



Title: An Open-Label, Single-center, Parallel, Phase 1 Study to Determine the Pharmacokinetics of Single- and Multiple- Oral Doses of TAK-438 10 mg and 20 mg in Healthy Adult Chinese

NCT Number: NCT03085836

Protocol Approve Date: 21 December 2016

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PHASE 1 PROTOCOL

An Open-Label, Single-center, Parallel, Phase 1 Study to Determine the Pharmacokinetics of Single- and Multiple- Oral Doses of TAK-438 10 mg and 20 mg in Healthy Adult Chinese Subjects

Pharmacokinetic Study of TAK-438 in Healthy Adult Chinese Subjects

Sponsor: Takeda Development Center Asia Pte Ltd.
21 Biopolis Road
Nucleos North Tower, Level 4
Singapore 138567

Study Number: TAK-438_114

IND Number: Not applicable **EudraCT Number:** Not applicable

Compound: TAK-438

Date: 21 December 2016

Amendment History

Date	Amendment Number	Region
01 August 2012	Initial Protocol	Asia Pacific
29 August 2016	01	Asia Pacific
21 December 2016	02	Asia Pacific

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1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

A separate contact information list will be provided.

TDC sponsored Asian Pacific investigators will be provided with emergency medical contact information cards to be carried by each subject.

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

Issue	China Contact
Serious adverse event, pregnancy and special interest adverse event reporting	Quintiles Lifecycle Safety (Refer to the Study Team Contact list)
Medical Monitor (medical advice on protocol, compound, and medical management of subjects)	Quintiles Asia Medical Sciences Group (Refer to the Study Team Contact list)
Responsible Medical Officer (carries overall responsibility for the conduct of the study)	PPD [REDACTED] sia, Pte Ltd 21 Biopolis Road Nucleos North Tower, Level 4 Singapore 138567 Tel: PPD Fax: PPD

1.2 Approval

REPRESENTATIVES OF TAKEDA

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

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

SIGNATURES

PPD _____ Date PPD _____ Date



PPD _____ Date PPD _____ Date



1.3 Protocol Amendment 02 Summary of Changes

Rationale for Amendment No. 02

This document describes the changes in reference to the protocol incorporating Amendment No. 02. In addition, minor grammatical, editorial, and formatting changes were included for clarification purposes only.

For specific descriptions of text changes and where the changes are located, see [Appendix G](#).

Changes in Amendment No. 02

1. Reduced the fasting period after dosing from 4 hours to 2 hours in the once daily dosing regimen only.
2. For the collection of demographic data, replaced the requirement to collect date of birth with a requirement to collect age.
3. Clarified clinical laboratory sample collection volume and time points.
4. Change in compounds or parameters tested during clinical laboratory testing.
5. Reduced the frequency in 12-lead electrocardiogram monitoring, and revised procedure for abnormal (not clinically significant) ECGs at Screening.
6. Clarified that genotyping will be conducted at the local laboratory.
7. Clarified liver function test monitoring.
8. Removed the requirement for genitourinary monitoring as part of the physical examination.
9. Clarified the Chinese population eligible for inclusion into the study.
10. Minor updates for protocol consistency.
11. Clarified the time point for vital sign measurements.
12. Follow-up Visit changed from a site visit to a Telephone Contact.
13. Clarification of 4-digit enrollment number assignment.
14. Addition of table describing window for urine sample collection.
15. Clarification of meals given during the Confinement Period.
16. Clarification for urinalysis on Day 3 and Day 9.

INVESTIGATOR AGREEMENT

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

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.2 of this protocol.
- Terms outlined in the Clinical Study Site Agreement.
- [Appendix B](#) – Responsibilities of the Investigator.

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

Signature of Investigator

Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State)

China

Location of Facility (Country)

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2.0 STUDY SUMMARY

Name of Sponsor(s): Takeda Development Center Asia Pte Ltd.				Compound: TAK-438 (vonoprazan)										
Title of Protocol: An Open-Label, Single-center, Parallel, Phase 1 Study to Determine the Pharmacokinetics of Single- and Multiple- Oral Doses of TAK-438 10 mg and 20 mg in Healthy Adult Chinese Subjects				IND No.: Not applicable		EudraCT No.: Not applicable								
Study Number: TAK-438_114				Phase: 1										
Study Design: This is a phase 1, parallel, open-label, single- and multiple-dose study of TAK-438 involving 36 healthy Chinese subjects between the ages of 18 and 45, inclusive, and considered eligible based on the inclusion and exclusion entry criteria. Screening for potential subjects will occur between 28 and 2 days prior to confinement at the phase 1 unit. Selected eligibility criteria will be reconfirmed on Day -1 prior to assignment to the 10 mg or 20 mg once daily or 20 mg twice daily cohort, predose blood and urine sampling for PK measurements will also be taken. Having fasted for a minimum of 10-hours a single oral dose of TAK-438 will be administered on Day 1 followed by a pharmacokinetic sampling period of 48 hours. On Days 3 through to Day 9 subjects will receive their assigned daily dose(s) of TAK-438 followed by another 12- or 48-hour pharmacokinetic sampling period (for the BID or QD regimens respectively). Besides monitoring concomitant medications and adverse events, physical examination, ECG, vital signs and clinical laboratory tests will be conducted to monitor safety. A schedule of assessments is listed in Appendix A . A schematic of the study design follows; routine diet and fluid controls are listed in Section 7.4 .														
Screening	Check -In	Single Dose and PK	48-hour PK	Multiple Dosing (a)	Dosing and PK	48-hour PK	Check -Out	Follow-Up (b) Telephone Contact						
Study Day -28 to -2	Day -1	Day 1	Day 2	Days 3-8	Day 9	Day 10	Day 11	Day 18 ±3 days						
		TAK-438 single dose 10 mg or 20 mg		TAK-438 once daily 10 mg or 20 mg or twice daily 20 mg										
	◀	Confinement				▶								
(a) Dosing on Day 3 will be after the 48-hour PK sample collection. (b) The follow-up telephone contact will assess adverse events, serious adverse events and any concomitant medications since the Day 11 visit (study exit).														
Primary Objective: To determine the pharmacokinetics of TAK-438 in healthy adult Chinese subjects after both single and multiple dose administration.														
Secondary Objectives: To determine the safety and tolerability of TAK-438 in healthy adult Chinese subjects after both single and multiple dose administration.														
Subject Population: Healthy subjects aged 18-45 inclusive.														
Number of Subjects: Per cohort: 12: Estimated Total: 36 enrolled				Number of Sites: 1 site in China										

Dose Level(s): TAK-438 10 mg QD; TAK-438 20 mg QD TAK-438 20 mg BID	Route of Administration: Oral	
Duration of Treatment: Single dose on Day 1 followed by 7 days from Day 3 until Day 9	Period of Evaluation: Approximately 18 days after completion of the screening period	
Main Criteria for Inclusion:		
<ol style="list-style-type: none"> 1. Healthy (male or non-pregnant, non-lactating female) Chinese adults. 2. Subject has BMI of ≥ 19 and $\leq 26\text{kg}/\text{m}^2$ and weighs ≥ 50 kg. 		
A complete list of study inclusion criteria is provided in Section 7.1.		
Main Criteria for Exclusion:		
Subjects who have a clinically significant history of hypersensitivity to any drug or food or any excipients of TAK-438, a history of gastroesophageal reflux disease (GERD), symptomatic GERD, erosive esophagitis, duodenal ulcer, gastric ulcer, dyspepsia, Barrett's esophagus, or Zollinger-Ellison syndrome, and subjects with a liver function test $>$ upper limit of normal are excluded. A complete list of Exclusion criteria can be found in Section 7.2 and standard concomitant medications to be excluded in Section 7.3.		
Main Criteria for Evaluation and Analyses:		
- Pharmacokinetics: The concentrations of TAK-438F (free base of TAK-438) and the four major metabolites (M-I, M-II, M-III and M-IV-Sul) in plasma and urine will be measured as per the following summary:		
Sample Type	Dosing Day	Time Postdose (hours)
Plasma	Day 1, *Day 9	Predose (0 hours) and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, and 48 hours postdose
Plasma	*Days 4-8	Predose
Urine	Day 1, *Day 9	Predose, 0 to 6, 6 to 12, 12 to 24, 24 to 36 and 36 to 48 hours postdose
*note that for the 20 mg twice daily cohort: from Day 4 to Day 8 PK sampling should be drawn relative to the morning dose and, on Day 9 PK samples should only be taken until the 12-hour time point following the morning dose.		
The primary pharmacokinetic variables will be assessed after the single dose on Day 1 and after the multiple dose on Day 9.		
Pharmacokinetic variables will be derived from the plasma concentrations of TAK-438F and its metabolites M-I, M-II, M-III, M-IV-Sul as required. These will include, where appropriate, maximum observed plasma concentration (C_{\max}), time to reach C_{\max} (t_{\max}), area under the plasma concentration-time curve from time 0 to infinity (AUC_{∞}), area under the plasma concentration-time curve during a dosing interval (AUC_{τ}) and terminal disposition half-life ($t_{1/2z}$) on Day 1, and maximum observed plasma concentration, at steady state ($C_{\max,ss}$), time to reach C_{\max} at steady state ($t_{\max,ss}$), and area under the plasma concentration-time curve during a dosing interval, at steady state ($AUC_{\tau,ss}$) on Day 9.		
Pharmacokinetic variables derived from the urine concentrations of TAK-438 and its metabolites M-I, M-II, M-III and M-IV-Sul will include amount excreted in urine from time 0 to time t (Ae_t), fraction of administered dose of drug excreted in urine from time 0 to time t ($f_{e,t}$), and renal clearance (CL_R) on Day 1, and amount of drug excreted in urine during a dosing interval (Ae_{τ}), the fraction of the dose excreted unchanged in urine (f_{et}), and renal clearance (CL_R) on Day 9.		
- Pharmacogenomics:		
CYP2C19 genotype will be tested for each subject in order to ensure that we can fully interpret the study results. Although it is noted that cytochrome P450 3A4 (CYP3A4) is the main enzyme responsible for TAK-438 metabolism, the polymorphic CYP2C19 also has a minor contribution.		

- Safety:

Standard safety assessments for phase 1 studies will be collected which include physical examinations, vital signs, and ECG as described in Section [9.1](#).

- Laboratory tests:

Standard laboratory tests will be assessed as provided in Section [9.1.8](#). The total volume of blood to be drawn for study participants is 328.5 mL if a catheter is used.

Statistical Considerations:

For TAK-438F and its four metabolites M-I, M-II, M-III and M-IV-Sul plasma and urine concentration and pharmacokinetic parameters will be tabulated and descriptive statistics computed.

Sample Size Justification:

The sample size of 12 subjects per cohort is sufficient to evaluate the PK profile after single- and multiple-dose administration of TAK-438 10 mg and 20 mg. And, it is also consistent with CFDA guideline “Technical guideline for clinical pharmacokinetics study of chemicals”.

3.0 STUDY REFERENCE INFORMATION

3.1 Study Related Responsibilities

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

3.2 Principal Investigator

PPD

Zhongshan Hospital, Fudan University
180 Fenglin Road, Xuhui District,
Shanghai, P.R. China

3.3 List of Abbreviations

ADME	absorption, distribution metabolism, excretion
AE	adverse event
Ae_t	amount of drug excreted in urine time 0 to t,
Ae_τ	amount of drug excreted in urine time 0 to tau,
ALT	alanine aminotransferase
ANOVA	analysis of variance
aPTT	activated prothrombin time
AST	aspartate aminotransferase
AUC_∞	area under the plasma concentration-time curve from time 0 to infinity.
AUC_τ	area under the plasma concentration-time curve during the dosing interval.
AUC_{last}	area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration (tlqc).
$C_{\text{av,ss}}$	average plasma concentration during a dosing interval, at steady state
CFR	Code of Federal Regulations
CL/F	apparent clearance.
CL _R	renal clearance.
C_{\max}	maximum observed plasma concentration
eCRF	case report form (electronic)
CRO	contract research organization
$C_{\max,ss}$	maximum observed plasma concentration during a dosing interval, at steady state.
$C_{\min,ss}$	minimum observed plasma concentration during a dosing interval, at steady state
ECG	electrocardiogram
EDC	electronic data capture
EMEA	European Medicines Agency
FDA	Food and Drug Administration
FAS	full analysis set
f_e	fraction of administered dose of drug excreted in urine, from time 0 to time t.
$f_{e,\tau}$	fraction of administered dose of drug excreted in urine during a dosing interval
GCP	Good Clinical Practice
GGT	γ -glutamyl transferase
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IRB	institutional review board
IVRS	interactive voice response system
IWRS	interactive web response system
LDH	lactate dehydrogenase

LLN	lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
MRT	mean residence time
PTE	pretreatment event
PTF%	peak/trough fluctuation during a dosing interval, at steady state.
PT/INR	prothrombin time/international normalized ratio
Rac _(AUC)	accumulation ratio based on AUC.
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SOP	standard operating procedure
t _{1/2z}	terminal disposition phase half-life.
t _{max}	time of first occurrence of C _{max}
ULN	upper limit of normal
Vz/F	apparent volume of distribution.
WBC	white blood cell
WHO	World Health Organization
λ _z	terminal disposition phase rate constant.

3.4 Corporate Identification

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

4.0 INTRODUCTION

4.1 Background

The proton pump inhibitors (PPIs), such as lansoprazole, represent the drugs of first choice for gastric and duodenal ulcers, as well as non-erosive or erosive esophagitis and are being widely used.

