Title: A Single-Sequence, Open-Label, 2-Period, Crossover Trial to Evaluate the Effect of the Potent CYP3A4 Inhibitor Itraconazole on the Single-Dose Pharmacokinetics of Oral TAK-906 in Healthy Adult Subjects.

NCT Number: NCT03161405

SAP Approve Date: 3 August 2017

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

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

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-906-1003

A Single-Sequence, Open-Label, 2-Period, Crossover Trial to Evaluate the Effect of the Potent CYP3A4 Inhibitor Itraconazole on the Single-Dose Pharmacokinetics of Oral TAK-906 in Healthy Adult Subjects

PHASE 1

Version**:** Final

Date**:** 03 August 2017

Prepared by:

PPD

Based on:

Protocol Version: Amendment 01

Protocol Date: 25 May 2017

1.1 Approval Signatures

Electronic signatures can be found on the last page of this document.

2.0 TABLE OF CONTENTS

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

3.0 LIST OF ABBREVIATIONS

%CV	percent coefficient of variation
hCG	human chorionic gonadotropin
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC_{last}	area under the concentration-time curve from time 0 to time of the last quantifiable concentration
AUC_{∞}	area under the concentration-time curve from time 0 to infinity, calculated using the observed value of the last quantifiable concentration
BLQ	below the limit of quantification
BMI	body mass index
BUN	blood urea nitrogen
CPK	creatine phosphokinase
CFR	Code of Federal Regulations
CI	confidence interval
CL_R	renal clearance
C_{max}	maximum observed concentration
CNS	central nervous system
CRU	clinical research unit
CYP	cytochrome P-450
DA	dopamine
DNA	deoxyribonucleic acid
DDI	drug-drug interaction
ECG	electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
EPS	extrapyramidal symptoms
f_e	fraction of administered dose of drug excreted in urine
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GI	gastrointestinal
GM	geometric mean
HIV	human immunodeficiency virus
HR	heart rate
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IRB	institutional review board

LFT	liver function test
LLN	lower limit of normal
MAV	markedly abnormal value
MedDRA	Medical Dictionary for Regulatory Activities
PD	pharmacodynamics
PGx	pharmacogenomics
PK	pharmacokinetic(s)
PO	oral(ly)
PT	preferred term
QD	once daily
QTcF	QT interval with Fridericia correction method
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SDB	standard database
SOC	system organ class
SUSAR	suspected unexpected serious adverse reactions
$t_{1/2}$	half-life
t_{max}	time of first occurrence of C_{max}
TEAE	treatment-emergent adverse event
TLGs	tables, listings, and graphs
ULN	upper limit of normal
WBC	white blood cell
WHODrug	World Health Organization Drug Dictionary

4.0 OBJECTIVES

4.1 Primary Objectives

The primary objective of the trial is to evaluate the effect of the potent CYP3A4 inhibitor itraconazole on the single-dose pharmacokinetics (PK) of PO TAK-906 maleate.

4.2 Secondary Objectives

The secondary objective of the trial to evaluate the safety and tolerability of single PO dose of TAK-906 maleate in the presence and absence of a potent CYP3A4 inhibitor.

4.3 Exploratory Objectives

Exploratory objectives of this trial include:

CCI

4.4 Study Design

This is a phase 1, single-sequence, open-label, 2-period crossover trial in approximately 12 healthy male and female (nonchildbearing-potential) subjects. The trial is designed to investigate the effect of a potent CYP3A4 inhibitor (itraconazole) on the PK of TAK-906.

The trial will include a Screening Visit, a Period 1 (Days 1 to 3), followed by a minimum of a 4-day washout from the time of TAK-906 maleate dose, a Period 2 (Days 1 to 6), and a Follow-up Visit.

On Day 1 of Period 1, eligible subjects will be enrolled into the trial and will receive a single PO dose of TAK-906 maleate 25 mg. On Days 1 to 5, inclusive, of Period 2, subjects will receive itraconazole 200 mg once daily (QD) PO solution. Following after an overnight fast of at least 8 hours, a single PO dose of TAK-906 maleate 25 mg will be administered 1 hour after the itraconazole dose on Day 4 of Period 2. Both doses of TAK-906 maleate will be administered after an overnight fast of at least 8 hours as food reduces its bioavailability by approximately 40%.

