of study drug (TAK-418 or matching placebo) in a double-blind manner in period A. After a washout interval of at least 14 days after the dose of study drug and following the review of the safety, tolerability, and PK data from period A, subjects in cohort 1 may receive a second single dose of study drug in period B. In multiple-rising dose (MRD) cohorts 2 to 6, subjects will receive study drug QD for 10 days in a double-blind manner. In each SRD and MRD cohort, 6 subjects will be randomly assigned to receive TAK-418 and 2 to receive placebo. The cohorts will be enrolled in a consecutive, staggered, or parallel manner.

For all SRD and MRD cohorts, blood samples will be collected for PK (TAK-418), CCI [redacted] and CCI [redacted]. For MRD cohort 3 only, serial lumbar cerebrospinal fluid (CSF) samples will be collected through an indwelling temporary catheter for 48 hours after the last dose of study drug for PK (TAK-418) and CCI [redacted]. Urine samples will be collected from selected non-Japanese MRD cohorts.

The planned TAK-418 dosing regimens and ethnicity of subjects are presented below. Non- Japanese subjects will be enrolled in cohorts 1 to 4 and Japanese subjects in cohorts 5 and 6. Planned CCI [redacted], but the actual doses administered after cohort 1 (period A) and cohort 2 will be based on emerging safety, tolerability, and PK data available from the previous doses.

Planned Dosing Regimens and Ethnicity of Subjects

Cohort	Ethnicity	Planned TAK-418 Dosing Regimen	Comments
1 (period A)	Non-Japanese	CCI [redacted] single dose	Cohort 1 (period A) may receive a second single dose (period B).
1 (period B)		single dose	
2		D (10 days)	Cohort 2 may be run in parallel with cohort 1 (period A or period B).
3		D (10 days)	Serial CSF samples will be collected.
4		D (10 days)	
5	Japanese	D (10 days)	Cohort 5 may be run in parallel with cohort 1, 2, or 3.
6		D (10 days)	

Trial Primary Objective:

- To characterize the safety and tolerability of TAK-418 in non-Japanese and Japanese healthy female subjects when administered at single or multiple (QD) oral escalating doses.

Trial Secondary Objective:

- To characterize the PK of TAK-418 in non-Japanese and Japanese healthy female subjects when administered at single or multiple (QD) oral escalating doses.

Trial Subject Population: Healthy female non-Japanese and Japanese subjects, aged 18 to 55 years, inclusive.

Planned Number of Subjects:	**Planned Number of Sites:**
Approximately 48 subjects randomized	Approximately 2
Dose Levels: SRD Cohort: TAK-418 [CCI] single dose TAK-418 [redacted] single dose Matching placebo MRD Cohorts: TAK-418 [CCI] QD TAK-418 [redacted] QD TAK-418 [redacted] QD TAK-418 [redacted] QD TAK-418 [redacted] QD Matching placebo	**Route of Administration:** Oral
Duration of Treatment: SRD Cohort: single dose MRD Cohorts: QD for 10 Days	**Planned Trial Duration:** SRD Cohort: Up to 15 weeks (including screening period, periods A and B, and follow-up period) MRD Cohorts: Up to 14 weeks (including screening period and follow-up period)

Main Criteria for Inclusion:

To be eligible for study participation, subjects must:

For All Cohorts

- Be female and aged 18 to 55 years, inclusive, at the screening visit.
- Have a body mass index (BMI) ≥18.5 and ≤30.0 kg/m^2 at the screening visit. (cohorts 1 to 4 only)
- Be a nonsmoker who has not used tobacco- or nicotine-containing products (eg, nicotine patch) for at least 6 months before administration of the first dose of study drug or invasive procedure.
- Be judged to be in good health by the investigator, based on clinical evaluations performed at the screening visit and before administration of the first dose of study drug or invasive procedure.
- Either be of nonchildbearing potential, as defined in the protocol, or if of childbearing potential, be using at least 1 of the highly effective methods of contraception, as defined in the protocol, during the entire duration of the study.
- For MRD Cohorts 5 and 6 (Japanese Subjects) Only
- Have a BMI ≥18.0 and ≤26.0 kg/m^2, at the screening visit.
- Have been born in Japan to a Japanese mother and father and have maternal and paternal Japanese grandparents.

- Have not been away from Japan for more than 10 years, at the screening visit.
- Have a lifestyle that did not change significantly since relocation from Japan.

Main Criteria for Exclusion:

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

For All Cohorts:

- Has a positive alcohol or drug screen.
- Has a positive serum pregnancy test or is breastfeeding.
- Is unable to refrain from or anticipates using any medication beginning approximately 7 days before administration of the first dose of study drug, throughout the trial (including washout intervals between treatment periods), until the final follow-up visit.
- Has a substance abuse disorder.
- Has a risk of suicide according to the investigator's clinical judgment per 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 (history of a seizure within 3 months prior to randomization).
- Has a lifetime history of major psychiatric disorder, such as major depressive disorder, bipolar disorder, or schizophrenia.
- Has luteinizing hormone, follicle-stimulating hormone, or estradiol levels that are clinically abnormal.

For MRD Cohort 3 Only (Includes CSF Sample Collection)

- The subject has had CSF collection performed within 30 days before Check-in (Day -1).
- The subject has a known hypersensitivity to the anesthetic or its derivatives used during CSF collection or any medication used to prepare the area of lumbar puncture.
- The subject has significant vertebral deformities (scoliosis or kyphosis) that, in the opinion of the investigator, may interfere with the lumbar puncture procedure.
- The subject has a history of major (lumbar) back surgery, clinically significant back pain, and/or injury, in the opinion of the investigator.
- The subject has a local infection at the puncture site.
- The subject has thrombocytopenia or other suspected bleeding tendencies noted before the procedure.
- The subject has developed signs and symptoms of spinal radiculopathy, including lower extremity pain and paresthesia.
- The subject has any focal neurological deficit that might suggest an increase in intracranial pressure.
- The subject has any abnormal finding on ophthalmological assessment/fundoscopy indicative of raised intracranial pressure (ie, optic disc swelling/edema; or [uncontrolled] hypertensive retinopathy).
- The subject regularly has moderate-to-severe headaches requiring analgesics.
- The subject has any bleeding abnormality or history of bleeding abnormalities.
- The subject has abnormal coagulation tests (prothrombin time/international normalized ratio, activated partial thromboplastin time) at screening.

Main Criteria for Evaluation and Analyses:

The primary endpoints of the study are as follows:

For All Cohorts

- Number and percentage of subjects with at least 1 treatment-emergent adverse event (TEAE).
- Number and percentage of subjects with at least 1 serious adverse event.

- Number and percentage of subjects who meet the markedly abnormal criteria for clinical laboratory values at least once postdose.
- Number and percentage of subjects who meet the markedly abnormal criteria for vital signs at least once postdose.
- Number and percentage of subjects who meet the markedly abnormal criteria for safety 12-lead electrocardiogram (ECG) parameters at least once postdose.

The secondary endpoints of the study are as follows:

For SRD Cohort 1 (Periods A and B)

- Area under the plasma concentration-time from time 0 to infinity (AUC_∞) after a single dose of TAK-418.

For MRD Cohorts 2 to 6

- Area under the plasma concentration-time curve during a dosing interval (AUC_τ) on Day 1 and after the final dose following multiple (QD) dosing of TAK-418.

For All Cohorts

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

Statistical Considerations:

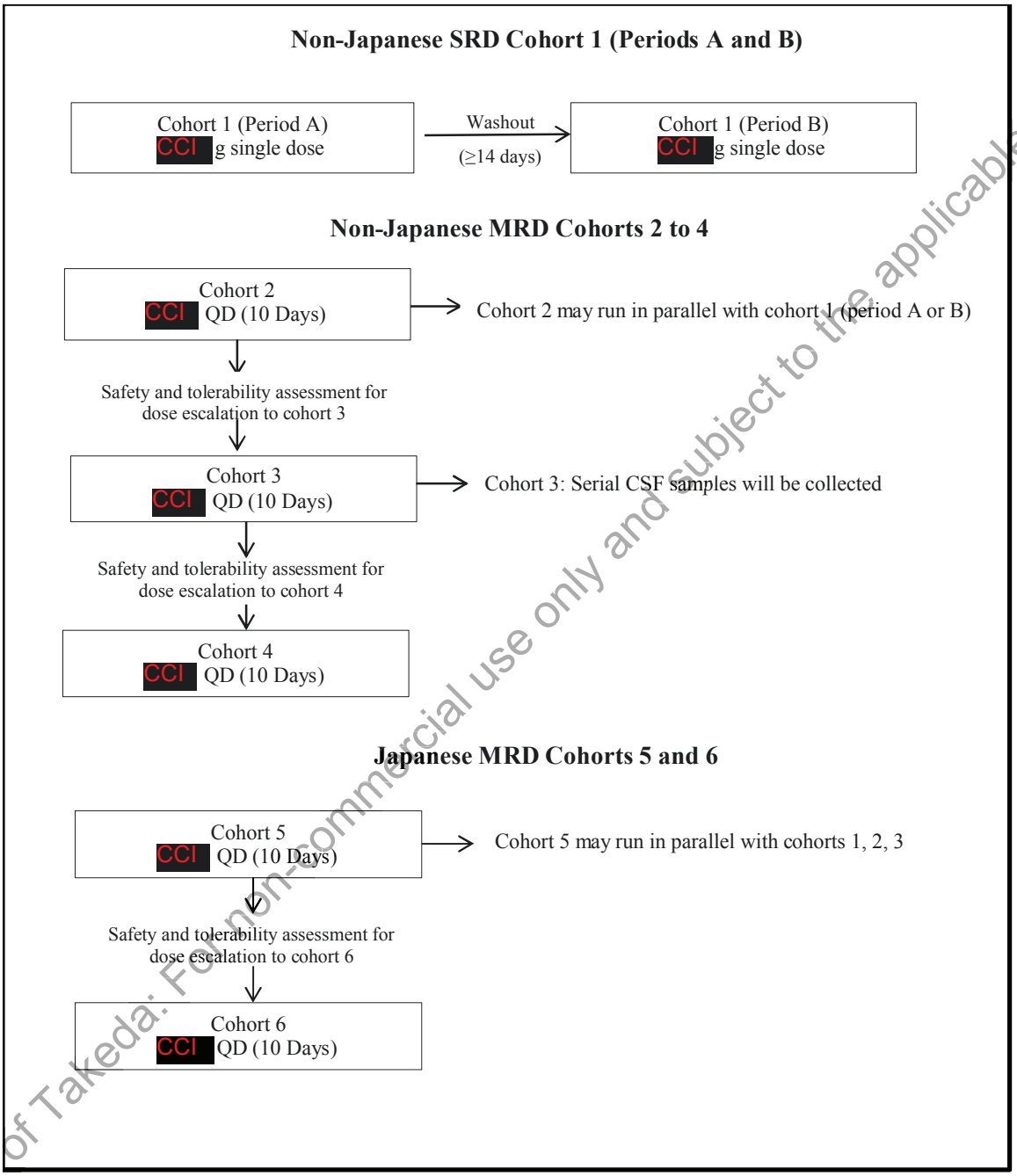
TEAEs will be summarized by placebo, TAK-418 dose level, and TAK-418 overall. Individual results of clinical laboratory tests, vital signs, and quantitative 12-lead ECG parameters that meet Takeda's markedly abnormal criteria will be listed and summarized by placebo, TAK-418 dose level, and TAK-418 overall.