The PPIs inhibit the H^+, K^+ -ATPase enzyme (proton pump) which represents the final step in acid secretion by the parietal cells in the gastric mucosa, and produce potent anti-secretory efficacy for acid-related disorders.

However, even with these potent acid-inhibitory effects, the PPIs are not without their limitations and have not necessarily produced adequate improvements in extent and speed of symptom relief [1]. Indeed, the PPIs appear to leave room for improvement, the reasons being that:

1. Being less resistant to acid exposure and provided as enteric-coated drugs, the PPIs vary in time for onset of their action;
2. About 3 to 5 days are required to obtain maximum acid-inhibitory effects with the PPIs;
3. Acid-inhibitory effects with the PPIs appear to be satisfactory during daytime, but not adequate to inhibit acid regurgitations from the stomach to the esophagus occurring during nighttime, leading to nocturnal acid breakthroughs in some individuals;
4. Metabolized by CYP2C19 associated with polymorphisms, the PPIs are associated with varying serum concentrations, thus producing disparate acid-inhibitory effects in extensive metabolizers (EM) versus poor metabolizers (PM).

Developed at Takeda Pharmaceutical Company Ltd, TAK-438 belongs to a new class of acid-inhibitory agents called “potassium-competitive acid blockers” (P-CAB). TAK-438 is shown not only to inhibit the H^+, K^+ -ATPase enzyme in the final step of acid secretion, as the PPIs do, but does not require the presence of acid for its activation and inhibits the H^+, K^+ -ATPase enzyme in a potassium-competitive fashion. Furthermore, TAK-438 is shown to be stable in the presence of acid and is water-soluble, requires no particular pharmacological preparations, such as an enteric coating, suggesting that TAK-438 may likely vary less in time for onset of action than the PPIs among those receiving the drug. Furthermore, in contrast to the PPIs which take 3 to 5 days to produce their maximum acid-inhibitory effects, TAK-438 is expected to produce its maximum acid-inhibitory effects in a much shorter time and to produce better outcomes than the PPIs with its potent and sustained acid-inhibitory effects.

In Japan, TAK-438 has been evaluated for the doses ranging between 1 mg and 120 mg in a phase I study (TAK-438/CPH-001) as well as for safety, pharmacokinetics, and acid-inhibitory effects in a 7-day repeated-dose study (TAK-438/CPH-002) at the doses ranging between 10 mg and 40 mg. TAK-438 has been found to be well tolerated when given at the dose of 40 mg in the 7-day repeated-dose study, where the pH4 holding time ratio (pH4 HTR) with TAK-438 10 mg on day 7 was shown to be similar to that with lansoprazole 30 mg. However pH4 HTR was found to increase greatly with TAK-438 15 mg and 20 mg, and exceed 90% and remain stable with

TAK-438 30 mg and 40 mg, thus providing evidence of TAK-438's potent and sustained acid-inhibitory effects. Furthermore, no specific trend was found with any of the CYP2C19 polymorphisms, suggesting that these polymorphisms lead to very little difference in the pharmacokinetics of TAK-438. Additionally, in a study evaluating interactions between TAK-438 and various non-steroidal anti-inflammatory drugs (NSAIDs) (eg, loxoprofen sodium, diclofenac sodium, meloxicam) (TAK-438/CPH-003), none of these drugs were shown to significantly affect the pharmacokinetics of TAK-438.

Studies of single-dose (TAK-438_101) and repeated-dose (TAK-438_107) TAK-438 were conducted in the UK as well, where TAK-438 was evaluated for its safety, pharmacokinetics and acid-inhibitory effects in the 7-day repeated-dose study at the doses ranging between 10 mg and 40 mg. TAK-438 was shown to be well tolerated at the dose of 40 mg in the repeated-dose study, with the pH4 HTR on day 7 shown to be similar to that in the repeated-dose study conducted in Japan at either of the doses examined, supporting the potent and sustained acid-inhibitory effects of TAK-438. Again, in a study evaluating interactions between TAK-438 and clarithromycin conducted in the UK (TAK-438_110), repeated-dose clarithromycin was examined for its influence on the pharmacokinetics of TAK-438, where, while the plasma concentration of TAK-438F increased by 1.35-fold for C_{max} and by 1.58-fold for AUC in combination with clarithromycin, a potent inhibitor of the CYP3A4 enzyme, TAK-438 was shown to be well tolerated.

In a phase II dose-ranging study of TAK-438 in subjects with erosive esophagitis (TAK-438/CCT-001), TAK-438, given once daily at doses 5 mg, 10 mg, 20 mg, and 40 mg for 8 weeks, was evaluated for its dose-response efficacy and safety in a randomized, double-blind, parallel-group comparison with lansoprazole serving as control, demonstrating that the rate of endoscopic healing of erosive esophagitis 4 weeks after the start of treatment, the primary endpoint of the study, was 92.3%, 92.5%, 94.4%, and 97.0% with TAK-438 5 mg, 10 mg, 20 mg and 40 mg, respectively, compared to 93.2% with lansoprazole, showing the non-inferiority of TAK-438 to lansoprazole 30 mg at the doses examined. No particular safety concerns were identified with TAK-438 at the doses examined.

TAK-438 has been studied in a number of acid-related diseases and noninferiority with lansoprazole has been confirmed in several phase 3 studies including reflux esophagitis healing and prevention of recurrence studies, gastric ulcer (GU)/duodenal ulcer (DU) healing and for the prevention of recurrence of a gastric or duodenal ulcer during NSAID or aspirin administration and has subsequently been launched in Japan for these indications. Of note, in a phase 3 *Helicobacter pylori* eradication study, 7-day treatment with TAK-438 20 mg (n=329) or lansoprazole 30 mg (n=321) in combination with amoxicillin 750 mg plus clarithromycin 200 or 400 mg, *Helicobacter pylori* eradication rates were 92.6% and 75.9%, respectively. Furthermore, the first 50 treatment failures with good compliance received second-line triple-therapy with TAK-438 20 mg (in combination with amoxicillin 750 mg and metronidazole 250 mg) in an open-label manner and an eradication rate of 98% was observed. All treatments were well-tolerated.

4.2 Rationale for the Proposed Study

TAK-438 has been evaluated in both Japanese healthy volunteers (TAK-438/CPH-001, TAK-438/CPH-002, and TAK-438/CPH-003 and non-Japanese healthy volunteers (TAK-438_101, TAK-438_103, TAK-438_107, TAK-438_109 and TAK-438_110). TAK-438 has been evaluated in single-dose studies at doses of 1 to 120 mg, in multiple-dose studies at doses of 10, 15, 20, 30, and 40 mg, and in a phase 2 study at doses of 5, 10, 20 and 40 mg for 8 weeks. TAK-438 has also been evaluated for the effect of food at 10 and 40 mg doses in Japanese subjects, and for the effect of food and gender at a 20 mg dose in non-Japanese subjects. An ADME study using the 20 mg dose and a clarithromycin drug-drug interaction study using single doses of 40 mg TAK-438 and multiple doses of 500 mg clarithromycin have also been completed. TAK-438 is considered safe and has been well-tolerated at all doses administered and at doses \geq 20 mg had a rapid onset and prolonged duration of action. The effects of food and gender have no clinically relevant effect on the PK profile, however the use of the strong CYP3A4 inhibitor increased the exposure of TAK-438F and its metabolites by up to 2-fold. Completed PK studies indicate that four major metabolites should be assessed: M-I, M-II, M-III and M-IV-Sul.

This study is designed based on the requirements of the China Food and Drug Administration (CFDA) for successful registration of TAK-438 in China. Phase 3 efficacy and safety trials will be performed concurrently in China and other countries within the Asian region. This single- and multiple-dose study design will provide adequate information on the pharmacokinetic profile of TAK-438 in adult Chinese subjects at the 10 mg, 20 mg and 40 mg dose levels.

This study will evaluate the PK of unchanged TAK-438F and the 4 metabolites following single- and multiple-doses of 10 mg and 20 mg, ie, the doses used in the concurrent Asian Phase 3 efficacy and safety studies.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

To determine the pharmacokinetics of TAK-438 in healthy adult Chinese subjects after both single and multiple dose administration.

5.1.2 Additional Objectives

CCI



5.2 Endpoints

5.2.1 Primary Endpoints

The Primary endpoints for this study are the pharmacokinetic parameters derived from the plasma and urine concentrations of TAK-438F and its metabolites M-I, M-II, M-III, M-IV-Sul assessed after the first dose on Day 1 and after the final repeat dose on Day 9 as required.

The following pharmacokinetic parameters will be calculated from plasma concentrations of TAK-438F, M-I, M-II, M-III and M-IV-Sul:

Day 1

- Maximum observed plasma concentration (C_{max}).
- Time to reach C_{max} (t_{max}).
- Area under the plasma concentration-time curve from time 0 to infinity (AUC_{∞}).
- Area under the plasma concentration-time curve during a dosing interval (AUC_{τ}).
- Terminal disposition half-life ($t_{1/2z}$).

Day 9

- Maximum observed plasma concentration, at steady state ($C_{max,ss}$).
- Time to reach C_{max} at steady state ($t_{max,ss}$).
- Area under the plasma concentration-time curve during a dosing interval, at steady state ($AUC_{\tau,ss}$).

The following pharmacokinetic parameters will be calculated from urine concentrations of TAK-438F, M-I, M-II, M-III and M-IV-Sul:

Day 1

- Amount of drug excreted in urine from time 0 to time t (Ae_t).

- Fraction of administered dose of drug excreted in urine from time 0 to time t ($f_{e,t}$).
- Renal clearance (CL_R).

Day 9

- Amount of drug excreted in urine during a dosing interval (Ae_τ).
- Fraction of administered dose of drug excreted in urine during a dosing interval ($f_{e,\tau}$).
- Renal clearance (CL_R).

5.2.2 Additional Endpoints

CCI



6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is a phase 1, parallel, open-label, single- and multiple-dose study of oral TAK-438 involving 36 healthy Chinese subjects between the ages of 18 and 45, inclusive, and considered eligible based on the inclusion and exclusion entry criteria.

Screening for potential subjects will occur between 28 and 2 days prior to confinement at the phase 1 unit. Selected eligibility criteria will be reconfirmed on Day -1 prior to assignment to the 10 mg or 20 mg once daily or 20 mg twice daily cohort, predose blood and urine sampling for PK measurements will also be taken. Having fasted for a minimum of 10-hours a single oral dose of TAK-438 will be administered on Day 1 followed by a pharmacokinetic sampling period of 48 hours. On Days 3 through 9 subjects will receive their assigned daily dose(s) of TAK-438 followed by another pharmacokinetic sampling period of 48 hours (for subjects on a once daily regimen), or 12 hours (for those assigned to the 20 mg twice daily regimen). The subject will be confined to the phase 1 unit from Day -1 (Check-In) through to Day 11 (Check-Out) and will be contacted by the study site for a follow-up telephone visit on Day 18.

Besides monitoring concomitant medications and adverse events, physical examination, ECG, vital signs and clinical laboratory tests will be conducted to monitor safety. A schedule of assessments is listed in [Appendix A](#). A schematic of the study design follows; routine diet and fluid controls are listed in Section [7.4](#).

Figure 6.a Schematic of Study Design

Screening Period		Treatment Period						Follow-Up
Screening	Check-In	Single Dose/ PK	48-hour PK	Multiple Dosing (a)	Dosing and PK	48-hour PK / Observation	Check-Out	Follow-up Telephone Visit
Days -28 to -2	Day -1	Day 1	Day 2	Days 3-8	Day 9	Day 10	Day 11	Day 18 ± 3 days
		TAK-438 single dose 10 mg or 20 mg		TAK-438 once daily 10 mg or 20 mg or twice daily 20 mg				
		← Confinement →						

PK=pharmacokinetic.

A summary of the dose cohorts is presented in [Table 6.a](#).

Table 6.a Summary of Dose Cohorts

Cohort	TAK-438 Dose (shown as free base amount)	Subjects
1	TAK-438 10 mg once daily	12
2	TAK-438 20 mg once daily	12
3	TAK-438 20 mg twice daily	12

A schematic of the dosing schedule and sampling, by cohort, is provided in [Table 6.b](#).

Table 6.b Schematic of Dosing and PK Sampling, by Cohort

Regimen	Event	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11
Cohort 1 (10 mg QD)	Dosing	↑		↑	↑	↑	↑	↑	↑	↑		
	PK sampling	↔		•	•	•	•	•	•	↔		
Cohort 2 (20 mg QD)	Dosing	↑		↑	↑	↑	↑	↑	↑	↑		
	PK sampling	↔		•	•	•	•	•	•	↔		
Cohort 3 (20 mg BID)	Dosing	↑		↑↓	↑↓	↑↓	↑↓	↑↓	↑↓	↑↓	↑↓	
	PK sampling	↔		•	•	•	•	•	•	↔		

↑: Morning dose,; ↓: Evening dose; ↔: Serial PK; • Trough PK

6.2 Justification for Study Design, Dose and Endpoints

For the patient population studied

This study will be performed in healthy subjects rather than the target subject population (ie, disease patients) in order to collect pharmacokinetic, safety and tolerability information that will not be biased by any comorbidities. This is also in compliance with CFDA data requirements.

For study design, sample size and genotyping used

1. Study design.

The study design is open label, since the primary objective is to assess objective variables, ie, pharmacokinetics. This is not a subjective measurement and there is consequently no risk of potential bias of the study results; hence there are no requirements for blinding and a placebo group.

2. Sample size.

The sample size is sufficient to establish the complete pharmacokinetic profile for TAK-438 and its major metabolites. It is also selected to be compliant with CFDA requirements.