Itraconazole will be administered to subjects under clinic supervision on an outpatient basis on the morning of Days 1 to 3 of Period 2 and during confinement on Days 4 to 5 of Period 2.

Blood samples for assessment of TAK-906 concentrations will be collected from predose to 48 hours after each dose of TAK-906 maleate. Samples may be assayed for TAK-906 metabolites if deemed necessary. Urine samples will be collected through 48 hours and may be assayed for TAK-906 concentrations and metabolites if deemed necessary for the interpretation of data.

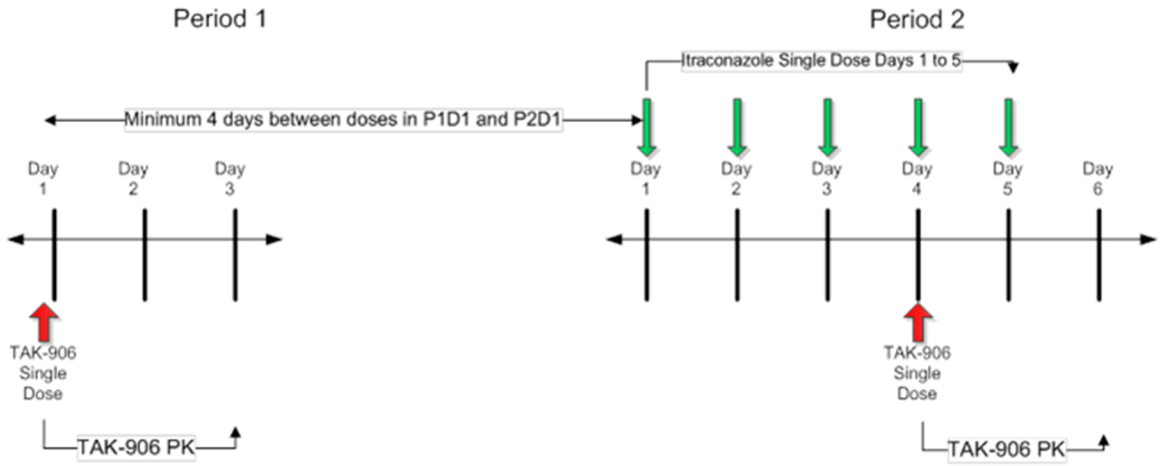
Whole blood samples for deoxyribonucleic acid (DNA) pharmacogenomics (PGx) analysis and ribonucleic acid (RNA) isolation will be collected predose on Day 1 of Trial Period 1.

Safety will be assessed by monitoring for adverse events, vital signs, ECGs, clinical laboratory results, and physical examinations throughout each dosing period.

After completion of the trial (or following subject withdrawal), all subjects will return for a Follow-up Visit 10 to 14 days after their last dose of TAK-906 maleate.

A schematic of the study design is shown in Figure 4.a. A schedule of assessments is listed in Appendix A.

Figure 4.a Trial Schematic



5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoints

The primary endpoints of the trial are the following plasma PK parameters for TAK-906 on Days 1 and 4:

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

5.2 Safety Endpoints

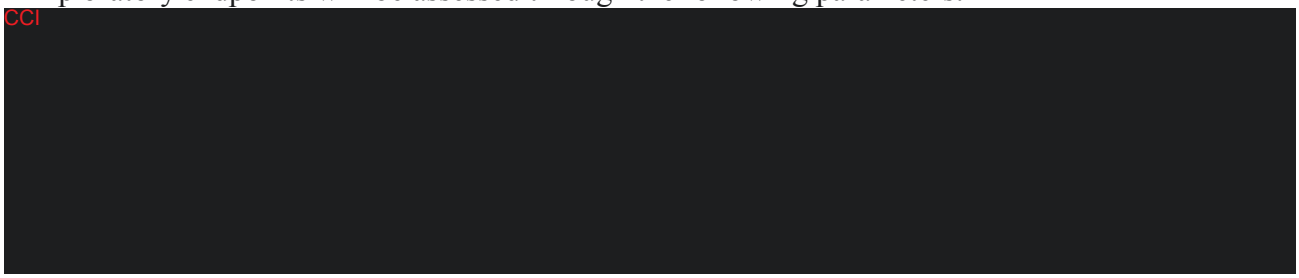
Safety endpoints include the following:

- Safety and tolerability will be assessed through physical examinations, ECGs, vital signs, clinical laboratory results, and collection of spontaneous adverse events (AEs).