TAK-418 concentrations in plasma (including trough concentrations for the MRD cohorts) will be summarized by dose over each scheduled sampling time point using descriptive statistics. Individual plasma concentration data versus time will be presented in a data listing. Descriptive statistics (arithmetic mean, SD, %CV, median, minimum, maximum, and/or geometric mean) will be used to summarize the plasma PK parameters for TAK-418, as appropriate.

Sample Size Justification:

The sample sizes chosen are considered sufficient for evaluation of safety, tolerability, PK, and PD of each cohort but are not based on statistical considerations.

2.0 STUDY SCHEMATIC



Abbreviations: MRD, multiple-rising dose; SRD, single-rising dose; QD, once daily.

3.0 SCHEDULE OF STUDY PROCEDURES

3.1 Schedule of Study Procedures for SRD Cohort 1 (Periods A and B)

	Screening Period	Check-in [a]	Treatment Period [a]															ET	Follow-Up Period			
Study Day	**-28 to -2**	**-1**	**1**											**2**		**3**	**4**		**7± 1 [b]**	**13± 2 [c]**	**30± 2 [c]**	**60± 2 [c]**
Hour			**Predose**	**0**	**0.25**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**8**	**12**	**24**	**36**	**48**	**72**					
Administrative Procedures																						
Informed consent	X																					
Inclusion/exclusion criteria	X	X	X																			
Medical history/ demographics	X																					
Prior and concomitant medication review	X----------Continuous Review----------X																					
Clinical Procedures/Assessments																						
Full physical examination	X		X [d]				X		X					X				X	X	X	X	X
Neurological examination	X		X [d]											X			X	X	X	X	X	X
Height	X																					
Weight	X																					
Body mass index	X																					
Semirecumbent vital signs (HR, SBP, DBP)	X		X [e]				X		X					X				X	X	X	X	X
Vital signs (respiratory rate, temperature)	X		X [e]				X		X					X				X	X	X	X	X
12-lead ECG	X		X [e]				X		X					X				X	X	X	X	X
Study drug (TAK-418 or placebo) administration				X																		
C-SSRS	X		X							X				X			X	X	X	X	X	X
BL-VAS	X		X			X							X			X						

Footnotes are on the last table page.

3.1 Schedule of Study Procedures for SRD Cohort 1 (Periods A and B) (continued)

	Screening Period	Check -in [a]	Treatment Period [a]														ET	Follow-Up Period			
Study Day	**-28 to -2**	**-1**	**1**											**2**		**3**	**4**		**7 ±1 [b]**	**13± 2 [c]**	**30± 2 [c]**	**60± 2 [c]**
Hour			**Predose**	**0**	**0.25**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**8**	**12**	**24**	**36**	**48**	**72**					
Clinical Procedures/Assessments																					
CCI																					
Actigraphy [g]		X----------X														X					
AE monitoring	X----------Continuous Monitoring----------X																				
Laboratory Procedures/Assessments																					
Hematology	X		X [d]											X				X	X	X	X	X
Urinalysis	X		X [d]											X				X	X	X	X	X
Chemistry	X		X [d]											X				X	X	X	X	X
PT and aPTT	X																					
Serum hCG	X		X [d]																X	X	X	X
Serum FSH/LH/estradiol	X		X [d]														X	X	X	X	X	X
HIV screen	X																					
Hepatitis screen	X																					
Urine drug screen	X		X [d]																			
Alcohol test	X		X [d]																			
PK Evaluations																						
Plasma sample for TAK-418 PK			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X				
PD/Biomarker Evaluations																						
CCI																						

Footnotes are on the last table page.

3.1 Schedule of Study Procedures for SRD Cohort 1 (Periods A and B) (continued)

	Screening Period	Check -in [a]	Treatment Period [a]														ET	Follow-Up Period			
Study Day	**-28 to -2**	**-1**	**1**											**2**		**3**	**4**		**7± 1 [b]**	**13± 2 [c]**	**30± 2 [c]**	**60± 2 [c]**
Hour			**Predose**	**0**	**0.25**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**8**	**12**	**24**	**36**	**48**	**72**					
PD/Biomarker Evaluations																					
CCI																					
PGx Evaluations																					
CCI																					
Other																					
Confinement		X----------X																			
Standardized meals [i]		X----------X																			

Abbreviations: AE, adverse event; aPTT, activated partial thromboplastin time; CCI
CCI DBP, diastolic blood pressure; ECG, electrocardiogram; ET, Early Termination; CCI
FSH, follicle-stimulating hormone; hCG, human chorionic gonadotrophin; HR, heart rate; LH, luteinizing hormone; PD, pharmacodynamic; CCI , pharmacokinetic(s); CCI ; PT, prothrombin time; SBP, systolic blood pressure; SRD, single-rising dose.

[a] Subjects from cohort 1 (period A) may receive a second single dose of study drug in cohort 1 (period B) after a washout interval of at least 14 days after the dose of study drug in period A.

[b] For both periods A and B.

[c] For period B only.

[d] Will be performed within approximately 24 hours before the dose of study drug in each treatment period.

[e] Will be performed within approximately 1 hour before the dose of study drug in each treatment period.

[f] For period A only.

[g] Optional assessment (separate informed consent).

[h] Will be collected within approximately 1 hour before the dose of study drug in cohort 1 (period A) only.

[i] Standardized meals (approximately 30% fat content relative to total calories) will be administered during confinement and only up to 24 hours after the dose of study drug in each treatment period. On Day 1 in each treatment period, standardized meals will be administered at 4 (lunch), 7 (snack), 10 (dinner), and 13 (snack) hours postdose.

3.2 Schedule of Study Procedures for MRD Cohorts 2 to 6

	Screening Period	Check -in	Treatment Period										Follow-up & Discharge		ET	Follow-up Period			
Study Day	**-28 to -2**	**-1**	**1 (Predose)**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**		**14**	**22 ±2**	**40 ±2**	**70 ±2**
Administrative Procedures																				
Informed consent	X																			
Inclusion/exclusion criteria	X	X	X																	
Medical history/demographics	X																			
Prior and concomitant medication review	X----------Continuous Review----------X																			
Clinical Procedures/Assessments																				
Full physical examination	X		X [a]												X	X		X		
Neurology examination	X		X [a]							X					X	X				
Fundoscopic examination (cohort 3 only)	X												X							
Weight	X																			
Height	X																			
Body mass index	X																			
Semirecumbent vital signs (HR, SBP, DBP)	X		X [b]	X		X				X			X		X	X		X		
Vital signs (respiratory rate, temperature)	X		X [b]	X		X				X			X		X	X		X		
12-lead ECG	X		X [b]	X		X						X			X	X		X		
Continuous ECGs (12-lead Holter) [c]		X	X	X	X															
Study drug (TAK-418 or placebo) administration [d]				X	X	X	X	X	X	X	X	X	X							
C-SSRS	X		X							X			X		X	X				
BL-VAS			X										X		X					
CCI	[redacted]																			

Footnotes are on the last table page.

3.2 Schedule of Study Procedures for MRD Cohorts 2 to 6 (continued)

	Screening Period	Check -in	Treatment Period										Follow-up & Discharge		ET	Follow-up Period			
Study Day	**-28 to -2**	**-1**	**1 (Predose)**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**		**14**	**22 ±2**	**40 ±2**	**70 ±2**
Clinical Procedures/Assessments																				
Actigraphy [f]		X----------													----------X					
AE monitoring	X----------												Continuous Monitoring							----------X
Laboratory Procedures/Assessments																				
Hematology	X		X [a]							X			X					X		
Urinalysis	X		X [a]							X			X					X		
Chemistry	X		X [a]							X			X					X		
PT and aPTT	X																			
Serum hCG	X		X [a]										X					X	X	X
Serum FSH/LH/estradiol	X		X [a]							X			X						X	X
HIV screen	X																			
Hepatitis screen	X																			
Alcohol test	X		X [a]																	
Urine drug screen	X		X [a]																	
PK Evaluations																				
Plasma sample for TAK-418 PK [g]			X	X	X	X				X			X	X	X	X				
Urine sample for TAK-418 PK (selected cohorts only) [g]			X	X	X								X	X						
CSF sample for TAK-418 PK (cohort 3 only) [g]													X	X	X					
PD/Biomarker Evaluations																				
CCI [redacted]																				

Footnotes are on the last table page.

3.2 Schedule of Study Procedures for MRD Cohorts 2 to 6 (continued)

	Screening Period	Check -in	Treatment Period										Follow-up & Discharge		ET	Follow-up Period			
Study Day	**-28 to -2**	**-1**	**1 (Predose)**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**		**14**	**22 ±2**	**40 ±2**	**70 ±2**
PD/Biomarker Evaluations																				
CCI																				
CCI																				
CCI																				
CCI																				
PGx Evaluations																				
CCI																				
Other																				
Confinement		X----------														X				
Standardized meals [d, i]		X----------														X				

Abbreviations: AE, adverse event; aPTT, activated partial thromboplastin time; CCI CSF, cerebrospinal fluid; CCI , CCI DBP, diastolic blood pressure; ET, Early Termination; CCI FSH, follicle-stimulating hormone; hCG, human chorionic gonadotrophin; HR, heart rate; LH, luteinizing hormone; MRD, multiple-rising dose; PD, pharmacodynamic(s); CCI PK, pharmacokinetic(s); CCI PT, prothrombin time; SBP, systolic blood pressure.

[a] Will be performed within approximately 24 hours before the first dose of study drug.

[b] Will be performed within approximately 1 hour before the first dose of study drug.

[c] Continuous Holter ECG will be performed at the following time points: On Day -1 at 23.5, 23, 22.5, 22, 21, 20, 16, and 12 hours before the first (Day 1) dose of study drug (time-matched to Day 1 time points); and immediately before dosing (0 hours) and at 0.5, 1, 1.5, 2, 3, 4, 8, 12, and 24 hours after the first dose on Day 1.

[d] Study drug will be administered after a fast of at least 8 hours. Subjects will continue to fast for an additional 4 hours after dosing.

[e] Cognitive testing will be performed twice on Day 1, with a 10- to 15-minute break between administrations. The first administration is to familiarize subjects with test requirements.

[f] Optional assessment (separate informed consent).

[g] See Section 3.3 for details of collection time points.