3. CYP2C19 genotyping.

CYP2C19 genotype will be tested for each subject in order to ensure that we can fully interpret the study results. Although it is noted that cytochrome P450 3A4 (CYP3A4) is the main enzyme responsible for TAK-438 metabolism, the polymorphic CYP2C19 also has a minor contribution.

For doses of the study medications used

This study supports the ongoing development program for the TAK-438 in Asia which includes planned Phase 3 studies in peptic ulcer diseases, and erosive esophagitis. The 10 mg and 20 mg once daily and 20 mg twice daily dose levels are selected as they are consistent with the planned phase 3 studies.

For duration of treatment used

The half-life (mean) of a single oral dose of 20 mg of TAK-438 in healthy adult male subjects is 5.8 hours for unchanged drug, 9.6 hours for M-I, 8.2 hours for M-II, 5.2 hours for M-III and 3.8 hours for M-IV-Sul. Therefore a pharmacokinetic sampling period of 48 hours is considered sufficient to characterize the pharmacokinetic profile following a single dose of TAK-438. In addition it would be expected that following repeat dosing steady state would be achieved after 5 half-lives, therefore the collection of samples to determine the pharmacokinetic profile following Day 7 should capture the steady state pharmacokinetic parameters.

As supported by ADME study TAK-438_103, a follow-up examination (as an onsite visit) will be conducted 7 days after dosing, at which time the drug is considered to be completely eliminated from the body.

For endpoints used

The plasma concentration and urinary excretion rate of unchanged drug and major metabolites TAK-438 will be examined to establish the pharmacokinetics of dosing at 10 and 20 mg once daily and 20 mg twice daily.

The commonly used safety endpoints of adverse events, vital signs, ECG findings, and laboratory test results are used in this study determined as safety endpoints.

6.3 Premature Termination or Suspension of Study or Investigational Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

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

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

6.3.2 Criteria for Premature Termination or Suspension of Investigational Sites

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

6.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Investigational Site(s)

In the event that the sponsor, an institutional review board (IRB)/ independent ethics committee (IEC), or regulatory authority elects to terminate or suspend the study or the participation of an investigational site, a study-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 study suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria, including test results, need to be confirmed prior to first dose of study medication on Day 1.

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria:

1. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
2. The subject or, when applicable, the subject's legally acceptable representative signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures.
3. The subject is a healthy adult male or female Chinese subject.
4. The subject is aged 18 to 45 years, inclusive, at the time of signing the informed consent form.
5. The subject weighs at least 50 kg and has a body mass index (BMI) between 19 and 26kg/m², inclusive at Screening (Check-In Day -1).
6. A female subject of childbearing potential* who is sexually active with a nonsterilized* male partner agrees to use routinely adequate contraception* from signing of informed consent throughout the duration of the study and for 4 weeks after last dose of study medication.

*Definitions and acceptable methods of contraception are defined in Section [9.1.9](#) Contraception and Pregnancy Avoidance Procedure and reporting responsibilities are defined in Section [9.1.10](#) Pregnancy.

7. The subject is willing to abstain from caffeine and alcohol from 72 hours before first dose (Day 1) until the Follow-up Visit on Day 18.
8. The subject is willing to abstain from strenuous exercise from 72 hours before first dose (Day 1) until the Follow-up Visit on Day 18.
9. The subject is willing to provide a sample for pharmacogenetic analysis (for CYP2C19 genotyping).

7.2 Exclusion Criteria

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

1. The subject has received any investigational compound within 90 days prior to providing their informed consent.
2. The subject has received TAK-438 in a previous clinical study or as a therapeutic agent.
3. The subject is an immediate family member, study site employee, or in a dependant relationship with a study site employee who is involved in the conduct of this study (eg, spouse, parent, child, sibling) or may consent under duress.

4. The subject has uncontrolled, clinically significant cardiovascular disease or other abnormality, which may impact the ability of the subject to participate or potentially confound the study results.
5. Subject is lactose intolerant or has a known hypersensitivity to any component of the formulation of TAK-438.
6. The subject has a positive urine drug result for drugs of abuse at Screening or Check-in (Day -1).
7. The subject has a history of drug abuse (defined as any illicit drug use) or a history of alcohol abuse at any time prior to the screening visit or is unwilling to agree to abstain from alcohol and drugs throughout the study.
8. Subject has taken any excluded medication, supplements, or food products listed in the Excluded Medications and Dietary Products table listed in Section [7.3](#).
9. If female, the subject is pregnant or lactating or intending to become pregnant before, during, or within 1 month after participating in this study; or intending to donate ova during such time period.
10. Subject has evidence of current cardiovascular, central nervous system, hepatic, hematopoietic disease, renal dysfunction, metabolic or endocrine dysfunction, serious allergy, asthma hypoxemia, hypertension, seizures, or allergic skin rash. There is any finding in the subject's medical history, physical examination, or safety laboratory tests giving reasonable suspicion of a disease that would contraindicate taking TAK-438 or contraindicate any drug used to reduce acid secretion by the stomach or that might interfere with the conduct of the study. This includes, but is not limited to, peptic ulcer disease, seizure disorders, and cardiac arrhythmias.
11. The subject has a history of symptomatic GERD, GERD, Erosive Esophagitis, DU, GU, dyspepsia, Barrett's Esophagus, or Zollinger-Ellison (ZE) syndrome or has current or recent (within 6 months) gastrointestinal disease that would be expected to influence the absorption of drugs.
12. Subject has a history of cancer, other than basal cell or Stage 1 squamous cell carcinoma of the skin which has been in remission for at least 5 years prior to Day 1.
13. Subject has a positive test result for hepatitis B surface antigen (HBsAg), hepatitis C antibody (HCV), human immunodeficiency virus (HIV) antibody/antigen at Screening.
14. Subject has used nicotine-containing products (including but not limited to cigarettes, pipes, cigars, chewing tobacco, nicotine patch or nicotine gum) within 6 weeks prior to Check-in Day -1. Cotinine test is positive at Screening or Check-in (Day -1).
15. The subject has poor peripheral venous access.
16. Subject has donated or lost 400 mL or more of his or her blood volume (including plasmapheresis), or had a transfusion of any blood product within 90 days prior to Day 1; or subject has donated or lost more than 200 mL or more of his or her blood in the last 28 days.

17. Subject has a Screening or Check-in (Day -1) abnormal (clinically significant) ECG. Entry of any subject with an abnormal (not clinically significant) ECG must be approved, and documented by signature by the GCP-trained study doctor. Also refer to Section 9.1.11 for further instructions on ECG review.
18. Subject has abnormal Screening or Day -1 laboratory values that suggest a clinically significant underlying disease or subject with the following laboratory abnormalities:
 - Creatinine levels: >2 mg/dL (>177 µmol/L).
 - Alanine aminotransferase (ALT), aspartate aminotransferase (AST) or total bilirubin > the upper limit of normal (ULN).

7.3 Excluded Medications and Dietary Products

Use of the agents in Table 7.a (prescription or nonprescription) is prohibited from the time points specified until completion of all study activities.

Table 7.a Prohibited Medications

6 weeks prior to Check-In (Day -1)	28 days prior to Check-In (Day -1)	14 days prior to Check-In (Day -1)	7 days prior to Check-In (Day -1)	72 hours prior to Check-In (Day -1)
Nicotine-containing products	Prescription medications	OTC medications including salicylates (a)	Foods or beverages containing grapefruit or grapefruit products, Seville-type (sour) oranges and marmalade or other Seville orange products.	Alcohol-containing products or medications
Immunization/ vaccines	St. John's wort, ginseng, kava, ginkgo biloba, Chinese herbs, melatonin, other herbal or homeopathic preparations or other nutraceuticals.	Vitamin supplements		Products or medications containing caffeine or xanthine

OTC=over-the-counter.

(a) Occasional use of paracetamol (\leq 2 g/day) is allowed or other OTC medication as approved by Takeda's or designated CRO's Medical Monitor on a case-by-case basis during the 14 days prior to Day -1. Neither paracetamol nor any other OTC medication is allowed from Day 1 to Day 11 (after last PK sample collection).

Subjects must be instructed not to take any medications, including over-the-counter medications, without first consulting with the investigator.

Use of concomitant medications will not be allowed during the study except for those approved by Takeda's (or designated CRO's) Medical Monitor on a case-by-case basis during the screening phase. No concomitant medications will be allowed from Day 1 until Day 11 (after last PK sampling time point) unless deemed necessary in a medical emergency. Concomitant medications will include all medications the subject has taken from signing of informed consent to the end of the study (Day 18).

The use of oral hormonal contraceptives and hormone replacement therapy is not allowed. Exceptions to the above prohibited medication will be reviewed on a case-by-case basis by the Takeda (or designated CRO) Medical Monitor.

If the subject reports taking any medication or if administration of any medication becomes necessary during the course of this study, the Takeda (or designated CRO) Medical Monitor must be notified. All medications must be recorded in the source documents as well as on the appropriate electronic case report form (eCRF) along with dosage information, dates of administration, and reasons for use.

7.4 Diet, Fluid, and Activity Control

Subjects will be confined to the clinic for the duration of each treatment period (Day -1 through Day 11).

During the confinement period, subjects will be given a menu for the dosing period that includes 3 meals. Each meal will contain approximately 20% to 25% fat (relative to the total calories), according to the local phase 1 unit standard. The menu of the standardized meals from the clinical research site will be approved by Takeda before the implementation. 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.

If a blood draw or any study procedure coincides with a meal, the study procedure will take precedence followed by the blood draw and then the meal.

For subjects receiving QD regimen, they should be fasted overnight for a minimum of 10 hours prior to dosing and will continue to fast for 2 hours after dosing. They should take the dose with 240 mL water and refrain from drinking for at least 1 hour postdose, after which water can be given *ad libitum*.

For subjects receiving BID regimen they should be fasted overnight for a minimum of 10 hours prior to breakfast. Breakfast and dinner should be given at approximately the same time each day on Day 1 to Day 10. Breakfast and dinner should be completed within 0.5 hours and then TAK-438 should be administered 0.5 hours after the start of breakfast/dinner on the day of dosing. Subjects will continue to fast for 4 hours after dosing. They should take the dose with 240 mL water and refrain from drinking for at least 1 hour postdose, after which water can be given *ad libitum*.

Subjects will refrain from strenuous exercise for 72 hours prior to the first dose and for the duration of their participation in the study (Day 18).

Subjects will be informed that blood donation is not allowed for at least 12 weeks after the final examination of this study.

If a subject visits another medical institution during the study period, the investigator should be informed of the circumstances and therapy, and should communicate with the medical institution about the subject's participation in the study.

7.5 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study should be recorded in the case report form ([e]CRF) using the following categories. For screen failure subjects, refer to Section [9.1.15](#).

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

- Liver Function Test Abnormalities

Study medication 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 [9.1.8](#)), if the following circumstances occur at any time during study medication treatment:

- ALT, AST, or total bilirubin $>2 \times$ ULN.
- 2. Significant protocol deviation. The discovery after administration of the first dose of study medication 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.
- 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. The procedure is described in Section [9.1.10](#).

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 terminate a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section [7.5](#). In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded. In

addition, efforts should be made to perform all procedures scheduled for the Final/Study Exit Visit.

Discontinued or withdrawn subjects will not be replaced after treatment assignment.

8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

This section contains information regarding all medication and materials provided directly by the sponsor, and/or sourced by other means, that are required by the study protocol, including important sections describing the management of clinical trial material.

8.1 Study Medication and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

In this protocol, the term study medication refers to TAK-438 10 mg and 20 mg tablets.

8.1.1.1 Investigational drug

The chemical name of TAK-438 is:

1-[5-(2-Fluorophenyl)-1-(pyridin-3-ylsulfonyl)-1*H*-pyrrol-3-yl]-N-methyl methanamine monofumarate. Note that there is no generic name assigned at the time of writing this protocol.

Table 8.a Investigational Drug

Name, strength and dose form	Description	Manufacturer
TAK-438 10 mg tablets	Pale yellow film-coated tablet	Takeda Pharmaceutical Company Limited, Osaka, Japan
TAK-438 20 mg tablets	Pale red film-coated tablet scored on both sides	Takeda Pharmaceutical Company Limited, Osaka, Japan

TAK-438 investigational drug will be foil/foil blistered packaged into 10-dose child-resistant blister cards, containing a total of 10 tablets. Each blister card will be labeled in an open fashion with a single panel label which will include the investigational drug Name, strength and dose form, pertinent study information and the country-specific regulatory caution statement.

8.1.2 Storage

TAK-438 should be stored at 25°C; with excursions permitted 15°C to 30°C. Protect from moisture and humidity. Study medication is to remain in the blister card until time of dosing.

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

Temperature excursion must be reported to the sponsor or designee.

8.1.3 Dose and Regimen

Each subject who qualified to enter into the open label treatment on Day 1 will be assigned to receive a single dose of TAK-438 at either the 10 mg or 20 mg dose level. Subjects will

subsequently receive additional multiple doses of TAK-438 from Day 3 to Day 9 at the same dose level, note that for subjects in Cohort 3 this will be a 20 mg single dose, on Day 1, followed by a 20 mg dose on a BID regimen, for total 40 mg daily dose from Day 3 to 9.

Table 8.b describes the dose and tablet count that will be provided to each group.