5.3 Exploratory Endpoints

Exploratory endpoints will be assessed through the following parameters:

CCI



6.0 DETERMINATION OF SAMPLE SIZE

Approximately 12 subjects will be enrolled in this trial. The sample size justification is based on an acceptance range of 50% to 200% and assumes that the intrasubject %CV for AUC_{last} and C_{max} of TAK-906 will not exceed 25%. This sample size will provide 80% power to conclude plasma concentration of TAK-906 will not increase more than 2-fold in presence of itraconazole.

Subjects who drop out for nonsafety reasons may be replaced at the discretion of the investigator in consultation with the sponsor. Subjects who drop out for safety reasons will not be replaced.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

Continuous data will be summarized using descriptive statistics, including the number of subjects, mean, standard deviation (SD), median, minimum, and maximum. The coefficient of variation (%CV) and geometric mean will be included in the summary of continuous data where indicated. Categorical data will be summarized as the number and percentage of subjects in each category.

Arithmetic means, geometric means, and medians will be presented to 1 more decimal place than the recorded data, and SDs will be presented to 2 more decimal places than the recorded data, where appropriate. Where applicable, confidence intervals about a parameter estimate will be presented using the same number of decimal places as the parameter estimate and p-values will be rounded to 3 decimal places prior to assessment of statistical significance.

All study-related raw data for enrolled subjects, including derived data, will be presented in data listings. In addition, the actual day relative to the first dose will be presented, where applicable.

All statistical analyses will be performed using the SAS System Version 9.4.

7.1.1 Definition of Study Days and Baseline

Study Day 1 is defined as the date of the first dose of study drug, as recorded on the electronic case report form (eCRF) study drug administration page. Other study days are defined relative to Study Day 1, with Day 1 being Study Day 1 and Day -1 being the day prior to Study Day 1. Study days prior to the first dose of study drug will be calculated as: [date of assessment/event – date of first dose of study drug]. Study days on or after the first dose of study drug will be calculated as: [date of assessment/event – date of first dose of study drug + 1].

Unless specified otherwise, baseline is defined as the last non-missing measurement prior to the first dose of study drug.

7.1.2 Missing Data

There will be no imputation of incomplete or missing data.

Plasma concentrations that are below the limit of quantification (BLQ) will be treated as zero in the summarizing concentration values and deriving of PK parameters. These values will be flagged in the data listings.

7.2 Analysis Sets

The following analysis sets will be used for analysis and presentation of the study data:

- Safety Set: The safety set will consist of all subjects who are enrolled and received at least 1 dose of study drug. Subjects in this analysis set will be used for demographic, baseline characteristics, and safety summaries.

- PK Set: The PK set will consist of all subjects who are enrolled, receive at least 1 dose of trial drug, and have at least 1 measurable plasma TAK-906 concentration.

All subjects in the PK set with valid PK parameter estimates will be included in the summaries and analyses for that parameter. Decisions regarding inclusion or exclusion of data from PK analysis for subjects who are noncompliant with the dosing schedule, or who have incomplete data, will be made on a case-by-case basis, but the data will be presented in data listings regardless.

7.3 Disposition of Subjects

Study Information, including date of first subject signing Informed Consent Form (ICF), date of first/last study drug, date of last subject's last visit/contact, date of last subject's last procedure for collection of data for primary endpoint, Medical Dictionary for Drug Regulatory Activities (MedDRA) Version, World Health Organization Drug Dictionary (WHODrug) Version, and SAS Version, will be tabulated.

The eligibility of subjects will be summarized, along with the primary reasons of screen failure as recorded in eCRF.

The number and percentage of subjects who comprised each analysis set will be summarized.

Disposition of all enrolled subjects will be tabulated. Categories will include:

- Subjects who were enrolled but not dosed.
- Subjects who completed the study.
- Subjects who prematurely discontinued study.
- Primary reasons for discontinuing study, as entered on the eCRF.

7.4 Demographic and Other Baseline Characteristics

Demographic and study baseline characteristics, including age at informed consent, gender, ethnicity, race, height (cm), weight (kg), and body mass index (kg/m^2), will be summarized.

There will be no inferential analysis of demographic and baseline characteristics.