[h] Will be collected 96 hours after the last dose of study drug.

[i] Standardized meals (approximately 30% fat content relative to total calories) will be administered during confinement and only up to 24 hours after the last dose of study drug. On each dosing day, standardized meals will be administered at 4 (lunch), 7 (snack), 10 (dinner), and 13 (snack) hours postdose.

3.3 Schedule for PK and Biomarker Sample Collection for MRD Cohorts 2 to 6

	Treatment Period					Follow-up & Discharge	
Study Day	**1 (First Dose)**	**2**	**3**	**7**	**10 (Last Dose)**	**11**	**12**
PK Evaluations							
Plasma sample for TAK-418 PK	Predose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 8, and 12 h postdose	24 h after first dose (before second dose)	Predose	Predose	Predose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 8, and 12 h postdose	24 and 36 h after last dose	48 h after last dose
Urine sample for TAK-418 PK (selected cohorts only)	Predose (spot collection) and 0 to 6, 6 to 12, and 12 to 24 h postdose				Predose (spot collection) and 0 to 6, 6 to 12, and 12 to 24 h postdose		
CSF sample for PK (cohort 3 only)					Predose and 1, 2, 4, 8, and 12 h postdose	24 and 36 h after last dose	48 h after last dose
PD/Biomarker Evaluations							
CCI [redacted]							

Abbreviations: CCI [redacted] CSF, cerebrospinal fluid; CCI [redacted] MRD, multiple-rising dose; PD, pharmacodynamic(s); PK, pharmacokinetic(s); PBMC, peripheral blood mononuclear cells.

4.0 INTRODUCTION

4.1 Background

Lysine-specific demethylase 1A (LSD1), a member of the lysine-specific demethylase family 1 (KDM1), is involved in a wide variety of cellular processes and pathologies, including signal transduction, transcriptional regulation, viral pathogenesis, cell proliferation, cancer, and metastasis, cell development, cell differentiation, and chromatin remodeling [1]. As such, LSD1 has emerged as a potential therapeutic target for development disorders involving chromatin remodeling defects, such as autism spectrum disorder (ASD) and other neurodevelopmental disorders [2].

One of the modifications that has been extensively studied in patients with ASD is methylation of lysine in position 4 of type 3 histone (H3K4) [3], and LSD1 is an important regulator of H3K4 methylation. CCI [redacted].
The first reported specific substrate of LSD1 was histone H3K4me1/2, and subsequently additional specific substrates have been identified [4].

TAK-418 is a novel small molecule that inhibits the activity of human LSD1, also known as KDM1A. CCI [redacted]

TAK-418 is currently being evaluated in a phase 1, first-in-human clinical study in healthy non-Japanese adult subjects (Study TAK-418-1001); dosing for this study has been completed. This randomized, double-blind, placebo-controlled, single-rising dose (SRD) study is designed to assess the safety, tolerability, and pharmacokinetics (PK) of the oral capsule formulation of TAK-418. Subjects have been enrolled into 5 sequential cohorts of 8 subjects each (6 TAK-418; 2 placebo), with a minimum of 4 male subjects per cohort. Subjects received a single dose of TAK-418 or placebo after an overnight fast of at least 10 hours. To allow for a preliminary assessment of the effect of food on the PK of TAK-418, subjects in the 30-mg cohort also received study drug under fed conditions (high fat/high calorie breakfast), with a washout interval of at least 7 days between dose administrations.

The preliminary blinded safety and PK data from this single-dose study are summarized below.

- In Study TAK-418-1001, a total of 40 subjects (in 5 cohorts) have completed treatment at single dose levels of up to CC[redacted] mg. The following safety summary is preliminary and based on blinded data reported by the study investigator. Headache and nausea were the most common treatment-emergent adverse events (TEAEs) potentially related to study drug. All episodes of headache and nausea were mild in intensity and generally self-limiting. There were no

concerning trends in clinical laboratory, electrocardiogram (ECG), or vital sign data. Although not expected, these data may change upon finalization following study monitoring, source data verification, and discrepancy query management prior to database lock.

- The systemic exposure of TAK-418, as measured by mean maximum observed plasma concentration (C_{max}) and area under the plasma concentration-time curve from time 0 to infinity (AUC_{∞}), increased approximately dose proportionally from CCI. The mean terminal disposition phase half-life ($t_{1/2z}$) was short, ranging from 3.2 to 4.6 hours (Table 4.a). As evaluated in the CCI cohort, a standard high-fat meal significantly decreased mean C_{max} by 40.3%. There was no effect of a high-fat meal on AUC_{∞}.

Table 4.a Summary of Preliminary Plasma PK Parameter Estimates of TAK-418F (TAK-418 as Free Base) Following a Single Oral Dose of TAK-418 to Fasted Healthy Subjects

TAK-418 Dose	t_{max} (h) [a]	C_{max} (ng/mL)	AUC_{last} (h*ng/mL)	AUC_{∞} (h*ng/mL)	V_z/F (L)	CL/F (L/h)	$t_{1/2z}$ (h)
	Mean (%CV)						
CCI	1 (1-1)	22.7 (35)	85.4 (43)	94 (43)	279 (34)	63 (46)	3.2 (12)
	1 (1-2)	63.5 (22)	311 (22)	317 (22)	313 (20)	49.2 (22)	4.43 (5)
	1 (0.5-1)	166 (18)	683 (8)	693 (8)	286 (10)	43.5 (8)	4.57 (10)
	1.25 (1-1.5)	162 (31)	728 (24)	735 (24)	313 (25)	57.5 (28)	3.83 (14)
	1 (1-1)	324 (14)	1640 (30)	1660 (30)	218 (25)	39.3 (34)	3.92 (10)

Abbreviations: AUC_{∞}, area under the plasma concentration-time curve from time 0 to infinity; AUC_{last}, area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration; %CV, percent coefficient of variation; CL/F, apparent clearance after extravascular administration; C_{max}, maximum observed plasma concentration; $t_{1/2z}$, terminal disposition phase half-life; t_{max}, time of first occurrence of C_{max}; Vz/F, apparent volume of distribution during the terminal disposition phase after extravascular administration.
[a] Median (min-max).
Note: n=6 for each dose level.

Please refer to the current TAK-418 Investigator's Brochure for additional background information.

4.2 Rationale for the Proposed Study

The primary objective of the current study is to evaluate the safety, tolerability, PK, and pharmacodynamics (PD) of TAK-418 in healthy female subjects of non-Japanese and Japanese origin to support further development of TAK-418 as a potential treatment for patients with neurodevelopmental disorders. The available nonclinical pharmacology, PK, and toxicology data and the preliminary clinical data from the first-in-human (FIH) trial (TAK-418-1001) support the current trial and the development of TAK-418. 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 the treatment of cognitive deficits in patients with ASD.

The safety, tolerability, PK, and PD data from the current trial may inform the design of and dosing regimen selection for subsequent proof-of-mechanism and proof-of-concept trials in subjects of Japanese and non-Japanese origin.

4.3 Benefit/Risk Profile

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

TAK-418 is a potential first-in-class drug, and therefore, there are no known contraindications based on drug class. Potential risks are based on the mechanism of action and nonclinical findings. Potential risks include adverse effects on hematologic parameters, cardiovascular effects, hepatotoxicity, convulsions, and effects on embryo-fetal development. The potential risks related to hematology, cardiovascular effects, and hepatotoxicity can be monitored clinically and/or with laboratory tests and have been considered when determining the stopping rules for this clinical trial. CCI

[redacted]

5.0 TRIAL OBJECTIVES AND ENDPOINTS

5.1 Trial Objectives

5.1.1 Trial Primary Objective

- To characterize the safety and tolerability of TAK-418 in non-Japanese and Japanese healthy female subjects when administered at single or multiple (once daily [QD]) oral escalating doses.

5.1.2 Trial Secondary Objective

- To characterize the PK of TAK-418 in non-Japanese and Japanese healthy female subjects when administered at single or multiple (QD) oral escalating doses.

5.1.3 Trial Exploratory Objectives

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5.2 Endpoints

5.2.1 Primary Endpoints

For All Cohorts

- Number and percentage of subjects with at least 1 TEAE.
- Number and percentage of subjects with at least 1 serious adverse event (SAE).
- Number and percentage of subjects who meet the markedly abnormal criteria for clinical laboratory values at least once postdose.
- Number and percentage of subjects who meet the markedly abnormal criteria for vital signs at least once postdose.
- Number and percentage of subjects who meet the markedly abnormal criteria for safety 12-lead ECG parameters at least once postdose.

5.2.2 Secondary Endpoints

For SRD Cohort 1 (Periods A and B)

- AUC_{∞} after a single dose of TAK-418.

For MRD Cohorts 2 to 6

- Area under the plasma concentration-time curve during a dosing interval (AUC_{τ}) on Day 1 and after the final dose following multiple (QD) dosing of TAK-418.

For All Cohorts

- C_{max}.
- Time of first occurrence of C_{max} (t_{max}).

5.2.3 Exploratory Endpoints

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[redacted]

CCI

[redacted]

CCI

[redacted]

5.2.3.3 Exploratory Biomarker Endpoints

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[redacted]

5.2.3.4 Other Exploratory Endpoints

CCI

[redacted]

6.0 TRIAL DESIGN AND DESCRIPTION

6.1 Trial Design

This phase 1, randomized, double-blind, placebo-controlled trial is designed to evaluate the safety, tolerability, PK, and PD of single and multiple (QD) rising oral doses of TAK-418 (capsule formulation) in healthy adult female subjects.

Approximately 48 subjects are planned for enrollment in 6 cohorts (n=8 per cohort). In SRD cohort 1, subjects will receive a single oral dose of study drug (TAK-418 or matching placebo) in a double-blind manner in period A. After a washout interval of at least 14 days after the dose of study drug and following the review of the safety, tolerability, and PK data from period A, subjects in cohort 1 may receive a second single dose of study drug in period B. In multiple-rising dose (MRD) cohorts 2 to 6, subjects will receive study drug QD for 10 days in a double-blind manner. In each SRD and MRD cohort, 6 subjects will be randomly assigned to receive TAK-418 and 2 to receive placebo. The cohorts will be enrolled in a consecutive, staggered, or parallel manner (see Section 2.0).

For all SRD and MRD cohorts, blood samples will be collected for PK (TAK-418), CCI and CCI. For MRD cohort 3 only, serial lumbar CSF samples will be collected through an indwelling temporary catheter for 48 hours after the last dose of study drug for PK (TAK-418) and CCI. Urine samples will be collected from selected non-Japanese MRD cohorts.

The planned TAK-418 dosing regimens and ethnicity of subjects are presented in Table 6.a. Non-Japanese subjects will be enrolled in cohorts 1 to 4 and Japanese subjects in cohorts 5 and 6. Planned doses range from CCI mg, but the actual doses administered after cohort 1 (period A) and cohort 2 will be based on emerging safety, tolerability, and PK data available from the previous doses (see Section 6.3.2 for dose selection rationale).