Table 8.b Sponsor-Supplied Drug

Cohort	Group Description	Single Dose (Day 1)	Multiple Dose (Days 3-9)	Regimen
1	TAK-438 10 mg	One 10 mg TAK-438 tablet	One 10 mg TAK-438 tablet daily	After fasting for 10 hours (continue fasting for 2 hours after dosing)
2	TAK-438 20 mg	One 20 mg TAK-438 tablet	One 20 mg TAK-438 tablet daily	After fasting for 10 hours (continue fasting for 2 hours after dosing)
3	TAK-438 20 mg twice	One 20 mg TAK-438 tablet	One 20 mg TAK-438 tablet twice daily	After fasting for 10 hours, 1 tablet 0.5 hours after breakfast and 1 tablet approximately 12 hours later and 0.5 hours after dinner

8.1.4 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.

All cases of overdose (with or without associated adverse events) will be documented on an Overdose page of the eCRF, in order to capture this important safety information consistently in the database. Adverse events associated with an overdose will be documented on AE CRF(s) according to Section [10.0](#), Pretreatment Events and Adverse Events.

Serious adverse events (SAEs) of overdose should be reported according to the procedure outlined in Section [10.2.2](#), Collection and Reporting of SAEs.

In the event of drug overdose, the subject should be treated symptomatically.

8.2 Investigational Drug Assignment and Dispensing Procedures

Subjects will be assigned to receive a 4-digit enrollment number. The number will be assigned by the clinic site personnel in sequential order as follows:

Cohort 1: 10mg TAK-438 QD beginning with 1001

Cohort 2: 20mg TAK-438 QD beginning with 2001

Cohort 3: 20mg TAK-438 BID beginning with 3001

This 4-digit number will be used by the clinical site to facilitate the prelabeling of pharmacokinetic samples, and will be the only subject identifier used on all sample collections. It should also be contained on the pharmacokinetic transport vials shipped to the bioanalytical laboratory, and will

be used by the laboratory to report the subject data results. This 4-digit number should only be used for the purposes described in this section. It does not replace the 3-digit subject number which is assigned at the time the informed consent is obtained and which is used for all other procedures to identify the subjects throughout the study.

8.3 Accountability and Destruction of All Study Medication

Drug supplies will be counted and reconciled at the site before being returned to Takeda or designee or being destroyed.

The investigator or designee must ensure that the study medication is used in accordance with the approved protocol and is dispensed only to subjects enrolled in the study. To document appropriate use of study medication (TAK-438 10 mg and 20 mg), the investigator must maintain records of all study medication delivery to the site, site inventory, use by each subject, and return to the sponsor or designee.

Upon receipt of study medication, the investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct and is in good condition. If quantity and conditions are acceptable, investigator or designee should acknowledge the receipt of the shipment by signing bottom half of the packing list and faxing per instructions provided on the form. If there are any discrepancies between the packing list versus the actual product received, Takeda must be contacted to resolve the issue. The packing list should be filed in the investigator's essential document file.

The investigator must maintain 100% accountability for all study medication received and dispensed during his or her entire participation in the study. Proper drug accountability includes, but is not limited to:

- Continuously monitoring expiration dates (drug label).
- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the log is completed for the drug lot used to prepare each dose.
- Verifying that all containers used are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.

If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately.

The investigator must record the current inventory of all study medication, TAK-438 10 mg and 20 mg on a sponsor-approved drug accountability log. The following information will be recorded at a minimum: protocol number and title, name of investigator, site identifier/number, description of study medication, expiry or retest date, date and amount dispensed including the initials of the person dispensing and receiving the study medication. The same information will also be captured in the subject-level documentation.

Prior to site closure or at appropriate intervals, a representative from the sponsor or its designee will perform clinical study material accountability and reconciliation before clinical study materials are returned to the sponsor or its designee for destruction or destroyed at the site, as

applicable. The investigator will retain the original documentation regarding clinical study material accountability, return, and/or destruction, and copies will be sent to the sponsor or designee.

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

In the event of expiry date extension of supplies already at the study site, supplies may be relabeled with the new expiry date at that site. In such cases, Takeda or its designee will prepare additional labels and all necessary documentation for completion of the procedure at the sites.

9.0 STUDY PLAN

9.1 Study Procedures

The following sections describe the study procedures and data to be collected. For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. The Schedule of Study Procedures is located in [Appendix A](#).

9.1.1 Informed Consent Procedure

The requirements of the informed consent are described in Section [15.2](#).

Informed consent must be obtained prior to the subject entering into the study, and before any protocol-directed procedures are performed.

A unique subject identification number (subject number) will be assigned to each subject at the time that informed consent is obtained; this subject number will be used throughout the study.

9.1.1.1 Pharmacogenomic Informed Consent Procedure

The sampling of whole blood for CYP2C19 genotyping analysis is mandatory; every subject must sign the informed consent in order to participate in this study. The informed consent for the CYP2C19 genotyping analysis is a component of the overall study informed consent.

9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include age, sex, race, alcohol and caffeine consumption and smoking status of the subject at Screening.

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the condition/disease under study that stopped at or prior to informed consent. Ongoing conditions are considered concurrent medical conditions (see Section [9.1.7](#)).

Medication history information to be obtained includes any medication relevant to eligibility criteria stopped at or within 28 days prior to signing of informed consent.

9.1.3 Physical Examination Procedure

A physical examination will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes and (11) other.

Any abnormal finding on a pretreatment physical examination assessment must be assessed as Not Clinically Significant (NCS) or Clinically Significant (CS) by the investigator and recorded in the source document and eCRF. All CS findings may be recorded either as a pretreatment event (only if they occurred after informed consent and before first dose of study medication) or as a

concurrent medical condition (if they were present before informed consent) in the source document and on the appropriate eCRF described in Section 10.0 or Section 9.1.7.

On subsequent examinations, any abnormal change from the pretreatment physical examination assessment occurring immediately prior to the start of the investigational drug (Day 1) must be assessed as NCS or CS by the investigator and recorded in the source document and eCRF. Any CS change, as determined by the investigator, will be recorded as an AE in source documentation and on the pretreatment event/AE eCRF described in Section 10.0.

9.1.4 Weight, Height, and BMI

A subject should have weight and height measured while wearing indoor clothing and with shoes off. The BMI is calculated, using metric units with the formula provided below:

$$\text{Metric: } \text{BMI} = \text{weight (kg)}/\text{height (m)}^2$$

Height will be collected in centimeters to 1 decimal place and weight will be collected in kilograms to 1 decimal place. Results for BMI will be expressed with 1 decimal place.

Example:

-Height=176.2 cm (or 1.762 m), weight=79.2 kg; BMI=79.2/1.76.2²=25.5 kg/m².

9.1.5 Vital Sign Procedure

Vital signs will include body temperature (oral, tympanic, or axillary measurement), sitting blood pressure (after 5 minutes resting), respiration rate and pulse (bpm). On dosing days, vital sign measurements should be taken at predose in the morning, and it is recommended that for the remaining days, measurements should be taken at approximately the same time as on the dosing days.

If a blood draw or any study procedure coincides with a meal, the study procedure will take precedence, followed by the blood draw and then the meal.

9.1.6 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study medication. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by Takeda. At each study visit, subjects will be asked whether they have taken any medication other than the study medication (used from signing of informed consent through the end of the study), and all medication, including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the eCRF. Documentation will include dose and frequency (although only 'total daily dose' may be captured on the eCRF), as well as generic medication name, unit, route of administration, start and end dates, and reason for use.

9.1.7 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent. This includes clinically significant laboratory, electrocardiogram

(ECG), or physical examination abnormalities noted at Screening or Day -1 examinations. The condition (ie, diagnosis) should be described.

9.1.8 Procedures for Clinical Laboratory Samples

All samples for clinical laboratory testing will be collected in accordance with acceptable laboratory procedures. The maximum volume of blood at any single visit is approximately 14.7 mL, and the approximate total volume of blood is 53.5 mL. Except for urinalysis on Day 3 and Day 9, laboratory samples will be taken following a minimum 10-hour overnight fast on the days stipulated in the Schedule of Study Procedures ([Appendix A](#)). On dosing days, samples for clinical laboratory testing should be drawn at predose in the morning (except for urinalysis on Day 3 and Day 9 when urine PK collection shall be taken as priority). At the Screening Visit, Day-1 and Day 11, it is recommended that samples are drawn at approximately the same time as the dosing days.

[Table 9.a](#) lists the tests that will be obtained for each laboratory specimen.

Table 9.a Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis
Red blood cells	Alanine aminotransferase (a, b)	pH
White blood cells (with differential: neutrophils, eosinophils, basophils, monocytes, lymphocytes)	Albumin	Specific gravity
Hemoglobin	Alkaline phosphatase	Protein
Hematocrit	Amylase	Glucose
Platelets	Aspartate aminotransferase (a, b)	Nitrites
PT/INR	GGT	Bilirubin
aPTT	Total bilirubin (a, b, c)	Ketones
Reticulocyte percentage	Direct bilirubin (b)	Urobilinogen
	Uric Acid	
	Total protein	<u>Microscopic Analysis:</u>
	Triglycerides (a)	RBC/high power field
	Serum creatinine	WBC/high power field
	Blood urea	Hyaline casts/low power field
	Creatine kinase	Granular casts/ low power field
	Potassium	Epithelial cells
	Sodium	
	Glucose (a)	
	Chloride	
	Calcium	
	Magnesium	
	Cholesterol (HDL and LDL)	
	Lactose dehydrogenase	

Diagnostic Screening:

Serum	Urine
HIV test	Drug screen, including amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, and cotinine
Hepatitis panel, including HBsAg and anti-HCV Ab	
<u>Female subjects of child-bearing potential only when menopause is suspected:</u>	<u>Female subjects of child-bearing potential only:</u>
- Follicle-stimulating hormone (FSH)	- hCG (for pregnancy)

Breath Test

Alcohol (d)

(a) To be measured under fasting conditions.

(b) Included in liver function tests.

(c) Direct bilirubin will be measured if total bilirubin is $>1.5 \times \text{ULN}$.

(d) A breathalyzer test will be performed and must be negative for alcohol at the Initial and preconfinement Screen Visits and at Check-in (Day -1).

The phase 1 unit's local laboratory will perform laboratory tests for hematology, serum chemistries, and urinalysis. The results of laboratory tests will be returned to the investigator, who is responsible for reviewing and filing these results.

If subjects experience an increase in any one of ALT, AST, or total bilirubin $>2 \times \text{ULN}$ the study medication shall be stopped according to the discontinuation criteria. Follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, GGT, and INR) should be performed within a maximum of 7 days and preferably within 48 to 72 hours after the abnormality was found.

(Please refer to Section 7.5 for discontinuation criteria, and Section 10.2.3 for the appropriate guidance on Reporting of Abnormal Liver Function Tests.)

All laboratory safety data will be transferred electronically to Takeda or designee in the format requested by Takeda. If the laboratory is unable to electronically transfer data, the study site coordinator or designee is responsible for transcribing laboratory results to the eCRF. The investigator will maintain a copy of the laboratory accreditation and the reference ranges for the laboratory used.

Laboratory reports must be signed and dated by the principal investigator or subinvestigator indicating that the report has been reviewed and any abnormalities have been assessed for clinical significance.

All clinically significant laboratory abnormalities must be recorded as a PTE/AE in the subject's source documents and on the appropriate eCRF. A clinically significant laboratory abnormality that has been verified by retesting will be followed until the abnormality returns to an acceptable level or a satisfactory explanation has been obtained.

9.1.9 Contraception and Pregnancy Avoidance Procedure

From signing of informed consent, throughout the duration of the study, and for 4 weeks after last dose of study medication, female subjects of childbearing potential* who are sexually active with a nonsterilized male partner** must use adequate contraception. In addition they must be advised not to donate ova during this period.

*Females NOT of childbearing potential are defined as those who have been surgically sterilized (hysterectomy, bilateral oophorectomy or tubal ligation) or who are postmenopausal (eg, defined as at least 1 year since last regular menses with an FSH>40 IU/L or at least 5 years since last regular menses, confirmed before any study medication is implemented).

**Sterilized males should be at least 1 year postvasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate.

An acceptable method of contraception is defined as one that has no higher than a 1% failure rate. In this study, where medications and devices containing hormones are excluded, the only acceptable methods of contraception are:

Barrier methods (each time the subject has intercourse): Intrauterine devices (IUDs):

- Cap (plus spermicidal cream or jelly) PLUS male condom.
- Diaphragm (plus spermicidal cream or jelly) PLUS male condom.
- Copper T.

Subjects will be provided with information on acceptable 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.

During the course of the study, regular urine human chorionic gonadotropin (hCG) pregnancy tests will be performed only for women of childbearing potential and subjects will receive continued guidance with respect to the avoidance of pregnancy as part of the study procedures ([Appendix A](#)). In addition to a negative urine hCG pregnancy test at Screening, subjects also must have a negative urine hCG pregnancy test at Day -1 prior to receiving any dose of study medication.

9.1.10 Pregnancy

If any subject is found to be pregnant during the study she should be withdrawn and any sponsor-supplied drug (TAK-438 10 mg or 20 mg tablets) should be immediately discontinued.

If the pregnancy occurs during administration of active study medication, eg, after Day 1 or within 30 days of the last dose of active study medication, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in Section [1.0](#).

If the female 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 treatment the subject received (blinded or unblinded, as applicable).

All reported pregnancies will be followed up to final outcome, using the pregnancy form. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

9.1.11 ECG Procedure

12-lead ECGs printed in standard format, will be collected at Screening, Check-in (Day -1), and on Confinement Days (Days 1-11/Early Termination). On dosing days, ECGs should be collected after dosing.

The investigator will be responsible for providing the interpretation of all safety ECGs (normal/abnormal). These results will be reviewed by the investigator for subject safety and will be provided in an appropriate format with the clinical study report. The time that the ECG was performed will be recorded. The following parameters will be recorded on the (e)CRF from the subject's ECG trace: heart rate, QT interval, PR interval, QRS interval and RR interval.

During Screening periods (Screening visit and Day -1), ECGs deemed abnormal but not clinically significant by the study doctor, should be sent to the CRO Medical Monitor for review in 24 hours (with subject de-identified). If consensus is not reached between site investigators and CRO Medical Monitor, the CRO medical monitor will consult Takeda Clinical Science on the same working day.

If ECG tracings are printed out on thermal paper which fades over time, any such tracings should be completely photocopied and both the original tracing and the counter-signed copy should be filed in the subject's medical record.

9.1.12 Sample Collection for Genotype Analysis

The sample of whole blood for CYP2C19 genotyping analysis is mandatory. Every subject must sign the informed consent in order to participate in this study.

One 2 mL whole blood sample for DNA isolation will be collected on Day -1 from each subject in the study, into plastic K₂EDTA spray-coated tubes, and stored under frozen condition. A second aliquot of blood may be taken if isolation of DNA from the first sample was not successful or possible.

Detailed instructions for the handling of samples are provided in [Appendix F](#).

9.1.13 Pharmacokinetic Sample Collection

9.1.13.1 Collection of Blood for Pharmacokinetic Sampling

Blood samples (one 6-mL sample per scheduled time) for pharmacokinetic analysis of TAK-438 and its metabolites will be collected into chilled vacutainers containing anticoagulant sodium heparin according to the schedule in [Appendix A](#). Instructions for sample processing and shipment are provided in [Appendix E](#).

Serial blood samples for determination of TAK-438F and its metabolites will be collected according to [Table 9.b](#).

Table 9.b Collection of Blood Samples for Pharmacokinetic Analysis

Cohorts	Matrix	Dosing Day	Scheduled Time (hours)
TAK-438 10 mg QD and TAK-438 20 mg QD	Blood	1 and 9	Predose (0 hours), 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, and 48 hours postdose
	Blood	4-8	Predose
TAK-438 20 mg BID	Blood	1	Predose (0 hours), 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, and 48 hours postdose
	Blood	4-8	Predose (relative to morning dose)
	Blood	9	Predose (0 hours), 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10 and 12 hours postdose (relative to morning dose)

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 pharmacokinetic data collected from prior cohort(s), but the total number of samples collected per subject should not exceed the planned number.

9.1.13.2 Collection of Urine for Pharmacokinetic Sampling

Serial urine samples for determination of TAK-438F and its metabolites will be collected according to [Table 9.c](#).

Table 9.c Collection of Urine Samples for Pharmacokinetic Analysis

Cohorts	Matrix	Dosing Day	Time Postdose (hours)
TAK-438 10 mg QD and TAK-438 20 mg QD	Urine	1 and 9	Predose (spot urine), 0 to 6, 6 to 12, 12 to 24 hours, 24 to 36 hours and 36 to 48 hours postdose
TAK-438 20 mg BID	Urine	1	Predose (spot urine), 0 to 6, 6 to 12, 12 to 24 hours, 24 to 36 hours and 36 to 48 hours postdose
	Urine	9	Predose (spot urine), 0 to 6 and 6 to 12 hours postdose (relative to morning dose)

Instructions for sample processing and shipment are provided in [Appendix E](#).

9.1.13.3 Bioanalytical Methods

Plasma and urine concentrations of TAK-438F and its metabolites will be measured by high-performance liquid chromatography with tandem mass spectrometry.

9.1.14 Pharmacokinetic Parameters

The pharmacokinetic parameters of TAK-438F and its metabolites will be determined from the concentration-time profiles for all evaluable subjects. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. The following pharmacokinetic parameters will be calculated for plasma concentration values of TAK-438F and its metabolites:

Symbol/Term	Definition
Plasma	
AUC _∞	Area under the plasma concentration-time curve from time 0 to infinity, calculated using the observed value of the last quantifiable concentration.
AUC _{last}	Area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration.
AUC _{last,ss}	Area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration, at steady state.
AUC _t	Area under the plasma concentration-time curve from time 0 to time t.
AUC _τ	Area under the plasma concentration-time curve during a dosing interval.
AUC _{τ,ss}	Area under the plasma concentration-time curve during a dosing interval, at steady state.
C _{av,ss}	Average plasma concentration during a dosing interval, at steady state.
C _{max}	Maximum observed plasma concentration.
C _{max,ss}	Maximum observed plasma concentration during a dosing interval, at steady state.
C _{min,ss}	Minimum observed plasma concentration during a dosing interval, at steady state.

Symbol/Term	Definition
Plasma	
CL/F	Apparent clearance after extravascular administration, calculated using the observed value of the last quantifiable concentration.
CL/F _{ss}	Apparent clearance after extravascular administration, at steady state, calculated using AUC _τ .
λ _z	Terminal disposition phase rate constant.
MRT _{∞,ev}	Mean residence time after extravascular administration, calculated using the observed value of the last quantifiable concentration.
PTF%	Peak trough fluctuation during a dosing interval, at steady state, expressed as a percentage of C _{av,ss} .
R _{ac(AUC)}	Accumulation ratio based on AUC _τ .
R _{ac(Cmax)}	Accumulation ratio based on C _{max} .
t _{1/2z}	Terminal disposition phase half-life.
t _{max}	Time of first occurrence of C _{max} .
t _{max,ss}	Time of first occurrence of C _{max} , at steady state.
V _z /F	Apparent volume of distribution during the terminal disposition phase after extravascular administration, calculated using the observed value of the last quantifiable concentration.
V _z /F _{ss}	Apparent volume of distribution during the terminal disposition phase after extravascular administration, calculated using AUC _τ .

The following urine pharmacokinetic parameters of TAK-438F and its metabolites will be derived from urine concentrations of TAK-438F and its metabolites:

Urine	
A _e _t	Amount of drug excreted in urine from time 0 to time t.
A _e _τ	Amount of drug excreted in urine during a dosing interval.
f _{e,t}	Fraction of administered dose of drug excreted in urine from time 0 to time t. Molecular weight adjustment needed for metabolites.
f _{e,τ}	Fraction of administered dose of drug excreted in urine during a dosing interval. Molecular weight adjustment needed for metabolites.
CL _R	Renal clearance.

9.1.15 Documentation of Screen Failure

Investigators must account for all subjects who sign informed consent. If the subject is found to be not eligible at this visit, the investigator should complete the eCRF.

The primary reason for screen failure is recorded in the eCRF using the following categories:

- Pretreatment event/AE.
- Did not meet inclusion criteria or did meet exclusion criteria <specify reason>.
- Significant protocol deviation.

- Lost to follow-up.
- Voluntary withdrawal <specify reason>.
- Study termination.
- Other <specify reason>.

Subject numbers assigned to subjects who fail screening should not be reused.

9.1.16 Documentation of Study Entrance

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for entrance into the treatment phase.

If the subject is found to be not eligible for entrance, the investigator should record the primary reason for failure on the applicable eCRF.

9.2 Monitoring Subject Treatment Compliance

Study medication will be administered while subjects are under observation in the clinical research unit. Following administration of the study medication, appropriate mouth and/or hand checks will be performed to ensure that the dose is swallowed and noted in the source document. The date and time of each dose will be recorded in the source documents and on the eCRFs. An inventory of the study medication supplies dispensed will be performed by the site pharmacist or authorized study designee and recorded onto the Drug Accountability Log in the subject's source document records or equivalent. The exact dose time of consecutive subjects may be staggered to facilitate logistics at the site.

9.3 Schedule of Observations and Procedures

The schedule for all study-related procedures for all evaluations is shown in [Appendix A](#). Assessments should be completed at the designated visit/time point(s).

9.3.1 Screening (Day -28 to Day -2)

Subjects will be screened for the study within 28 days prior to the first dose of study medication. Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section [7.0](#). See Section [9.1.15](#) for procedures for documenting screening failures.

Procedures to be completed at the Screening Visit include:

- Informed consent.
- Demographics, medical history, and medication history.
- Physical examination.
- Vital signs.
- Weight, height and BMI.

- Concomitant medications.
- Concurrent medical conditions.
- Pretreatment event assessment.
- Fasting clinical laboratory tests and HIV, Hepatitis panel and urine drug, cotinine screening tests. Also, a urine pregnancy test will be done for female subjects of child-bearing potential or FSH will be measured for female subjects where menopause is suspected.
- Fasting liver function tests.
- ECG procedure.
- Breath test for alcohol.
- Guidance on avoidance of strenuous exercise, pregnancy, ova or blood donation.

9.3.2 Check-in (Day -1)

Screening will be completed at the Check-in Day -1 visit. The following procedures will be performed and documented during this Check-in Visit:

- Confinement begins (and will continue until Check-Out Day 11).
- Physical examination.
- Vital signs.
- Weight and BMI.
- Concomitant medications.
- Concurrent medical conditions.
- Pretreatment event assessment.
- Fasting clinical laboratory tests (hematology, chemistry, and urinalysis) additionally urine drug and cotinine screening tests.
- Fasting liver function tests.
- Urine pregnancy test for females of child-bearing potential.
- Collection of blood sample for CYP2C19 genotyping.
- ECG procedure.
- Breath test for alcohol.
- Reconfirm study eligibility (ie, inclusion and exclusion criteria).
- Guidance on avoidance of strenuous exercise, pregnancy, ova or blood donation.

9.3.3 Study Entrance (Day 1)

Study entrance will take place on Day 1 while the subject remains confined to the phase 1 unit. The following procedures will be performed and documented during Study Entrance:

- Vital signs (predose).
- Concomitant medications.
- ECG procedure (postdose).
- Collection of predose and postdose blood samples for PK analysis.
- Collection of predose and postdose urine samples for PK analysis.
- Pretreatment event and adverse event assessment.

The subject should be assigned to treatment as described in Section 8.2. Subjects will be administered the first dose (ie, single dose) of study medication in the unit under the supervision of the investigator or designee, as described in Section 8.2.

9.3.4 Day 2 and Day 10

While remaining confined at the phase 1 unit, the following procedures will be performed on Day 2 and also on Day 10:

- Vital signs.
- Concomitant medications.
- ECG procedure.
- Collection of postdose blood samples for PK analysis (not required on Day 10 for subjects assigned to 20 mg BID regimen in multiple dosing phase).
- Collection of postdose urine samples for PK analysis (not required on Day 10 for subjects assigned to 20 mg BID regimen in multiple dosing phase).
- Adverse event assessment.

9.3.5 Multiple Dosing Phase (Days 3-9)

While remaining confined at the phase 1 unit, the following procedures will be performed between Day 3-9:

- Vital signs (predose).
- Concomitant medications.
- Fasting clinical laboratory tests (hematology, and chemistry) at pre-dose on Days 3 and 9 only.
- Urinalysis on Day 3 and 9 only
- Fasting liver function tests at pre-dose on Days 3 and 9 only.

- ECG procedure (postdose).
- Collection of predose blood samples for PK analysis Days 3-9 inclusive, and also of postdose blood samples on Day 9 only.
Note that the predose time point for Day 3 is actually the 48-hour postdose time point following the Day 1 dose. Note also that for subjects assigned to the 20 mg BID multiple dose regimen PK draws should be taken relative to the morning dose.
- Collection of urine samples for PK analysis at predose and postdose on Day 9.
Note also that for subjects assigned to the 20 mg BID multiple dose regimen PK draws should be taken relative to the morning dose.
- Adverse event assessment.
- Administration of study medication.

9.3.6 Check-Out (Day 11)

The Check-Out will be performed on Day 11 and after completion of all required study procedures the subject will be released from the phase 1 unit (ie, confinement period ends). The following procedures will be performed and documented:

- Physical examination.
- Vital signs.
- Weight and BMI.
- Concomitant medications.
- Fasting clinical laboratory tests (hematology, chemistry, urinalysis); additionally a urine pregnancy test only for females of child-bearing potential.
- Fasting liver function tests.
- ECG procedure.
- Collection of postdose blood and urine samples for PK analysis (not required for subjects assigned to 20 mg BID regimen in the multiple dosing phase).
- Adverse event assessment.
- Guidance on avoidance of strenuous exercise, pregnancy, ova or blood donation.

For all subjects receiving study medication, the investigator must complete the End of Study eCRF page.

9.3.7 Early Termination

The reason for discontinuation must be documented in the source document and eCRF. The following procedures will be performed and documented:

- Physical examination.
- Vital signs (predose).
- Concomitant medications.
- Fasting clinical laboratory tests at pre-dose (hematology, chemistry, urinalysis); additionally urine pregnancy test for female subjects of child-bearing potential only.
- Fasting liver function tests at pre-dose.
- ECG procedure postdose.
- Collection of predose or postdose blood samples for PK analysis as required by study schedule.
- Collection of predose or postdose urine samples for PK analysis as required by study schedule.
- Adverse event assessment.
- Guidance on avoidance of strenuous exercise, pregnancy, ova or blood donation.

For all subjects receiving study medication, the investigator must complete the End of Study eCRF page.

9.3.8 Follow-up (Telephone Contact)

Follow-up will begin the first day after the Check-out or Early Termination and the telephone visit will be at Day 18 (\pm 3 days). The follow-up will document the following:

- Concomitant medications.
- Adverse event assessment.
- Guidance on avoidance of strenuous exercise, pregnancy, ova or blood donation.

9.4 Blood Volume

Total blood sampling volume for an individual subject is shown in [Table 9.d](#).