Table 6.a Planned Dosing Regimens and Ethnicity of Subjects

Cohort	Ethnicity	Planned TAK-418 Dosing Regimen	Comments
1 (period A)	Non-Japanese	CCI single dose	Cohort 1 (period A) may receive a second single dose (period B).
1 (period B)		single dose	
2		D (10 days)	Cohort 2 may run in parallel with cohort 1 (period A or period B).
3		D (10 days)	Serial CSF samples will be collected.
4		D (10 days)	
5	Japanese	D (10 days)	Cohort 5 may run in parallel with cohort 1, 2, or 3.
6		D (10 days)	

Abbreviations: CSF, cerebrospinal fluid; QD, once daily.

The trial may be conducted at multiple phase 1 units to support both CSF collection and recruitment of Japanese subjects.

6.2 Dose Escalation

Dose escalation and subsequent dose levels will be based on a blinded review of available safety, tolerability, and PK data from the previous dose levels and will only occur following agreement between the investigator and the sponsor.

6.3 Rationale for Trial Design, Dose, and Endpoints

6.3.1 Rationale of Trial Design

This phase 1 trial is designed to characterize the safety, tolerability, PK, and PD of single and multiple rising oral doses of TAK-418 in healthy female subjects of non-Japanese and Japanese origin. The safety and tolerability of single and multiple TAK-418 doses will be evaluated, some of which may exceed doses anticipated to be therapeutically effective. However, it should be noted that the trial is not intended to determine the maximum tolerated dose.

Only female subjects will be enrolled because of nonclinical findings of testicular toxicity and pending results from the long-term (13- and 26-week) testicular health analyses in the FIH trial (TAK-418-1001). Healthy female Japanese subjects will be included to investigate any ethnic differences in the safety, tolerability, and PK of TAK-418.

The randomized, double-blind, placebo-controlled design employed is considered adequate to characterize the safety, tolerability, and PK of TAK-418. Subjects will be confined during dosing up until at least 48 hours after the last dose of study drug to ensure adherence to study procedures and to monitor safety and tolerability.

For SRD cohort 1, a washout interval of at least 14 days between dosing in periods A and B is considered adequate to ensure washout of TAK-418, given the mean $t_{1/2z}$ of 3.2 to 4.6 hours estimated in Study TAK-418-1001.

CCI [redacted] For MRD cohort 3 only, additional CSF samples will be collected to characterize TAK-418 exposure in the CNS.

6.3.2 Rationale for Dose

Planned doses for the current study range from CCI [redacted] mg, but the actual doses administered after cohort 1 (period A) and cohort 2 will be based on emerging safety, tolerability, and PK data available from the previous doses. If needed, higher or lower doses may be evaluated providing the predicted steady-state exposure does not exceed limits set by nonclinical toxicology findings. In the 13-week rat and monkey toxicity studies, the monkey was the most sensitive species. NOAELs in the 13-week monkey toxicity study was 4 mg/kg/day in males based on potential treatment-related testicular findings at ≥20 mg/kg/day, and 60 mg/kg/day in females based on convulsions, inappetence, and body weight changes at ≥75 mg/kg/day. CCI [redacted]

CCI

) and cohort 1 (CCI ; period B) were selected to explore the highest tolerated dose in healthy subjects, while not exceeding the exposure limits set by the nonclinical toxicity studies (C_{max} of 1,007 ng/mL and AUC_{τ} of 71,500 h*ng/mL for female subjects). Based on the population PK analysis of preliminary data from Study TAK-418-1001, the predicted C_{max} and AUC_{∞} are 928 ng/mL and 4,320 h*ng/mL, respectively, after a single CCI dose. The dose level for cohort 1 (period B) may be adjusted based on emerging safety, tolerability, and PK data.

The starting dose for the MRD cohorts CCI QD; cohort 2) was selected to approximate the predicted pharmacologically active dose (PAD) estimated based on the nonclinical pharmacology models. The C_{max} and AUC_{τ} at the PAD are estimated to be 156 ng/mL and 171 h*ng/mL, respectively; and based on the population PK analysis, the C_{max} and AUC_{τ} at 20 mg QD are predicted to be 86.3 ng/mL and 361 h*ng/mL, respectively. The C_{max} and AUC_{τ} at the highest planned MRD dose (CCI QD; cohort 4) are predicted to be 320 ng/mL and 1360 h*ng/mL, respectively. The planned MRD dose levels may be adjusted, and additional MRD cohort(s) with QD or other dosing regimens may be added based on emerging safety, tolerability, and PK data to explore the highest tolerated dose in healthy subjects, while not exceeding the exposure limits (C_{max} of 1,007 ng/mL and AUC_{τ} of 71,500 h*ng/mL for female subjects). Based on the population PK analysis of preliminary data from Study TAK-418-1001, the predicted C_{max} and AUC_{∞} are 1,000 ng/mL and 4,530 h*ng/mL, respectively, after CCI QD.

The lower dose planned for the Japanese MRD cohorts (CCI QD; cohort 5) was selected to evaluate the safety, tolerability, and PK of TAK-418 in Japanese subjects. The planned higher dose (CCI QD; cohort 6) may be adjusted based on the emerging safety, tolerability, and PK data in both non-Japanese and Japanese subjects.

6.3.3 Rationale for Endpoints

6.3.3.1 Safety Endpoints

The safety endpoints of TEAEs, clinical laboratory test results, vital signs, and 12-lead ECG parameters are standard methods for assessing safety and tolerability of drugs in clinical trials.

ECGs derived from Holter monitoring are not intended to be analyzed for real-time safety monitoring but will be used for future retrospective ECG analyses, unless an earlier analysis is warranted by the emerging safety data.

6.3.3.2 PK Endpoints

The PK endpoints will provide measures of TAK-418 exposure in plasma, CSF, and urine following single and/or multiple doses of TAK-418 and are standard parameters to assess the PK of drugs in clinical trials.

6.3.3.3 PD Endpoints

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[redacted]

6.3.3.4 Exploratory Biomarker and Other Exploratory Endpoints

CCI

[redacted]

6.3.4 Critical Procedures Based on Trial Objectives: Timing of Procedures

For this trial, the PK blood and CSF sample collections are the critical procedures.

- At any postdose time point, the PK blood and CSF sample collections need to be performed as close to scheduled times as possible.
- All other procedures should be performed as close as possible (either before or after) the scheduled times.
- ECG and vital signs measurements should be performed before the nominal time of the PK blood and CSF sample collections, if scheduled together.
- If a blood draw or any study procedure coincides with a meal, the blood draw will take precedence followed by the study procedure and then the meal.
- 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 trial 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, as 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.

As such, the following alterations from the currently outlined dose and/or dosing regimen may be permitted based on newly available data, but the maximum daily dose/exposure, will not exceed that currently outlined in Section 6.3.2:

- The dose of study drug administered may be repeated or decreased in any given period/cohort.
- Doses between cohorts/periods may be interchanged.
- Entire period(s) or cohort(s) may be omitted.
- The duration of study drug administration (ie, number of days) in the trial may be decreased or increased, but will not exceed 4 weeks in any cohort.
- The dosing interval may be adjusted (eg, twice daily to QD, QD to twice or 3 times daily).
- The length of the washout interval between doses may be increased.
- The length of the washout interval between doses may be decreased, if supported by safety and PK data.

- A planned PK data review may be removed if there are no further increases in total daily dose, if agreed by the sponsor and investigator.
- A PK data review may be added.
- Instructions to take study drug with or without food or drink may be modified based on newly available data.
- The PK/PD sampling scheme may be modified during the trial based on newly available PK or PD data (eg, to obtain data closer to t_{max}). 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 for PK and/or PD analyses. This blood volume may include repeat samples or modified PK/PD 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, ECGs, clinical laboratory tests) may be modified during the trial based on newly available safety, tolerability, PK, or PD data (eg, to obtain data closer to t_{max}). These changes will not increase the number of trial procedures for a given subject during his/her participation in the entire trial.
- Additional clinical laboratory tests may be added to blood samples previously drawn to obtain additional safety data.

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 Discontinuation

Trial discontinuation because of nonsafety reasons, such as the following:

- 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 nonsafety-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 clinical trials or nonclinical studies with the trial treatment(s), comparator(s), drug(s) of the same class, or methodology(ies) used in this trial.

6.5.4 Criteria for Premature Termination or Suspension of the Trial

6.5.4.1 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, or is unable to ensure adequate performance of the trial, or as otherwise permitted by the contractual agreement.

6.5.4.2 Procedures for Premature Termination or Suspension of the Trial or the Participation of Trial Sites

In the event that the sponsor, an IRB/IEC, 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

All entry criteria, including test results, need to be confirmed before the first dose of study drug.

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria before entry into the study:

For All Cohorts

1. The subject understands the trial procedures and agree to participate by providing written informed consent.
2. The subject is willing and able to comply with all trial procedures and restrictions.
3. The subject is female and aged 18 to 55 years, inclusive, at the screening visit.
4. The subject has a body mass index (BMI) ≥18.5 and ≤30.0 kg/m^2 at the screening visit. (cohorts 1 to 4 only)
5. The subject is a nonsmoker who has not used tobacco- or nicotine-containing products (eg, nicotine patch) for at least 6 months before administration of the first dose of study drug or invasive procedure.
6. The subject is 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 first dose of study drug or invasive procedure.
7. The subject EITHER is of nonchildbearing potential, defined by at least 1 of the following criteria:
   a) Is postmenopausal (defined as 12 months of spontaneous amenorrhea with serum follicle-stimulating hormone [FSH] levels >40 mIU/mL). Appropriate documentation of FSH levels is required.
   b) Is surgically sterile by hysterectomy and/or bilateral oophorectomy with appropriate documentation of surgical procedure.
   c) Had a bilateral tubal occlusion or ligation with appropriate documentation of surgical procedure.
   d) Has a congenital condition resulting in no uterus or infertility with appropriate documentation.

   OR, if of childbearing potential, is using at least 1 of the following highly effective methods of contraception with low user dependency during the entire duration of the trial:
   a) Intrauterine device (IUD).
   b) Bilateral tubal occlusion or ligation with appropriate documentation of surgical procedure.

For MRD Cohorts 5 and 6 (Japanese Subjects) Only

1. The subject has a BMI ≥18.0 and ≤26.0 kg/m^2, at the screening visit.
2. The subject was born in Japan to a Japanese mother and father and has maternal and paternal Japanese grandparents.
3. The subject has not been away from Japan for more than 10 years, at the screening visit.
4. The subject has a lifestyle that did not change significantly since relocation from Japan.
5. The subject understands and voluntarily signs an informed consent form written in English or Japanese prior to any study related procedures being performed and can adhere to restrictions and examination schedules.

7.2 Exclusion Criteria

Any subject who meets any of the following criteria will not qualify for entry into the study:

For All Cohorts

1. The subject has participated in another investigational trial within 4 weeks before the 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 screening visit of the current trial.
2. The subject is an employee or immediate family member (eg, spouse, parent, child, sibling) of the clinical research unit or sponsor.
3. The subject has a history of cancer (malignancy).
4. The subject 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. The subject has a positive alcohol or drug screen.
6. The subject has a positive serum pregnancy test.
7. The subject is breastfeeding.
8. The subject has a positive test result for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody, or HIV antibody/antigen, at screening. Note: Subjects with positive hepatitis B virus (HBV) or HCV serology may be enrolled if quantitative polymerase chain reaction for HBV or HCV RNA is negative.
9. The subject had major surgery, donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks before the screening visit.
10. The subject is unable to refrain from or anticipates using any medication (as defined in Section 9.1.4) beginning approximately 7 days before administration of the first dose of study drug, throughout the trial (including washout intervals between treatment periods), until the final follow-up visit. Certain medications may be permitted (Section 7.3.1).

11. The subject has a history of alcohol consumption exceeding 2 standard drinks per day on average (1 glass is approximately equivalent to beer [354 mL/12 oz], wine [118 mL/4 oz], or distilled spirits [29.5 mL/1 oz] per day).
12. The subjects 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.
13. The subject has a substance abuse disorder.
14. The subject has a risk of suicide according to the investigator's clinical judgment per the Columbia-Suicide Severity Rating Scale (C-SSRS) at screening or has made a suicide attempt in the 6 months before screening.
15. The subject has a clinically significant history of head injury, trauma, or seizures (history of a seizure within 3 months prior to randomization).
16. The subject has a lifetime history of major psychiatric disorder, such as major depressive disorder, bipolar disorder, or schizophrenia.
17. There is 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.
18. The subject has a history of serious skin reactions (hypersensitivity) to adhesives, metals, or plastic. (Only for subjects participating in the actigraphy assessment.)
19. The subject has luteinizing hormone (LH), FSH, or estradiol levels that are clinically abnormal.
20. The subject has an ECG at the screening visit or predose on Day 1 that reveals a QT interval with Fridericia correction method (QTcF) >470 milliseconds.
21. The subject has a resting heart rate outside of the range of 50 to 100 beats per minute, confirmed on repeat testing within a maximum of 30 minutes, at the screening visit or predose on Day 1.

<u>For MRD Cohort 3 Only (Includes CSF Sample Collection)</u>

1. The subject has had CSF collection performed within 30 days before Check-in (Day -1).
2. The subject has a known hypersensitivity to the anesthetic or its derivatives used during CSF collection or any medication used to prepare the area of lumbar puncture.
3. The subject has significant vertebral deformities (scoliosis or kyphosis) that, in the opinion of the investigator, may interfere with the lumbar puncture procedure.
4. The subject has a history of major (lumbar) back surgery, clinically significant back pain, and/or injury, in the opinion of the investigator.
5. The subject has a local infection at the puncture site.

6. The subject has thrombocytopenia or other suspected bleeding tendencies noted before the procedure.
7. The subject has developed signs and symptoms of spinal radiculopathy, including lower extremity pain and paresthesia.
8. The subject has any focal neurological deficit that might suggest an increase in intracranial pressure.
9. The subject has any abnormal finding on ophthalmological assessment/fundoscopy indicative of raised intracranial pressure (ie, optic disc swelling/edema; or [uncontrolled] hypertensive retinopathy).
10. The subject regularly has moderate-to-severe headaches requiring analgesics.
11. The subject has any bleeding abnormality or history of bleeding abnormalities.
12. The subject has abnormal coagulation tests (prothrombin time [PT]/international normalized ratio [INR], activated partial thromboplastin time [aPTT]) at screening.

7.3 Excluded/Allowed Concomitant Medications, Supplements, Dietary Products

7.3.1 Concomitant Medications

The use of concomitant medications (as defined in Section 9.1.4) after randomization (ie, Day 1) until the final follow-up visit is not permitted. Subjects must be instructed not to take any medications without first consulting with the investigator. Any concomitant medication use must first be discussed with the sponsor, unless the investigator or designee considers immediate administration is necessitated.

The occasional use of acetaminophen (approximately <1 g/day) is allowed.

7.3.2 Fruit Juice

Subjects will refrain from consuming grapefruit juice, grapefruits, and products containing grapefruit beginning approximately 2 weeks prior to administration of the first dose of study drug, throughout the trial (including any washout interval between treatment periods), and until the final follow-up visit.

Subjects also will refrain from consuming all juices 24 hours prior to and after administration of each dose of study drug on PK sampling days. Consumption of all fruits other than grapefruit is allowed on all days of the trial.

7.3.3 Alcohol

Subjects will refrain from consuming alcohol 7 days prior to the screening visit and each follow-up visit and from 7 days prior to and until the last PK blood sample has been collected. At all other times, alcohol consumption is limited to no more than approximately 2 alcoholic beverages or equivalent (1 alcoholic beverage is approximately equivalent to: beer [354 mL/12 oz], wine [118 mL/4 oz], or distilled spirits [29.5 mL/1 oz]) per day.

7.3.4 Caffeine

Subjects will refrain from consuming caffeinated beverages 24 hours prior to the screening visit and each follow-up visit and from 24 hours prior to and until the last PK blood sample has been collected. At all other times, caffeinated beverages or xanthine-containing products will be limited to amounts of no more than 6 units per day (1 unit=120 mg of caffeine).

7.3.5 Smoking

Smoking is not permitted during the trial.

7.4 Diet, Fluids, and Activity

7.4.1 Diet and Fluids

During confinement and only up to 24 hours after the last dose (Days -1 to 2 for SRD cohort 1; Days -1 to 11 for MRD cohorts 2 to 6), subjects will be given 2 standardized meals and 2 standardized snacks, each containing approximately 30% fat (relative to total calories). The meals served on dosing days should be similar in composition and caloric content for each cohort in the trial. Whether the standardized meals were fully consumed (100%), or if not, the percentage consumed (0, 25%, 50%, 75%) will be recorded on these days. For MRD cohorts 5 and 6 (Japanese), subjects may continue with a Japanese diet provided it contains approximately 30% fat (relative to total calories).

After the 24-hour postdose procedures have been completed following the last dose of study drug, subsequent meals and snacks will be unrestricted in caloric content, composition, and timing. The study menu should be recorded and submitted to the study file with a copy provided to the sponsor prior to the start of the study.

Study drug (TAK-418 or matching placebo oral capsules) will be administered with approximately 240 mL of water after a fast of at least 8 hours. Subjects will continue to fast for an additional 4 hours after dosing. If a subject is unable to continue fasting for 4 hours postdose, a light snack may be provided no earlier than 2 hours postdose on nonintense PK collection days (Days 2 to 9 and Days 11 and 12 for the MRD cohorts). Subjects may consume water ad libitum except for 1 hour before and 1 hour after study drug administration.

7.4.2 Activity

Subjects will avoid unaccustomed strenuous physical activity (ie, weight lifting, running, bicycling) from the screening visit, throughout the trial (including washout intervals between treatment periods), and until the final follow-up visit.

7.5 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study drug should be recorded in the electronic case report form (eCRF) using the following categories.

1. Pretreatment event (PTE) or AE. The subject has experienced a PTE or 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 PTE or AE.

   Liver Function Test (LFT) Abnormalities

   Study 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 9.3.1), if the following circumstances occur at any time during study drug treatment:

   – Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >8×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 INR >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%).
2. Significant protocol deviation. The discovery postrandomization 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.
3. 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 documents.
4. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the 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).
5. Study termination. The sponsor, IRB/IEC, or regulatory agency terminates the study.
6. Pregnancy. The subject is found to be pregnant.

   Note: If the subject is found to be pregnant, the subject must be withdrawn immediately.
7. Other.

   Note: The specific reasons should be recorded in the "specify" field of the eCRF.

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 of subject's treatment assignment and allocation number.

Replacement subjects will be allocated to the same cohort as the subject they replace. Subjects in cohort 1 who discontinue after receiving the first single dose (cohort 1, period A) may be replaced with subjects who only receive the second single dose (cohort 1, period B).

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

8.1 Clinical Study Drug

Details of the dosage form description and strengths, or of composition for the extemporaneous preparation, for the active drug and placebo, can be found in the pharmacy manual or in the referenced compounding manual, when applicable. Clinical study drug will be packaged to support enrollment and replacement subjects as required. When a replacement subject is required, the sponsor needs to be contacted prior to dosing.

8.1.1 Clinical Study Drug Labeling

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

8.1.2 Clinical Study Drug Inventory and Storage

Clinical study drug must be stored in a secure, limited-access location under the storage conditions specified on the label and remain in the original container until dispensed. The temperature excursion information can be found in the pharmacy manual or in the referenced compounding manual, when applicable. Receipt and dispensing of study drug must be recorded by authorized personnel at the trial site.

8.1.3 Clinical Study Drug Blinding

This is a double-blind trial; the investigator and subjects are blinded to treatment assignment. The unblinded study drug supply will be provided to an unblinded pharmacist or other qualified trial site personnel who will blind the study drug supplies. Treatment identity (name and strength or potency) will be included on the study drug container label; randomization code/disclosure envelopes or lists will be provided in accordance with the standard operating procedures of the clinical site.

8.1.4 Randomization Code Creation and Storage

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

8.1.5 Clinical Trial Blind Maintenance/Unblinding Procedure

The clinical study drug blind will be maintained through a randomization schedule held by the site unblinded pharmacist. The clinical study drug blind shall not be broken by the investigator unless information concerning the clinical study drug is necessary for the medical treatment of the subject. If possible, the medical monitor should be contacted before the study drug blind is broken. Unblinding will be performed per the standard operating procedures of the clinical site.

8.1.6 Accountability and Destruction of Sponsor-Supplied Drugs

The investigator is responsible for keeping accurate records of the clinical study 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 study drug accountability, return, and destruction.

8.2 Ancillary Supplies

All ancillary supplies will be provided by either the clinical site or the sponsor or designee, based upon availability. The list of ancillary supplies and source information can be found in the pharmacy manual or in the referenced compounding manual, when applicable. If provided by Takeda, unused ancillary supplies will be accounted for and disposed of as directed by Takeda or a Takeda designee.

9.0 STUDY PROCEDURES

The following sections describe the trial procedures to be performed and data to be collected as indicated in the schedules of study 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 points, per the discretion of the investigator.

9.1 Administrative Procedures

9.1.1 Informed Consent Procedure

Informed consent must be obtained before the subject enters the trial and before any protocol-directed procedures are performed. The requirements of informed consent are described in Appendix B.

9.1.1.1 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 one screening number. Screening numbers must not be reused 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 one randomization number.