Table 9.d Approximate Blood Volume

Sample Type	Sample Volume	Volume per Period (mL)						Total Volume
		Screening and Day -1	Single Dose	Multiple Dose	Study Exit	Follow-Up		
Clinical laboratory (safety) tests	9.7-14.7 mL	24.4	0	19.4	9.7	(only if clinically significant at last draw)	53.5	
CYP2C19 genotyping	2 mL	2	0	0	0	0	2	
PK blood collection	6 mL	0	102	132	0	0	234	
Total Approximate Blood Sampling Volume							289.5	

Direct venipuncture is the preferred method of blood collection; however, a catheter with a single saline flush may be used.

A catheter with a heparin-containing saline flush may be used; however, the 289.5-mL total blood volume does not include discarded blood from predraws (assuming approximately 1 mL of blood is discarded each time a sample is collected from a catheter). Should a catheter be used, the total blood volume taken during the study must not exceed 328.5 mL.

9.5 Biological Sample Retention and Destruction

In this study, specimens for genome/gene analysis will be collected as described in Section 9.1.12. The genetic material will be sent to the local laboratory to determine the CYP2C19 metabolic status of each subject. Any remaining sample after testing will be destroyed.

10.0 PRETREATMENT EVENTS AND ADVERSE EVENTS

10.1 Definitions

10.1.1 Pretreatment Events

A pretreatment event (PTE) is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but prior to administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

10.1.2 AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this 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.

10.1.3 Additional Points to Consider for PTEs and AEs

An untoward finding generally may:

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

Diagnoses vs 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 a PTE(s) or as an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG parameters are only considered to be PTEs or AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory re-test and/or continued monitoring of an abnormal value are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.

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

Pre-existing conditions:

- Pre-existing conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should NOT be recorded as PTEs or AEs. Baseline evaluations (eg, laboratory tests, ECG, X-rays etc.) should NOT be recorded as PTEs unless related to study procedures. However, if the subject experiences a worsening or complication of such a concurrent condition, the worsening or complication should be recorded appropriately as a PTE (worsening or complication occurs before start of study medication) or an AE (worsening or complication occurs after start of study medication). 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 a PTE/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 in the condition from Baseline (eg “worsening of...”).
- If a subject has a degenerative concurrent condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be captured as a PTE/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 PTEs or AEs:

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

Changes in severity of AEs /Serious PTEs:

- If the subject experiences changes in severity of an AE/serious PTE, 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 PTEs or 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 a PTE or an AE. Complications resulting from any planned surgery should be reported as adverse events.

Elective surgeries or procedures:

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

Overdose:

- Cases of overdose with any medication without manifested side effects are NOT considered PTEs or AEs, but instead will be documented on an Overdose page of the eCRF. Any manifested side effects will be considered PTEs or AEs and will be recorded on the AE page of the eCRF.

10.1.4 SAEs

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

1. Results in DEATH.
2. Is LIFE THREATENING.
 - The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Is a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
 - May require intervention to prevent items 1 through 5 above.
 - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
 - Includes any event or synonym described in the Takeda Medically Significant AE List ([Table 10.a](#)).

Table 10.a Takeda Medically Significant AE List

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

PTEs that fulfill 1 or more of the serious criteria above are also to be considered as serious and should be reported and followed up in the same manner as SAEs (see Sections 10.2.2 and 10.3).

10.1.5 Special Interest AEs

A Special Interest AE (serious or nonserious) is one of scientific and medical concern specific to the compound or program, for which ongoing monitoring and rapid communication by the investigator to Takeda may be appropriate. Such events may require further investigation in order to characterize and understand them and would be described in protocols and instructions provided for investigators as to how and when they should be reported to Takeda. There are no Special Interest AEs for this study.

10.1.6 Severity of PTEs and AEs

The different categories of intensity (severity) are characterized as follows:

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

10.1.7 Causality of AEs

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

Related An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug 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 drugs and concurrent treatments.

10.1.8 Relationship to Study Procedures

Relationship (causality) to study procedures should be determined for all PTEs and AEs.

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

10.1.9 Start Date

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

10.1.10 Stop Date

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

10.1.11 Frequency

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

10.1.12 Action Concerning Study Medication

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

10.1.13 Outcome

- Recovered/Resolved – Subject returned to first assessment status with respect to the AE/ PTE.
- Recovering/Resolving – the intensity is lowered by one or more stages: the diagnosis or signs/symptoms has almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to baseline; the subject died from a cause other than the particular AE/ PTE 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 got worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE/ PTE state remaining “Not recovered/not resolved”.

- Resolved with sequelae – the subject recovered from an acute AE/ PTE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis).
- Fatal – the AEs/ PTEs which are considered as the cause of death.
- Unknown – the course of the AE/ PTE cannot be followed up due to hospital change or residence change at the end of the subject’s participation in the study.

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 PTE and AE Collection Period

Collection of PTEs will commence from the time the subject signs the informed consent to participate in the study and continue until the subject is first administered study medication (Day 1) or until screen failure. For subjects who discontinue prior to study medication administration, PTEs are collected until the subject discontinues study participation.

Collection of AEs will commence from the time that the subject is first administered study medication (Day 1). Routine collection of AEs will continue until the follow-up visit on Day 18.

10.2.1.2 PTE and AE Reporting

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 a serious PTE must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or there is a satisfactory explanation for the change. Non-serious PTEs, related or unrelated to the study procedure, need not to be followed-up for the purposes of the protocol.

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

- Event term.
- Start and stop date.
- Severity.

- Investigator's opinion of the causal relationship between the event and administration of study medication(s) (related or not related) (not completed for PTEs).
- Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
- Action concerning study medication (not applicable for PTEs).
- Outcome of event.
- Seriousness.

10.2.2 Collection and Reporting of SAEs

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

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

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

The SAE form should be transmitted within 24 hours to the attention of the contact listed in Section 1.0.

Any SAE spontaneously reported to the investigator following the AE collection period should be reported to the sponsor if considered related to study participation. Also, investigators should report any SAE in appropriate format (ie, locally required form) to related authorities, IRB/IECs in accordance with local GCP and/or local regulations.

Reporting of Serious PTEs will follow the procedure described for SAEs.

10.2.3 Reporting of Abnormal Liver Function Tests

If during the treatment or follow-up period a subject is noted to have ALT or AST $>3 \times$ ULN **and** total bilirubin $>2 \times$ ULN for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 10.2.2. 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 9.1.8 must also be performed. In addition, a Liver Function Test Abnormality Form must be completed and transmitted with the Takeda SAE form (as per Section 10.2.2).

10.3 Follow-up of SAEs

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

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

10.3.1 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 STUDY-SPECIFIC COMMITTEES

No steering committee, data safety monitoring committee, or clinical endpoint committee will be used in this study.

12.0 DATA HANDLING AND RECORDKEEPING

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

12.1 CRFs (Electronic)

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

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

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

Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change.

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

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

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper should be copied and certified, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Furthermore, International Conference on Harmonisation (ICH) E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is

discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and sponsor.

Refer to the Phase 1 Site Specifications document for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

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

13.1.1 Analysis Sets

In this study, two kinds of analysis sets are defined: PK analysis set and safety analysis set. The PK analysis set used for primary analysis will consist of subjects who received the study drug, completed the minimum protocol specified procedures with no significant protocol deviations, and were evaluable for the pharmacokinetics. The definition of each analysis set will be described in the SAP.

The sponsor will verify the validity of the definitions of the analysis sets as well as the rules for handling data, consulting medical experts as needed.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarized overall and by cohort using the PK analysis set and safety analysis set.

13.1.3 Pharmacokinetic Analysis

The plasma concentration of TAK-438F and its metabolites M-I, M-II, M-III, and M-IV-Sul will be summarized by cohort over each scheduled sampling point using descriptive statistics (arithmetic mean, SD, median, minimum and maximum). Mean concentration-time profiles with SDs of TAK-438F and its metabolites M-I, M-II, M-III and M-IV-Sul will be provided by cohort. Individual plasma concentration data versus time will be presented in a data listing.

Descriptive statistics (arithmetic mean, SD, median, minimum and maximum) will be used to summarize the plasma and urine PK parameters for TAK-438F and its metabolites M-I, M-II, M-III, and M-IV-Sul. In addition, geometric mean and coefficient of variation will be computed for C_{max} and AUCs from plasma pharmacokinetics.

A more detailed analysis will be presented in the SAP.

13.1.4 Safety Analysis

13.1.4.1 Safety endpoints and analytical methods

All summaries of safety data will be presented based on the safety analysis set. No statistical testing or inferential statistics will be generated.

Adverse Events

A treatment-emergent adverse event (TEAE) is defined as an adverse event (AE) whose date of onset occurs on or after the start of study drug.

All TEAEs will be coded using MedDRA. Data will be summarized using preferred term and primary system organ class. All TEAEs, drug-related TEAEs and serious TEAEs will be summarized by cohort.

Clinical Laboratory Evaluations, Vital Signs and 12-lead ECGs

Observed values and changes (from baseline) for continuous variables will be summarized by cohort over time using descriptive statistics.

For categorical variables, shift tables will be presented for each cohort.

Method of data conversion and handling of missing data

No imputation of missing data or of excluded data in accordance with the Statistical Analysis Plan will be applied. Values below the lower limit of quantification will be handled as 0.

13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

13.3 Determination of Sample Size

The sample size of 12 subjects per cohort is sufficient to evaluate the PK profile after single- and multiple-dose administration of TAK-438 10 mg and 20 mg. The sample size chosen for this study is based on precedent set by other pharmacokinetic studies of similar nature and guidelines issued by the CFDA; it was not based on statistical considerations of power and sample size of TAK-438. The sample size is considered though to be sufficient for investigating the objectives of the study.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

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

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

14.2 Protocol Deviations

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

Every attempt will be made to collect each pharmacokinetic blood sample at the designated time point, and the actual time of each blood sample will be recorded on the source document and eCRF. However, blood samples not collected within the interval specified for the scheduled sample time should be reported to Takeda using the Protocol Deviation Form.

Protocol Deviation Forms are to be completed for pharmacokinetic samples collected outside of the following intervals:

Table 14.a Windows for Pharmacokinetic Blood Sample Collection

Minutes	Nominal Sampling Time
no more than 30 minutes predose	0 hour
±5	immediately postdose to ≤6 hours
±10	>6 hours postdose

Table 14.b Windows for Pharmacokinetic Urine Sample Collection

Minutes	Nominal Sampling Time
-60	0 hour
-30*	0 to 6 hours postdose
-60*	6 to 12 hours postdose
-60*	12 to 24 hours postdose
-60*	24 to 36 hours postdose
-60*	36 to 48 hours postdose

*Only refers to the last defined timepoint in each period.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the 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 and institution guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

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

15.1 IRB and/or IEC Approval

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

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

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

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

15.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The 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.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will 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 15.2).

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

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 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 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 Master Services Agreement or equivalent agreement. In the event of any discrepancy between the protocol and the Master Services Agreement or equivalent agreement the Master Services Agreement or equivalent agreement will prevail.

15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable law, regulation and guidance, Takeda will, at a minimum, register all clinical trials conducted in patients that it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites before trial initiation.

15.4.3 Clinical Trial Results Disclosure

Takeda will minimally post the results of clinical trials conducted in patients, regardless of outcome, on ClinicalTrials.gov or other publicly accessible websites, as required by applicable laws and/or regulations.

15.5 Insurance and Compensation for Injury

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

16.0 REFERENCES

1. Fass R, Shapiro M, Swell J. Systematic review: proton-pump inhibitor failure in gastro-oesophageal reflux disease—where next? *Aliment Pharmacol Ther.* 2005;22:79-94.
2. Peter J, et al. A randomized, comparative study of three doses of AZD0865 and esomeprazole for healing of reflux esophagitis. *Clin Gastroenterol Hepatol.* 2007;5:12.

Appendix A Schedule of Study Procedures

Study Day:	Screening		Treatment					Discontinuation	Follow-Up Phone Call
			Single Dose		Multiple Dose	Study Exit			
	Days -28 to -2	Day -1 (Check-in)	Day 1 (a)	Day 2	Days 3-9	Day 10	Day 11 (Check-Out)	Early Termination Visit (b)	Final Contact Day 18 ±3 days
Confinement		X	X	X	X	X	X		
Informed consent	X								
Inclusion/exclusion criteria	X	X							
Demographics and medical history	X								
Medication history	X								
Physical examination	X	X					X	X	
Vital signs	X	X	X	X	X	X	X	X	
Weight, height and BMI	X	X (n)					X (n)		
Concomitant medications	X	X	---	---	---	---	X	X	X
Concurrent medical conditions	X	X							
Clinical laboratory tests (c)	X	X			X (d)		X	X	
Liver function tests (e)	X	X			X		X	X	
HIV test	X								
Hepatitis panel	X								
Urine pregnancy test (f)	X	X					X	X	
FSH (g)	X								
Urine drug, cotinine screen (h)	X	X							
Breath (alcohol) test	X	X							
CYP2C19 genotyping		X							
ECG (i)	X	X	X	X	X	X	X	X	
PK blood collection			X	X	X (j)	X (o)	X (o)	X	
PK urine collection			X	X	X (k)	X (o)	X (o)	X	
Assignment to 10 mg or 20 mg cohort (l)			X						
Administer study medication (m)			X (p)		X				
Guidance on avoidance of strenuous exercise, pregnancy, ova or blood donation	X	X					X	X	X
PTE assessment	X	---	X						
AE assessment			X						X

Footnotes are on last table page.

- (a) The day of first study medication administration for Treatment period is Day 1.
- (b) Conduct procedures for subjects discontinued early per protocol Section 7.6. Any PK sampling due should be collected at the Early Termination Visit, if possible.
- (c) Hematology, serum chemistries, and urinalysis tests after fasting for 10 hours (except for urinalysis on Day 3 and Day 9); for dosing days should be taken predose in the morning (except for urinalysis on Day 3 and Day 9 when urine PK sampling shall take priority), for non-dosing days, it is recommended that sample be taken at approximately the same time as on the dosing days.
- (d) Safety sample for clinical hematology, chemistry and urinalysis should be taken on Day 3 and Day 9 only. Hematology and chemistry shall be after fasting for 10 hours predose.
- (e) Liver function tests are comprised of AST, ALT, total and direct bilirubin and measurements are to be taken at Screening, Day -1, Day 3, Day 9, Day 11, and Early Termination predose.
- (f) Women of childbearing potential.
- (g) Only when menopause is suspected.
- (h) Drug screen including: amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, cotinine methadone, and opiates.
- (i) A single 12-lead ECG will be performed once daily at the Screening Visit (Day -28 to -2), Day -1, and on all confinement days (Days 1-11/ Early Termination). On dosing days, ECGs should be performed after dosing.
- (j) Plasma PK sampling is only predose on Days 4 to 8. PK sampling on Day 3 is actually the 48 hours postdose sampling of Day 1
- (k) Urine PK samples collection is required during Day 3 and Day 9 (not on Day 4 to Day 8 inclusive). Urine PK sampling on Day 3 is actually the 48 hours post dose sampling of Day 1.
- (l) Assignment to a dosing group (10 mg or 20 mg once daily or 20 mg twice daily).
- (m) Study medication should be administered to subjects at a single dose or QD regimen after fasting for 10 hours, subjects should continue to fast for 2 hours after the dose. (throughout the study); for subjects assigned to the BID regimen in the multiple dosing phase (Days 3-9) subjects will be fed 0.5 hours prior to the dosing however note that those subjects are required to fast for 10 hours before clinical laboratory blood test sample collections which can be drawn before being fed.
- (n) Only measure height at Screening Visit
- (o) Not required for subjects assigned to 20 mg BID regimen.
- (p) All subjects will receive a single dose of TAK-438 at the dose level to which they are assigned, ie, for those subjects assigned to 20 mg BID in multiple dosing phase they will receive a single 20 mg dose on Day 1.

Appendix B 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 investigator agrees to assume the following responsibilities:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. Ensure that study related procedures, including study specific (non routine/non standard panel) screening assessments are NOT performed on potential subjects, prior to the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
5. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to ICH, and local regulatory requirements.
6. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
7. Ensure that requirements for informed consent, as outlined in ICH and local regulations, are met.
8. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each 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.
9. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.
10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
11. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs and return all unused sponsor-supplied drugs to the sponsor.

12. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

Appendix C 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 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. 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.
14. 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.
15. The anticipated prorated payment(s), if any, to the subject for participating in the study.
16. The anticipated expenses, if any, to the subject for participating in the study.
17. 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.
18. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject otherwise is entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

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

Appendix D Investigator Consent to Use of Personal Information

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

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

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

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

Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in 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 E Collection, Storage, and Shipment of Bioanalytical Samples for Pharmacokinetic Analysis

Instructions for Processing of Plasma Samples for Pharmacokinetic Analysis of TAK-438

1. Collect 6 mL of venous blood for the plasma into a chilled Becton-Dickinson Vacutainer. All TAK-438 blood samples should be collected into Vacutainers containing sodium heparin.
2. Gently invert the Vacutainer several times to mix the additive with the collected blood prior to centrifugation and place immediately on ice.
3. Within 45 minutes of the sample collection, centrifuge the Vacutainers for 10 minutes at approximately 1100 to 1300 (RCF) at approximately 4°C. Note: if using a collection device other than Becton-Dickinson, refer to manufacturer's instruction for proper centrifugation force and time.
4. Immediately following centrifugation, gently remove plasma from the packed cells. To ensure a more homogeneous sample, all plasma should first be transferred into 1 aliquot. From there, split the plasma evenly between the 2 aliquots. A minimum of 1.0 mL needs to be obtained for each sample. Labeling may include protocol number (TAK-438_114), sample matrix (ie, plasma) randomization/enrollment number, period, nominal day and time, and either "SET 1" (for original sample) or "SET 2" (for duplicate sample).
5. Cap the labeled storage tubes and freeze the plasma samples immediately at approximately -70°C or lower until shipment to PPD [REDACTED]
[REDACTED] No more than 60 minutes will elapse between blood collection and freezing the plasma sample.

Instructions for Processing of Urine Samples for Pharmacokinetic Analysis of TAK-438

1. Collect urine into polypropylene containers. During the collection interval, the urine will be stored at approximately 4°C.
2. Stir the urine in the polypropylene container vigorously.
3. Measure the urine volume at the end of the collection period.
4. Place two 5 mL aliquots of urine in polypropylene containers. Labeling may include protocol number (TAK-438_114), sample matrix (ie, urine), randomization number, nominal day and time, and either "SET 1" (for original sample), or "SET 2" (for duplicate sample).
5. Freeze the urine samples and store frozen at approximately -70°C or lower. Keep samples frozen at approximately -70°C or lower until shipment to PPD [REDACTED]
[REDACTED] No more than 2 hours will elapse between the end of the collection period and freezing the urine samples. .

Shipping of Plasma and Urine Samples

The following instructions are recommended unless they differ from the site's SOPs for labeling, packaging, or shipping of pharmacokinetic samples.

1. Biological samples (ie, plasma or urine) should be shipped on dry ice to prevent thawing during transit. Samples should be shipped only on Monday, Tuesday, or Wednesday, and at least 2 days prior to a national holiday, in order to minimize the possibility of samples in transit over a weekend or holiday. If duplicate samples are to be shipped, send SET 1 samples and await confirmation of arrival before shipping the duplicate SET 2 samples.
2. Before shipping, make sure the sample tubes are tightly sealed. Separate each subject's samples as follows:
3. Place SET 1 samples for each subject into self-sealing bag (eg, Ziploc[®]) containing additional absorbent material.
4. Using a permanent marker, write the 4-digit enrollment number, sample matrix (ie, plasma or urine), number of samples, and "SET 1" on each self-sealing bag.
5. Place the bags of individual subject's samples into a larger plastic bag so that samples are double bagged. Duplicate SET 2 samples should be returned to the freezer for storage. Repeat steps 3 through 5 above when preparing duplicate samples for shipment, except self-sealing bags should be marked "SET 2."
6. An inventory of individual samples should accompany each shipment and should include the Sponsor's name (Takeda), study medication (TAK-438), protocol number (TAK-438_114), investigator's name, sample type (ie, plasma or urine), subject enrollment number, period, nominal collection day and time, and intended sample storage conditions. When duplicate SET 2 samples are being shipped, make a copy of the original SET 1 sample inventory and mark as "SET 2." Place the inventory paperwork into a large self-sealing bag. SET 1 samples will be shipped first on dry ice, followed by shipment of duplicate SET 2 samples after SET 1 samples have been received by the analytical laboratory.
7. For sample packing, utilize dry ice generously (eg, 20-25 pounds or 10-11 kg per day of transit) to safeguard against longer than expected shipping times and delays. Use newspaper or other material to insulate the double-bagged samples from direct contact with the dry ice. Place the sample bundles into a Styrofoam container (or other suitable container) and fill the excess space with dry ice slabs or ice pellets (preferably the latter). Make a note of the estimated weight of the dry ice used per shipping container.
8. Place the inventory paperwork (in a large self-sealing bag) on top of the dry ice in the Styrofoam container. Place the lid on the Styrofoam container and seal completely with strapping tape. Place the Styrofoam container in a cardboard shipping carton and seal securely with strapping tape.
9. Mark the outside of shipping carton(s) with a tally number (eg, 1 of 5, 2 of 5).

10. Affix an address label to each shipping carton. Complete the address label with the following information:

Plasma and Urine Samples for TAK-438

Contact Name: PPD

Address: PPD

Phone: PPD

11. Affix a carbon dioxide label on each carton, specifically:

Carbon Dioxide Solid UN-1845

Class 9 PKG GR III

Quantity _____

(fill in weight to nearest lb/kg and specify unit of measure used)

12. Affix 2 dry ice symbol labels on opposite sides of the carton. Mark “KEEP FROZEN” on each carton. Specify a return address and contact person on the carton.

13. Obtain the airway bill number and a receipt of shipment from the carrier.

14. After shipping of the TAK-438 samples, please contact PPD at e-mail: PPD to notify him/her of next day delivery. When calling, provide the following information:

- Name of courier or transport company.
- Time and date the shipment left the clinical site.
- Airway bill number.

Appendix F Collection, Storage, and Shipment of Plasma Samples for Genotyping Analysis

Instructions for processing and shipping of plasma samples for genotyping analysis

1. Collect one 2 mL tube of venous blood into a plastic tube containing K₂EDTA.
2. Mix immediately by gently inverting the tube several times (at least 8-10 times) to mix the additive with the collected blood.
3. Send to the local laboratory in 2 hours upon collection for testing according to local site operating procedure. The alleles to be tested are *1/*1, *1/*2, *1/*3, *2/*2, *2/*3, *3/*3.

Appendix G Detailed Description of Amendments to Text

The primary section(s) of the protocol affected by the changes in Amendment No. 02 are indicated. The corresponding text has been revised throughout the protocol.

Change 1: Reduced the fasting period after dosing from 4 hours to 2 hours in the once daily dosing regimen only.

The primary change occurs in Section 7.4 Diet, Fluid, and Activity Control:

Initial wording	For subjects receiving QD regimen, they should be fasted overnight for a minimum of 10 hours prior to dosing and will continue to fast for 4 hours after dosing. They should take the dose with 240 mL water and refrain from drinking for at least 1 hour postdose, after which water can be given <i>ad libitum</i> .
Amended or new wording:	For subjects receiving QD regimen, they should be fasted overnight for a minimum of 10 hours prior to dosing and will continue to fast for 4 hours 2 hours after dosing. They should take the dose with 240 mL water and refrain from drinking for at least 1 hour postdose, after which water can be given <i>ad libitum</i> .

Rationale for Change:

This change has been made to allow subjects to have breakfast 2 hours after the dose (having already fasted for 10 hours predose). Given that TAK-438 is not known to show a food effect, and the peak plasma concentrations occur <2 hours postdose, it is not expected that this change will markedly impact the pharmacokinetic results of the study.

The following sections also contain this change:

- Section 8.1.3 Dose and Regimen
- Appendix A Schedule of Study Procedures (footnote m).

Change 2: For the collection of demographic data, replaced the requirement to collect date of birth with a requirement to collect age.

The primary change occurs in Section 9.1.2 Demographics, Medical History, and Medication History Procedure:

Initial wording	Demographic information to be obtained will include date of birth, sex, alcohol and caffeine consumption and smoking status of the subject at Screening.
Amended or new wording:	Demographic information to be obtained will include date of birth age , sex, race , alcohol and caffeine consumption and smoking status of the subject at Screening.

Rationale for Change:

China-FDA Technical Guidelines for Clinical Trial Data Management state that for reasons of subject privacy, the date of birth should not be collected if this is not necessary.

Change 3: Clarified clinical laboratory sample collection volume and time points.

The primary change occurs in Section 9.1.8 Procedures for Clinical Laboratory Samples:

Initial wording:	All samples will be collected in accordance with acceptable laboratory procedures. The maximum volume of blood at any single visit is approximately 20 mL, and the approximate total volume of blood for the study is 316 mL. Laboratory samples will be taken following a minimum 10-hour overnight fast on the days stipulated in the Schedule of Study Procedures (Appendix A).
Amended or new wording:	All samples for clinical laboratory testing will be collected in accordance with acceptable laboratory procedures. The maximum volume of blood at any single visit is approximately 20 mL 14.7 mL , and the approximate total volume of blood for the study is 316 mL 53.5 mL . Except for urinalysis on Day 3 and Day 9 , laboratory samples will be taken following a minimum 10-hour overnight fast on the days stipulated in the Schedule of Study Procedures (Appendix A). On dosing days, samples for clinical laboratory testing should be drawn at predose in the morning (except for urinalysis on Day 3 and Day 9 when urine PK collection shall be taken as a priority). At the Screening Visit, Day-1 and Day 11, it is recommended that samples are drawn at approximately the same time as the dosing days.

Rationale for Change:

To correct the single visit and total blood volume for clinical laboratory sample testing, and clarified the time point when collections should be made for consistency with [Appendix A](#).

The following sections also contain this change:

- **2.0 STUDY SUMMARY**
- **Section 9.4 Blood Volume.**
- **Appendix A** Schedule of Study Procedures (footnotes c, d, e, and k).

Change 4: Change in compounds or parameters tested during clinical laboratory testing.

The primary change occurs in **Table 9.a Clinical Laboratory Tests**

Amended **Hematology**

wording: Red blood cells

White blood cells (with differential: neutrophils, eosinophils, basophils, monocytes, lymphocytes)

Hemoglobin

Hematocrit

Platelets

PT/INR

aPTT

Reticulocyte ~~count~~ **percentage**

Urinalysis

pH

Specific gravity

Protein

Glucose

Nitrites

Bilirubin

Hemoglobin

Ketones

Urobilinogen

Microscopic Analysis:

RBC/high power field

WBC/high power field

Hyaline casts/ low power field

Granular casts/ low power field

~~Epithelial cells casts, crystals and organisms~~

Rationale for Change:

Minor changes have been made to be consistent with the local clinical laboratory's testing procedure. These changes will have no impact on subject safety monitoring.

Change 5: Reduced the frequency in 12-lead electrocardiogram monitoring, and revised procedure for abnormal (not clinically significant) ECGs at Screening.