9.1.1.2 Study Drug Assignment

On Day 1, subjects will be assigned a randomization number in ascending numerical order at each clinical site. The randomization number encodes the subject assignment to either TAK-418 or placebo, according to the randomization schedule generated before the trial. Each subject will be dispensed blinded study drug, labeled with his/her unique randomization number, throughout the trial.

9.1.2 Inclusion and Exclusion

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

9.1.3 Medical History and Demographics

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

9.1.4 Prior and Concomitant Medications

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

9.2 Clinical Procedures and Assessments

9.2.1 Full Physical, Neurological, and Fundoscopic Examinations

Qualified site personnel will conduct full physical and neurological examinations.

For MRD cohort 3 only, ophthalmological assessments of the retina (fundoscopy) will be conducted to determine whether subjects have abnormal findings suggestive of raised intracranial pressure.

9.2.2 Height and Weight

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

9.2.3 BMI

BMI equals a subject's weight in kilograms divided by height in meters squared (BMI=kg/m^2). 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.

9.2.4 Vital Signs

Body temperature will be measured with an oral (temperature taken at floor of the mouth) or tympanic thermometer. The same method (ie, 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 vital signs are measured. Vital signs will include heart rate, respiratory rate, and systolic and diastolic blood pressure. 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 should 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.

9.2.5 12-Lead ECG

9.2.5.1 Standard 12-Lead ECGs

Special care must be taken for proper lead placement by qualified personnel. Skin should be clean and dry before 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.

QTcF intervals will be calculated in this trial.

For each cohort, a predose ECG will be obtained within approximately 1 hour before study drug dosing. This measurement will be used as the baseline assessment. The principal investigator should arrange to have a trial cardiologist available as needed to review ECG tracings with abnormalities.

During the treatment period, if a subject demonstrates an increase in QTcF interval ≥40 milliseconds 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 milliseconds, the subject will continue to be monitored by repeat 12-lead ECGs every 60 minutes for at least 4 hours or until the QTcF interval is within 40 milliseconds of the baseline value. If prolongation of the QTcF interval ≥40 milliseconds persists, a consultation with a trial cardiologist may be appropriate and the sponsor should be notified.

If the QTcF interval is ≥500 milliseconds, the sponsor should be notified and the ECGs should be reviewed by a cardiologist. The subject should be monitored by telemetry (until the QTcF interval is <500 milliseconds) 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 by 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: heart rate, PR interval, QRS interval, QT interval, QTcF interval, and the interpretation of the ECG profile by the principal investigator.

9.2.5.2 Continuous 12-Lead Holter ECGs

The 12-lead Holter ECG monitoring will record a minimum of 13.5 hours of continuous cardiac monitoring. The Holter monitor will be connected at approximately 2 hours prior to the planned dosing time on Day 1 and will continuously be monitored for at least 13.5 hours with at least 12 hours of postdose monitoring. Holter ECGs on Day -1 will start and end at the time that is matched to those on Day 1. Holter ECGs are not intended for real-time safety monitoring, but they will be used for ECG assessment by a central ECG vendor.

Triplicate 12-lead ECGs will be extracted from stored data approximately 1 minute apart from one another. For each time point, the best 3 consecutive complexes in Lead II will be selected for measurement by the central ECG reader. Lead V5 will be used when Lead II is unsuitable. The same lead will be used for measurements for each subject. A study-specific assessment of inter-reader variability will be performed. This procedure will compare the ECG heart rate and

time intervals (RR, PR, QRS and QT intervals) of the first reading with an interpretation by a second reader.

The Holter procedure is further described in the procedure manual.

9.2.6 Study Drug Administration

For each cohort, study drug (TAK-418 or placebo) will be administered as described in Section 7.4.1 and in accordance with the schedules of study procedures (Section 3.0).

9.2.7 CCI

CCI [redacted]

9.2.8 CCI

CCI [redacted]

9.2.9 CCI

CCI [redacted]

CCI

[redacted]

9.2.10 CCI

CCI

[redacted]

9.2.11 AE Monitoring

AE monitoring begins after signing of the informed consent form. Changes in subject health status from the baseline assessment until study 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.

9.3 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 schedules of study procedures (Section 3.0).

9.3.1 Clinical Laboratory Tests

Hematology

The hematology assessment will include the following tests:

Erythrocytes (red blood cells)	Hemoglobin
Hematocrit	Platelets
Leukocytes (white blood cells) with absolute differential	

Chemistry

The chemistry assessment will include the following tests:

Albumin	Alkaline phosphatase
ALT	AST
Blood urea nitrogen	Calcium
Carbon dioxide	Chloride
Creatinine	Glucose
γ-glutamyl transferase	Sodium
Potassium	Bilirubin (total), if above the upper limit of normal total bilirubin will be fractionated
Protein (total)	

If subjects experience ALT or AST >3×ULN, follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, γ-glutamyl transferase, and INR) should be performed within a maximum of 7 days and preferably within 48 to 72 hours after the abnormality was noted.

If ALT or AST remains elevated >3×ULN on these 2 consecutive occasions, the investigator must contact the medical monitor for consideration of additional testing, close monitoring, possible discontinuation of study drug, and discussion of the relevant subject details and possible alternative etiologies. The abnormality should be recorded as an AE.

Please refer to Section 7.5 for subject discontinuation criteria regarding abnormal LFT results and Section 10.2.8.4 for guidance on reporting abnormal LFT results.

Urinalysis

The urinalysis assessment will include the following tests:

Protein	Glucose
Blood	Nitrite

Urine microscopy will be performed if urinalysis is abnormal. Microscopy consists of red blood cells/high-power field, white blood cells/high-power field, and casts.

Other

The following additional tests will be performed:

Serum estradiol	PT
Serum LH	aPTT
Serum FSH	

9.3.2 Diagnostic Screening

Serum

The serum diagnostic screening assessment will include the following tests:

HIV	Hepatitis screen (hepatitis B surface antigen, hepatitis C virus antibody)
hCG (pregnancy test)	

hCG, human chorionic gonadotropin.

Alcohol Screen

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

Urine

The urine drug screening assessment will include the following tests:

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

9.4 PK, PD, Biomarker, and Pharmacogenomic Evaluations

9.4.1 PK, PD, Biomarker, and Pharmacogenomic Samples

Samples for PK, CCI [redacted], and pharmacogenomic (PGx) analyses will be collected as specified in the schedules of study procedures (Section 3.0).

Please refer to the laboratory manual for information on the collection, processing, and shipment of samples to the central laboratory.

The decision as to which samples collected will be assayed for evaluation of PK, PD, CCI [redacted]s, and PGx will be determined by the sponsor. If indicated, these samples may also be assayed and/or pooled to measure metabolites and/or additional biomarkers in an exploratory manner.

It is anticipated that the total blood volume drawn for each subject in SRD cohort 1 (periods A and B) will be approximately 513 mL and for each subject in MRD cohorts 2 to 6 will be approximately 496 mL.

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

Table 9.a Primary Specimen Collections

Specimen Name	Primary Specimen	Primary Specimen Derivative	Description of Intended Use	Sample Collection
Plasma sample for TAK-418 PK	Blood	Plasma	Plasma sample for PK analysis	Mandatory
Urine sample for TAK-418 PK	Urine	Urine	Urine sample for PK analysis	Mandatory
CSF sample for TAK-418 PK	CSF	CSF	CSF sample for PK analysis	Mandatory
CCI				Mandatory
				Mandatory
				Mandatory
				Mandatory
				Mandatory
				Mandatory
				Optional
				Optional

Abbreviations: CCI CSF, cerebrospinal fluid; CCI CCI PK, pharmacokinetic(s); CCI

9.4.2 PK Measurements

9.4.2.1 PK Parameters

The PK parameters of TAK-418 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 computations involving sampling times. Nominal time intervals will be used for computations of urine PK parameters.

The following PK parameters will be calculated from plasma concentrations of TAK-418:

For SRD cohort 1 (periods A and B) after a single dose on Day 1

- AUC_{∞}
- C_{max}
- t_{max}
- AUC_t
- $t_{1/2z}$
- CL/F
- V_z/F

For MRD cohorts 2 to 6 on Day 1

- AUC_{τ}
- C_{max}
- t_{max}

For MRD cohorts 2 to 6 at steady state (after the final dose)

- AUC_{τ}
- C_{max}
- t_{max}
- AUC_t
- $t_{1/2z}$
- CL/F
- V_z/F
- $R_{ac(AUC)}$
- $R_{ac(Cmax)}$

The following PK parameters will be calculated from urine concentrations of TAK-418:

For selected MRD cohorts after a single dose on Day 1 and at steady state (after the final dose)

- Ae_t
- $f_{e,t}$
- CL_R

The following PK parameters will be calculated from CSF concentrations of TAK-418:

For MRD cohort 3 only at steady state (after the final dose)

- CSF C_{max}
- CSF AUC_{24}
- CSF AUC_{48}
- CSF AUC_{24}:plasma AUC_{24}
- CSF AUC_{48}:plasma AUC_{48}

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

9.4.2.2 Plasma for PK Measurements

Blood samples for PK analysis of TAK-418 in plasma will be collected into chilled blood collection tubes (vacutainer) containing the anticoagulant K_2EDTA according to the schedules in

Section 3.0. The collected blood samples may be archived for additional analysis of potential metabolites.

The actual time of sample collection will be recorded on the source document and eCRF. Sampling time points may be adjusted based on the preliminary emerging concentration data collected from prior subject(s), but the total number of samples collected per subject should not exceed the planned number.

9.4.2.3 Urine for PK Measurements

Urine samples for PK analysis of TAK-418 will be collected according to the schedules in Section 3.0. The collected urine samples may be archived for additional analysis of potential metabolites.

9.4.2.4 CSF for PK Measurements

CSF samples for PK analysis of TAK-418 will be collected, according to the schedules in Section 3.0, using an indwelling spinal catheter inserted into the lower spinal canal by trained personnel at the clinical site per their standard operating procedure.

The actual time of sample collection, time since last dose was administered, and time since last meal will be recorded on the source document and eCRF.

9.4.2.5 PK Sample Analysis

Plasma, urine, and CSF concentrations of TAK-418 be measured by a validated high-performance liquid chromatography with tandem mass spectrometry assay.

9.4.3 PD Measurements

CCI

[redacted]

9.4.4 CCI

CCI

[redacted]

CCI [redacted]

9.4.5 CCI [redacted]

CCI [redacted]

9.4.5.2 Biological Sample Retention and Destruction

In this trial, blood, urine, stool, and CSF samples CCI [redacted] Any leftover biomarker samples, if not utilized, will be preserved and retained at the sponsor-selected long-term storage facility for up to 15 years from the end of the trial. Genetic material will be initially stored at a vendor or comparable laboratory, under contract to Takeda, with validated procedures in place, and then preserved and retained at a long-term storage vendor, or a comparable laboratory, with validated

procedures in place, for up to but not longer than 15 years from the end of the trial when the trial 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 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 investigator and sponsor may continue to use and distribute any information and test results gathered before the request to withdraw.