The primary change occurs in Section 9.1.11 ECG Procedure:

Initial wording: 12-lead ECGs printed in standard format, will be collected at Screening, Check-in (Day-1), and on Dosing Days (ie, Day 1 and 3-9 inclusive) at predose (0 hours) and 1, 2, 4, 8, 12, 24 and 48 hours post dose, and at the Early Termination of the study for safety assessment. Note however that during the multiple dosing phase some 24-hour or 48-hour postdose ECG time points will coincide with subsequent dose ECG time points (ie, 24-hour post-dose ECG following the Day 3 dose coincides with the Day 4 pre-dose ECG) and in such cases it is only necessary to record one ECG trace at the appropriate time point.

The investigator will be responsible for providing the interpretation of all safety ECGs (normal/abnormal). These results will be reviewed by the investigator for subject safety and will be provided in an appropriate format with the clinical study report. The time that the ECG was performed will be recorded. The following parameters will be recorded on the (e)CRF from the subject's ECG trace: heart rate, QT interval, PR interval, QRS interval and RR interval.

As ECG tracings on thermal paper fade over time, any such tracings should be completely photocopied and both the original tracing and the counter-signed copy should be filed in the subject's medical record.

Amended 12-lead ECGs printed in standard format, will be collected at Screening, Check-in or new (Day -1), and on ~~Dosing Days (ie, Day 1 and 3-9 inclusive)~~ at predose (0 hours) and 1, 2, 4, 8, 12, 24 and 48 hours post dose, and at the Early Termination of the study for safety assessment. Note however that during the multiple dosing phase some 24-hour or 48-hour postdose ECG time points will coincide with subsequent dose ECG time points (ie, 24-hour post-dose ECG following the Day 3 dose coincides with the Day 4 pre-dose ECG) and in such cases it is only necessary to record one ECG trace at the appropriate time point. **Confinement Days (Days 1-11/Early Termination). On dosing days, ECGs should be collected after dosing.**

The investigator will be responsible for providing the interpretation of all safety ECGs (normal/abnormal). These results will be reviewed by the investigator for subject safety and will be provided in an appropriate format with the clinical study report. The time that the ECG was performed will be recorded. The following parameters will be recorded on the (e)CRF from the subject's ECG trace: heart rate, QT interval, PR interval, QRS interval and RR interval.

During Screening periods (Screening visit and Day -1), ECGs deemed abnormal but not clinically significant by the study doctor, should be sent to the CRO Medical Monitor for review in 24 hours (with subject de-identified). If consensus is not reached between site investigators and CRO Medical Monitor, the CRO medical monitor will consult Takeda Clinical Science on the same working day.

As If ECG tracings are printed out on thermal paper **which** fades over time, any such tracings should be completely photocopied and both the original tracing and the counter-signed copy should be filed in the subject's medical record.

Rationale for Change:

This change in frequency of ECGs is to reduce the number of interventions, and will have no impact on subject safety monitoring. The change in procedure for abnormal ECGs at Screening is to permit the immediate confirmation by a qualified study doctor of a subject's eligibility for whom their ECG is abnormal but not clinically significant, in addition to a second ECG review by the CRO Medical Monitor to ensure consistency in the ECG assessment. Revisions to the text pertaining to ECG tracings have been made as the selected phase 1 unit does not use thermal paper.

The following sections also contain this change:

- Section 7.2 Exclusion Criteria
- Section 9.3.3 Study Entrance (Day 1)
- Section 9.3.5 Multiple Dosing Phase (Days 3-9)
- Section 9.3.7 Early Termination
- **Appendix A** Schedule of Study Procedures (footnote i).

Change 6: Clarified that genotyping will be conducted at the local laboratory

The primary change occurs in Section 9.5 Biological Sample Retention and Destruction:

Initial wording:	The genetic material will be sent to a testing laboratory to determine the CYP2C19 metabolic status of each subject. Any remaining sample after testing will be destroyed.
Amended or new wording:	The genetic material will be sent to a testing the local laboratory to determine the CYP2C19 metabolic status of each subject. Any remaining sample after testing will be destroyed.

Rationale for Change:

Given the regulations in China on the shipment of biosamples containing human genetic information, it was determined that the local laboratory at the selected institution would perform the genetic testing.

The following sections also contain this change:

- Appendix F Collection, Storage, and Shipment of Plasma Samples for Genotyping Analysis.

Change 7: Clarified liver function test monitoring.

The primary change occurs in Table 9.a Clinical Laboratory Tests

Description In the column *Serum Chemistry*: alanine aminotransferase, aspartate of change: aminotransferase, total bilirubin, and direct bilirubin have been highlighted as being included in liver function tests, with a new footnote:

(b) Included in liver function tests.

Rationale for Change:

Highlight the tests involved in liver function monitoring.

The following sections also contain this change:

- Section 9.3 Schedule of Observations and Procedures
- Appendix A Schedule of Study Procedures.

Change 8: Removed the requirement for genitourinary monitoring as part of the physical examination.

The primary change occurs in Section 9.1.3 Physical Examination Procedure:

Initial wording:	A physical examination will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; (11) genitourinary system and (12) other.
Amended or new wording:	A physical examination will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes ;(11) genitourinary system and (12) (11) other.

Rationale for Change:

An examination of the genitourinary system is only required to be included if applicable to the indication under study. As the genitourinary system is not applicable to the proposed indication of TAK-438, an examination of this system is not necessary.

Change 9: Clarified the Chinese population eligible for inclusion into the study.

The primary change occurs in Section 7.1 Inclusion Criteria:

Initial wording:	3. The subject is a healthy adult male or female subject of Chinese descent. 5. The subject weighs at least 50 kg and has a body mass index (BMI) between 19 and 24, inclusive at Screening (Check-In Day -1).
Amended or new wording:	3. The subject is a healthy adult male or female Chinese subject of Chinese descent. 5. The subject weighs at least 50 kg and has a body mass index (BMI) between 19 and 26 kg/m² 24, inclusive at Screening (Check-In Day -1).

Rationale for Change:

To reflect the demography in China, and not limit the inclusion criteria to any one ethnic group in China, and to reflect the updated China FDA regulations for recommended BMI inclusion criteria in a phase 1 study.

The following sections also contain this change:

- **2.0 STUDY SUMMARY**

Change 10: Minor updates for protocol consistency.

The primary change occurs in [2.0 STUDY SUMMARY](#):

Deleted text: Healthy subjects aged 18-45 inclusive (~~it is recommended that there will be an equal number of males and females in each cohort~~).

Rationale for Change:

Removed to maintain consistency with the rest of the protocol. The study will still recruit both male and female subjects.

Change 11: Clarified the time point for vital sign measurements.

The primary change occurs in [Section 9.1.5 Vital Sign Procedure](#):

Initial wording: Vital signs will include body temperature (oral, tympanic, or axillary measurement), sitting blood pressure (after 5 minutes resting), respiration rate and pulse (bpm).

Amended or new wording: Vital signs will include body temperature (oral, tympanic, or axillary measurement), sitting blood pressure (after 5 minutes resting), respiration rate and pulse (bpm). **On dosing days, vital sign measurements should be taken at predose in the morning, and for the remaining days, measurements should be taken at approximately the same time as on the dosing days.**

Rationale for Change:

To clarify the time for each vital sign measurement in the study procedure.

Change 12: Follow-up Visit changed from a site visit to a Telephone Contact.

The primary change occurs in Section 9.3.8 Follow-up (Telephone Contact)

Initial wording:	9.3.8 Follow-up (Final Visit)
	Follow-up will begin the first day after the Check-out or Early Termination and the onsite visit will be at Day 18 (\pm 3 days). The follow-up will document the following:
Amended or new wording:	9.3.8 Follow-up (Final Visit) (Telephone Contact)
	Follow-up will begin the first day after the Check-out or Early Termination and the onsite visit telephone contact will be at Day 18 (\pm 3 days).

Rationale for Change:

Clarification of study site usual procedures. Procedures during the Final Visit can be conducted over the phone in accordance with the original protocol and will not have an impact on subject safety.

The following sections also contain this change:

- [Section 6.1 Study Design](#)
- [2.0 STUDY SUMMARY](#)
- [Appendix A Schedule of Study Procedures.](#)

Change 13: Clarification of 4-digit enrollment number assignment.

The primary change occurs in [8.2 Section Investigational Drug Assignment and Dispensing Procedures](#)

Initial wording:	Subjects will be assigned to receive a 4-digit enrollment number. The number will be assigned by the clinic site personnel in sequential order beginning with 1001.
Amended or new wording:	Subjects will be assigned to receive a 4-digit enrollment number. The number will be assigned by the clinic site personnel in sequential order beginning with 1001 as follows:
Cohort 1: 10mg TAK-438 QD beginning with 1001	
Cohort 2: 20mg TAK-438 QD beginning with 2001	
Cohort 3: 20mg TAK-438 BID beginning with 3001	

Rationale for Change:

Request from phase 1 study unit to use enrollment numbers to differentiate between cohorts.

Change 14: Addition of table describing window for urine sample collection.

The primary change occurs in Section 14.2 Protocol Deviations

Amended [New Table 14.b Windows for Pharmacokinetic Urine Sample Collection]
or new
wording:

Rationale for Change:

Upon request from the site, in accordance with their routine practice, the window for urine collection time has been clarified.

Change 15: Clarification of meals given during the Confinement Period

The primary change occurs in Section 7.4 Diet, Fluid, and Activity Control

Initial wording:	During the confinement period, subjects will be given a menu for the dosing period that includes 3 meals and an evening snack, each containing approximately 20% to 25% fat (relative to the total calories), according to the local phase 1 unit standard. The menu of the standardized meals from the clinical research site will be approved by Takeda before the implementation. The meals served on the day of dosing should be identical for each cohort in the study. 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.
Amended or new wording:	During the confinement period, subjects will be given a menu for the dosing period that includes 3 meals, and an evening snack, each Each meal will contain approximately 20% to 25% fat (relative to the total calories), according to the local phase 1 unit standard. The menu of the standardized meals from the clinical research site will be approved by Takeda before the implementation. The meals served on the day of dosing should be identical for each cohort in the study. 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.

Rationale for Change:

Given that subjects are required to fast for 4 hours post-dose, and an overnight fast is required to be more than 10 hours, subjects would need to quickly consume an evening snack at 2200 in order to be able to draw fasted blood at 0800. As this was not practical, the evening snack was removed from the study protocol.

The requirement for identical meals on dosing days was removed as subjects receiving once daily dosing would not receive breakfast (only a morning snack), while subjects receiving twice daily dosing will receive breakfast.

Change 16: Clarification of meals given during the Confinement Period 3 and Day 9

The primary change occurs in Section 9.3.5 Multiple Dosing Phase (Days 3-9)

Initial wording: While remaining confined at the phase 1 unit, the following procedures will be performed between Day 3-9:

- Vital signs.
- Concomitant medications.
- Fasting clinical laboratory tests (hematology, chemistry, and urinalysis) on days 3 and 9 only.
- ECG procedure.
- Collection of predose blood samples for PK analysis Days 3-9 inclusive, and also of postdose blood samples on Day 9 only.
Note that the pre-dose time point for Day 3 is actually the 48-hour post-dose time point following the Day 1 dose. Note also that for subjects assigned to the 20 mg BID multiple dose regimen PK draws should be taken relative to the morning dose.
- Collection of urine samples for PK analysis predose on day 3, predose and postdose on Day 9.
Note that the pre-dose time point for Day 3 is actually the 48-hour post-dose time point following the Day 1 dose. Note also that for subjects assigned to the 20 mg BID multiple dose regimen PK draws should be taken relative to the morning dose.
- Adverse event assessment.
- Administration of study medication.

Amended or new wording: While remaining confined at the phase 1 unit, the following procedures will be performed between Day 3-9:

- Vital signs (predose).
- Concomitant medications.
- Fasting clinical laboratory tests (hematology, and chemistry, ~~and urinalysis~~) at **pre-dose** on Days 3 and 9 only.
- **Urinalysis on Day 3 and 9 only**
- Fasting liver function tests **at pre-dose** on Days 3 and 9 only.
- ECG procedure (postdose).
- Collection of predose blood samples for PK analysis Days 3-9 inclusive, and also of postdose blood samples on Day 9 only.
Note that the predose time point for Day 3 is actually the 48-hour postdose time point following the Day 1 dose. Note also that for subjects assigned to the 20 mg BID multiple dose regimen PK draws should be taken relative to the morning dose.
- Collection of urine samples for PK analysis at predose and postdose on Day 9.
~~Note that the pre-dose time point for Day 3 is actually the 48-hour post-dose time point following the Day 1 dose.~~ Note also that for subjects assigned to the 20 mg BID multiple dose regimen PK draws should be taken relative to the morning dose.
- Adverse event assessment.
- Administration of study medication.

Rationale for Change:

Given that subjects are required to have urine PK 48 hours postdose, a timepoint which will be quite close to fasted urinalysis, urine PK shall be taken as priority in this PK study. Thus, fasting requirement for urinalysis is removed to facilitate the urine PK collection.

Amendment 2 – An Open-Label, Single-center, Parallel, Phase 1 Study to Determine the Pharmacokinetics of Single- and Multiple- Oral Doses of TAK-438 10 mg and 20 mg in Healthy Adult Chinese Subjects

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical Science Approval	22-Dec-2016 15:50 UTC
PPD	Biostatistics Approval	22-Dec-2016 16:02 UTC
PPD	Medical Monitor Approval	23-Dec-2016 02:52 UTC
PPD	Clinical Pharmacology Approval	25-Dec-2016 19:07 UTC