9.4.6 Confinement

9.4.6.1 SRD Cohort 1 (Periods A and B)

Subjects will report to the clinical site the morning before the scheduled day of study drug administration (Day -1) at the discretion of the investigator. Subjects will remain in the clinic until 48 hours postdose (Day 3). At the discretion of the investigator, subjects may be requested to remain at the clinical site longer.

9.4.6.2 MRD Cohorts 2 to 6

Subjects will report to the clinical site the morning before the scheduled day of study drug administration (Day -1) at the discretion of the investigator. Subjects will remain in the clinic until 48 hours after the last dose of study drug (Day 12). At the discretion of the investigator, subjects may be requested to remain at the clinical site 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 study; it does not necessarily have to have a causal relationship with the treatment.

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

An untoward finding generally may:

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

Diagnoses versus signs and symptoms:

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

Laboratory values and ECG findings:

- Changes in laboratory values or ECG parameters maybe considered AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory retest and/or continued monitoring of an abnormal value are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.
- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), the diagnosis only should be reported appropriately as an AE.

Pre-existing conditions:

- A pre-existing condition (present at the time of signing of informed consent) is considered a concurrent medical history condition and should NOT be recorded as an AE. A baseline evaluation (eg, laboratory test, ECG, X-ray) should NOT be recorded as an AE unless related to a study procedure. However, if the subject experiences a worsening or complication of such

a concurrent medical history condition, the worsening or complication should be recorded appropriately as an AE (worsening or complication occurs after informed consent is signed). Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of…").

- If a subject has a pre-existing episodic condition (eg, asthma, epilepsy), any occurrence of an episode should only be captured as an AE if the episodes become more frequent, serious, or severe in nature, that is, investigators should ensure that the AE term recorded captures the change from baseline in the condition (eg "worsening of…").
- If a subject has a degenerative concurrent condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be captured as an AE if occurring to a greater extent to that which would be expected. Again, investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Worsening of AEs:

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

Changes in severity of AEs:

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

Preplanned surgeries or procedures:

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

Elective surgeries or procedures:

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

Overdose:

- An overdose is defined as a known deliberate or accidental administration of investigational drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol. It is up to the investigator or the reporting physician to decide whether a dose is to be considered an overdose, in consultation with the sponsor.
- All cases of overdose (with or without associated AEs) will be documented on an overdose page of the eCRF, in order to capture this important safety information consistently in the

database. AEs associated with an overdose will be documented on AE CRF(s) according to Section 9.2.

- SAEs of overdose should be reported according to the procedure outlined in Section 10.2.8.
- In the event of drug overdose, the subject should be treated symptomatically.

10.1.1 SAEs

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

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

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

10.2 AE Procedures

10.2.1 Assigning Severity/Intensity of AEs

The different categories of severity/intensity are:

Mild:	An adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate:	An adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
Severe:	An adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

10.2.2 Assigning Causality of AEs

The relationship of each AE to study drug will be assessed using the following categories:

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

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

10.2.3 Start Date

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

10.2.4 End Date

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

10.2.5 Pattern of Adverse Event (Frequency)

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

10.2.6 Action Taken With Study Treatment

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

10.2.7 Outcome

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

10.2.8 Collection and Reporting of AEs, SAEs, and Abnormal LFTs

10.2.8.1 Collection Period

Collection of AEs (ie, AEs, SAEs, and abnormal LFTs) will commence at the time the subject signs the informed consent form. For each cohort, routine collection of AEs will continue until the last follow-up visit. For subjects who discontinue prior to the administration of study drug, AEs will be followed until the subject discontinues study participation.

10.2.8.2 Reporting AEs

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

All subjects experiencing AEs, whether considered associated with the use of the study drug 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 end date and time.
- Pattern of AE (frequency).
- Severity/Intensity.
- Causality (investigator's opinion of the causal relationship between the event and administration of study drug[s]).
- Action taken with study drug.
- Outcome of event.
- Seriousness.

10.2.8.3 Reporting SAEs

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

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

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

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

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

Reporting of SAEs that begin before first administration of study drug 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 but 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.

10.2.8.4 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 as per Section 10.2.8.3. 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 9.3.1 must also be performed. In addition, an LFT increases eCRF must be completed and transmitted with the Takeda SAE form (as per Section 10.2.9).

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

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, investigators, and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the 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 prior to unblinding of subjects' treatment assignments. The SAP will provide further details regarding the definition of analysis variables and analysis methods to address all trial objectives.

A targeted data review will be conducted prior to unblinding of subjects' treatment assignments. This review will assess the accuracy and completeness of the study database, subject evaluability, or appropriateness of the planned statistical methods. This review may be conducted on a cohort-by-cohort basis.

11.1.1 Analysis Sets

11.1.1.1 Safety Set

The safety set will include all subjects who were enrolled and received at least 1 dose of study drug. Subjects in this analysis set will be used for demographic, baseline characteristic, and safety summaries.

11.1.1.2 PK Set

The PK set will include all subjects who received at least 1 dose of study drug and have at least 1 measurable plasma or CSF concentration or amount of drug in urine for TAK-418.

11.1.1.3 PD Set

CCI

[redacted]

11.1.2 Analysis of Demography and Other Baseline Characteristics

Descriptive statistics (N, mean, SD, median, minimum, and maximum) will be generated for continuous demographic and other baseline characteristic variables (eg, age, height, weight, BMI) for the pooled placebo group, each TAK-418 dose level, and TAK-418 overall. The number and percentage of subjects in each class of the categorical demographic and other baseline characteristic variables (eg, sex, ethnicity, race) will be tabulated for the pooled placebo group, each TAK-418 dose level, and TAK-418 overall. Data from subjects who received placebo will be pooled across cohorts, as appropriate to each analysis. Individual subject demographic and other baseline characteristic data will be listed.

11.1.3 PK Analysis

TAK-418 concentrations in plasma (including trough concentrations for the MRD cohorts) and CSF will be summarized by dose over each scheduled sampling time point using descriptive statistics. Individual plasma concentration data versus time will be presented in a data listing. CSF samples will be collected on a more limited schedule than plasma samples, and not all PK analyses will be appropriate for these data.

Descriptive statistics (arithmetic mean, SD, %CV, median, minimum, maximum, and/or geometric mean) will be used to summarize the plasma and CSF PK parameters for TAK-418, as appropriate.

An analysis of variance (ANOVA) model may be used to assess time dependency in the PK of plasma TAK-418 between Day 1 and Day 10. Specifically, time invariance will be assessed by comparing AUC_{τ} for Day 10 to the AUC_{∞} for Day 1, separately for each dose. The model will include dose level, day, and interaction of dose level by day as factors and the natural logarithmic AUCs as the responses. Within the framework of the ANOVA, the point estimates for the ratios of AUC central values and their 90% CIs between Day 10 and Day 1 also will be provided for each dose level.

The amount of TAK-418 excreted in urine will be summarized by dose over each scheduled sampling interval using descriptive statistics. Individual urine TAK-418 excretion data by collection interval will be presented in a data listing.

Urine PK parameters will be summarized using descriptive statistics.

11.1.4 PD Analysis

Concentrations of CCI [redacted], will be summarized by dose using descriptive statistics for baseline, postdose, and change from baseline to postdose. AUEC will be calculated for each subject and summarized by dose.

The difference in CCI [redacted] TAK-418 dose level and placebo will be estimated. The distribution of this difference will be characterized. Further details will be provided in the SAP.

11.1.5 CCI [redacted]

CCI [redacted]

11.1.6 Safety Analysis

Safety summaries will be performed separately for cohort 1 (SRD cohort) and cohorts 2 to 6 (MRD cohorts); data for subjects who received placebo will be pooled across all cohorts, as appropriate to each analysis. All safety data will be presented in data listings.

11.1.6.1 AEs

TEAEs will be summarized by placebo, TAK-418 dose level, and TAK-418 overall.

11.1.6.2 Clinical Laboratory Evaluations

Individual results of clinical laboratory tests from hematology, chemistry, or urinalysis that meet Takeda's markedly abnormal criteria (to be defined in the SAP) will be listed and summarized by placebo, TAK-418 dose level, and TAK-418 overall. Baseline, postdose, and change from baseline to postdose clinical laboratory data will be summarized for placebo and TAK-418 dose levels.

11.1.6.3 Vital Signs

Individual results of vital signs that meet Takeda's markedly abnormal criteria (to be defined in the SAP) will be listed and summarized by placebo, TAK-418 dose level, and TAK-418 overall. Baseline, postdose, and change from baseline to postdose vital sign data will be summarized for placebo and each TAK-418 dose level.

11.1.6.4 ECGs

Individual quantitative ECG parameters from the 12-lead safety ECGs that meet Takeda markedly abnormal criteria (to be defined in the SAP) will be listed and summarized by placebo, each TAK-418 dose level, and TAK-418 overall. Baseline, postdose, and change from baseline to postdose quantitative ECG parameter data will be summarized for placebo and each TAK-418 dose level.

11.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned. However, a blinded review of the safety, tolerability, and available PK data, will be conducted after completion of each cohort and prior to dose escalation in the trial.

11.3 Determination of Sample Size

The sample sizes chosen are considered sufficient for evaluation of safety, tolerability, PK, and PD of each cohort but are not based on statistical considerations.

12.0 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Study-Site Monitoring Visits

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

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

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.

Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment.

12.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the study drug is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the Food and Drug Administration [FDA], the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator guarantees access for quality assurance auditors to all study documents as described in Section 12.1.

13.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual 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 study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix A. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

13.1 IRB and/or IEC Approval

This study will be conducted in accordance with the protocol and with the consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and CIOMS (Council for International Organizations of Medical Sciences) International Ethical Guidelines, ICH GCP guidelines, and laws and regulations applicable to clinical studies (including US 21 Code of Federal Regulations [CFR] and European regulation 536/2014).

The protocol, informed consent forms, investigator's brochure, and other relevant supporting documents (eg, advertisements, information on payments and compensation available to subjects) must be submitted to an IRB/IEC by the investigator. Written approval of the protocol from the IRB/IEC must be obtained before the study is initiated, ie, the first subject signs the study informed consent form.

The study cannot be initiated until notification is received from the sponsor.

Any amendment to the protocol, except when necessary to eliminate an immediate hazard to study participants, requires IRB/IEC written approval before implementation.

If required by either country or regional regulations or procedures, approval from the Competent Regulatory Authority will be obtained before commencement of the study or implementation of an amendment.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.

13.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses,

transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The informed consent form and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The informed consent form will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

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

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

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

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

All revised informed consent forms must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised informed consent form.

Subjects who consented and provided a PGx sample for DNA analysis can withdraw their consent and request disposal of a stored sample at any time prior to analysis. Notify the 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 study, a subject's source data will only be linked to the sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 13.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (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 study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

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

13.4.2 Clinical Trial Registration

In order 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 study, as defined in Takeda policy/standard. Takeda contact information, along with investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing.

For some registries, Takeda will assist callers in locating study sites closest to their homes by providing the investigator name, address, and phone number to the callers requesting 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 study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or designee will obtain clinical study insurance against the risk of injury to study subjects. Refer to the study site agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or designee.

14.0 ADMINISTRATIVE AND REFERENCE INFORMATION

14.1 Administrative Information

14.1.1 Study Contact Information

Trial contact numbers can be found in the study manual, the communication plan, or other similar documents provided to the site.

14.1.2 INVESTIGATOR AGREEMENT

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

- The ethical principles that have their origin in the Declaration of Helsinki.
- ICH, E6 GCP: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.2.9 of this protocol.
- Terms outlined in the study site agreement.
- Responsibilities of the Investigator (Appendix A).

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

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Provence)

Location of Facility (Country)

14.1.3 List of Abbreviations

Ae_t	amount of drug excreted in urine from time 0 to time t
ALT	alanine aminotransferase
ANOVA	analysis of variance
aPTT	activated partial thromboplastin time
ASD	autism spectrum disorder
AST	aspartate aminotransferase
AUC_{24}	area under the plasma concentration-time curve from time 0 to 24 hours
AUC_{∞}	area under the plasma concentration-time curve from time 0 to infinity
AUC_{last}	area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration
AUC_{τ}	area under the plasma concentration-time curve during a dosing interval
AUC_t	area under the plasma concentration-time curve from time 0 to time t
CCI	[redacted]
CCI	[redacted]
CCI	[redacted]
CCI	[redacted]
BMI	body mass index
%CV	percent coefficient of variation
CFR	Code of Federal Regulations
CCI	[redacted]
CL/F	apparent clearance after extravascular administration
CL_R	renal clearance
C_{max}	maximum observed plasma concentration
CNS	central nervous system
CSF	cerebrospinal fluid
CSF AUC_{24}	area under the CSF concentration-time curve from time 0 to 24 hours
CSF AUC_{48}	area under the CSF concentration-time curve from time 0 to 48 hours
CSF AUC_{24}:plasma AUC_{24}	ratio of CSF AUC_{24} to area under the plasma concentration-time curve from time 0 to 24 hours (AUC_{24})
CSF AUC_{48}:plasma AUC_{48}	ratio of CSF AUC_{48} to area under the plasma concentration-time curve from time 0 to 48 hours (AUC_{48})
CSF C_{max}	maximum observed concentration in CSF
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	electrocardiogram
eCRF	electronic case report form
CCI	[redacted]
FDA	Food and Drug Administration
$f_{e,t}$	fraction of administered dose of drug excreted in urine from time 0 to time t
CCI	[redacted]
FIH	first-in-human

FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
H3K4	lysine in position 4 of type 3 histone
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
ICH	International Council for Harmonisation
IEC	independent ethics committee
INR	international normalized ratio
IRB	institutional review board
IUD	intrauterine device
KDM1	lysine-specific demethylase family 1
LFT	liver function test
LH	luteinizing hormone
LSD1	lysine-specific demethylase 1A
CCI	[redacted]
MRD	multiple-rising dose
NOAEL	no-observed-adverse-event-level
PAD	pharmacologically active dose
CCI	[redacted]
PD	pharmacodynamic(s)
PGx	Pharmacogenomic(s)
PK	pharmacokinetic(s)
PT	prothrombin time
PTE	pretreatment event
QD	once daily
QTcF	QT interval with Fridericia correction method
$R_{ac(AUC)}$	accumulation ratio based on AUC_{τ}
$R_{ac(Cmax)}$	accumulation ratio based on C_{max}
CCI	[redacted]
SAE	serious adverse event
SAP	statistical analysis plan
SRD	single-rising dose
SUSAR	suspected unexpected serious adverse reactions
$t_{1/2z}$	terminal disposition phase half-life
TEAEs	treatment-emergent adverse events
t_{max}	time of first occurrence of C_{max}
ULN	upper limit of normal
Vz/F	apparent volume of distribution during the terminal disposition phase after extravascular administration

15.0 DATA HANDLING AND RECORDKEEPING

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate.

Detailed information regarding data management procedures for this protocol will be provided by the sponsor or designee.

16.0 REFERENCES

1. Burg JM, Link JE, Morgan BS, Heller FJ, Hargrove AE, McCafferty DG. KDM1 class flavin-dependent protein lysine demethylases. Biopolymers 2015;104(4):213-46.
2. Sanders SJ, He X, Willsey AJ, Ercan-Sencicek AG, Samocha KE, Cicek AE, et al. Insights into Autism Spectrum Disorder Genomic Architecture and Biology from 71 Risk Loci. Neuron 2015;87(6):1215-33.
3. Shen E, Shulha H, Weng Z, Akbarian S. Regulation of histone H3K4 methylation in brain development and disease. Philos Trans R Soc Lond B Biol Sci 2014;369(1652).
4. Rudolph T, Beuch S, Reuter G. Lysine-specific histone demethylase LSD1 and the dynamic control of chromatin. Biol Chem 2013;394(8):1019-28.
5. Posner K, Oquendo MA, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. Am J Psychiatry 2007;164(7):1035-43.
6. Posner K, Melvin GA, Stanley B, Oquendo MA, Gould M. Factors in the assessment of suicidality in youth. CNS Spectr 2007;12(2):156-62.
7. Bond A, Lader M. The use of analogue scales in rating subjective feelings. Br J Med Psychol 1974;47:211-8.

17.0 APPENDICES

Appendix A Responsibilities of the Investigator

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

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

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff that will assist in the protocol.
3. If the investigator/institution retains the services of any individual or party to perform 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 study related procedures, including study specific (nonroutine/nonstandard panel) screening assessments are NOT performed on potential subjects, prior to the receipt of written approval from relevant governing bodies/authorities.
5. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
6. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 CFR Part 56, ICH, and local regulatory requirements.
7. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
8. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
9. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each informed consent form should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an informed consent form does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
10. Prepare and maintain adequate case histories of all persons entered into the study, including 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 study involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the subject's participation.
4. A description of the procedures to be followed, including invasive procedures.
5. The identification of any procedures that are experimental.
6. The estimated number of subjects involved in the study.
7. A description of the subject's responsibilities.
8. A description of the conduct of the study.
9. A statement describing the treatment(s) 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 study.
17. The anticipated expenses, if any, to the subject for participating in the study.
18. An explanation of whom to contact for answers to pertinent questions about the research (investigator), subject's rights, and IRB/IEC and whom to contact in the event of a research-related injury to the subject.
19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject otherwise is entitled, and that the subject or the subject's

legally acceptable representative may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
21. A statement that the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
22. A statement that results of PGx analysis will not be disclosed to an individual, unless prevailing laws require the sponsor to do so.
23. The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated.
24. A written subject authorization (either contained within the informed consent form or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the study. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:
    a) that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs/IECs;
    b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer subjects the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;
    c) that personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the study drug(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical studies;
    d) that subjects agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and
    e) that the subject's identity will remain confidential in the event that study results are published.

25. Female subjects of childbearing potential (eg, nonsterilized, premenopausal female subjects) who are sexually active must use highly effective contraception (as defined in the informed consent) from signing the informed consent and throughout the duration of the study, and for 31 days after the last dose of study drug. Regular pregnancy tests will be performed throughout the study for all female subjects of childbearing potential. If a subject is found to be pregnant during study, study drug will be discontinued and the investigator will offer the subject the choice to receive unblinded treatment information.
26. 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 the Use of Personal Information

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

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

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

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

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

From signing of informed consent, throughout the duration of the study, and for 31 days after last dose of study drug, female subjects of childbearing potential* must use a highly effective method of contraception with low user dependency (from the list below).

In addition, they must be advised not to donate ova during this period.

Definitions and Procedures for Contraception and Pregnancy Avoidance

The following definitions apply for contraception and pregnancy avoidance procedures.

*A woman is considered a woman of childbearing potential, ie, fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level in the postmenopausal range (FSH >40 IU/L) may be used to confirm a postmenopausal state in younger women (eg, those <45 years old) or women who are not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

The following procedures apply for contraception and pregnancy avoidance.

1. Highly effective methods of contraception are defined as "those, alone or in combination, that result in a low failure rate (ie, <1% failure rate per year when used consistently and correctly). In this study, where medications and devices containing hormones are excluded, the only acceptable methods of contraception are as follows:
    - Nonhormonal Methods:
        - IUD.
        - Bilateral tubal occlusion or ligation.
2. Unacceptable methods of contraception are as follows:
    - 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.
    - Sexual abstinence is NOT an acceptable method of contraception.

3. Subjects will be provided with information on highly 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 donation of ova during the course of the study.
4. During the course of the study, regular serum human chorionic gonadotropin (hCG) pregnancy tests will be performed and all subjects will receive continued guidance with respect to the avoidance of pregnancy as part of the study procedures. Such guidance should include a reminder of the following:
   a) contraceptive requirements of the study
   b) assessment of subject compliance through questions such as the following:
      i. Have you used the contraception consistently and correctly since the last visit?
      ii. Have you forgotten to use contraception since the last visit?
      iii. Are your menses late? (Even in women with irregular or infrequent menstrual cycles a pregnancy test must be performed if the answer is "yes.")
      iv. Is there a chance you could be pregnant?
5. In addition to a negative serum hCG pregnancy test at screening, female subjects of childbearing potential must also have confirmed menses in the month before first dosing (no delayed menses), and a negative serum hCG pregnancy test prior to receiving the first dose of study drug on Day 1.

General Guidance With Respect to the Avoidance of Pregnancy

Such guidance should include a reminder of the following:

- contraceptive requirements of the study.
- 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?
  – Are your menses late (even in women with irregular or infrequent menstrual cycles a pregnancy test must be performed if the answer is "yes")
  – Is there a chance you could be pregnant?

Pregnancy

If any subject is found to be pregnant during the study she should be withdrawn and any sponsor-supplied drug (TAK-418 and placebo) should be immediately discontinued.

Should the pregnancy occur during or after administration of blinded drug, the investigator must inform the subject of their right to receive treatment information. If the subject chooses to receive

unblinded treatment information, the individual blind should be broken by the investigator. Subjects randomized to placebo need not be followed.

If the subject agrees to the primary care physician being informed, the investigator should notify the primary care physician that the subject was participating in a clinical study at the time she became pregnant and provide details of the study drug the subject received (blinded or unblinded, as applicable).

All pregnancies in subjects on active study drug will be followed up to final outcome, using the pregnancy form. Pregnancies will remain blinded to the study team. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical VP Approval	21-Mar-2018 18:49 UTC
	Clinical Pharmacology Approval	21-Mar-2018 20:06 UTC
	Biostatistics Approval	23-Mar-2018 15:57 UTC