7.5 Medical History and Concurrent Medical Conditions

Medical history is defined as significant conditions or diseases that resolved at or prior to the time of informed consent. Concurrent medical conditions are defined as significant conditions or diseases that are present at signing of informed consent.

Medical history and concurrent medical conditions will be coded using the MedDRA coding system, and will be presented in the data listing. There will be no summary or inferential analysis of medical history and concurrent medical conditions.

7.6 Medication History and Concomitant Medications

Medication history information includes any medication stopped at or within 28 days prior to signing of informed consent. Medications used from signing of informed consent through the end of study will be considered as concomitant medications.

Medication history and concomitant medications will be coded using the WHO Drug, and will be presented in the data listing. There will be no summary or inferential analysis of medication history and concomitant medications.

7.7 Study Drug Exposure and Compliance

The date and time of each dose for each subject will be reported in the data listing for all subjects. Summaries and listings of TAK-906 PK data will be provided. No summary statistics for the extent of exposure to study drug or compliance calculations will be performed for this study.

7.8 Efficacy Analysis

Not applicable.

7.9 Pharmacokinetic/Pharmacodynamic Analysis

7.9.1 Pharmacokinetic Analysis

The schedule for blood and urine samples for PK analysis of TAK-906 and any measured metabolites is specified in Appendix A.

The plasma of TAK-906 and any measured metabolites will be summarized by regimen (TAK-906 maleate alone and TAK-906 maleate with itraconazole) over each scheduled sampling time point using descriptive statistics (N, arithmetic mean, SD, CV%, median, minimum and maximum). Individual plasma and urine concentration data versus time will be presented together with the descriptive statistics as well as in separate data listings.

In addition, the figures for mean plasma concentrations of TAK-906 versus time (linear and semi-log scale) will be generated.

Plasma and urine PK parameters will be calculated from the plasma and urine concentration values versus time profile of TAK-906 and any measured metabolites using non-compartmental analysis. The key PK parameters are listed below:

Plasma

CCI

[redacted]

CCI [redacted]

Urine

CCI [redacted]

Additional plasma and/or urine PK parameters may be calculated if necessary, in accordance with the Clinical Pharmacology Analysis Plan (CPAP).

Plasma and urine PK parameters of TAK-906 and any measured metabolites will be summarized by regimen using descriptive statistics. In addition, geometric mean and %CV will be computed for C_{max} and AUCs (AUC_{last} and AUC_{∞}).

Box plots and scatter plots for Cmax and AUCs (AUC_{last} and AUC_{∞}) will be generated by regimen.

For evaluation of potential effect of itraconazole on TAK-906 PK, paired t-tests and associated 90% confidence intervals (CIs) will be determined on the natural logarithms of C_{max} and AUCs (AUC_{last} and AUC_{∞}) to compare the exposure between regimens. The geometric mean of the relative bioavailability of the TAK-906 maleate with itraconazole regimen relative to the TAK-906 maleate alone regimen and the associated 90% CIs will be determined by exponentiating the appropriate estimates for the difference between regimens in the log-transformed parameters.

All PK parameters calculated will be presented in data listings.

7.9.2 Pharmacodynamic Analysis

Not applicable.

7.10 Other Outcomes

Not applicable.

7.11 Safety Analysis

Safety analyses include adverse events (AEs), clinical laboratory parameters, vital sign parameters, 12-lead electrocardiogram (ECG) results, and physical examination.

All summaries of safety data are based on subjects in the Safety Analysis Set.

7.11.1 Adverse Events

A treatment-emergent adverse event (TEAE) will be defined as an AE or serious adverse event (SAE) that started or worsened after first study drug administration and within 30 days of last dose of study drug (onset date – date of last dose + 1 ≤30). All AE verbatim terms will be coded by system organ class (SOC) and preferred term (PT) using the MedDRA dictionary.

TEAEs will be summarized by overall and the following categories: Period 1 (onset on and after TAK-906 dosing on Period 1 Day 1 and before the dosing of itraconazole on Period 2 Day 1), Period 2 Day 1 post-dose to Day 4 pre-dose (after itraconazole dosing on Period 2 Day 1and before TAK-906 dosing on Period 2 Day 4), and Period 2 Day 4 post-dose and thereafter (after TAK-906 and itraconazole dosing on Period 2 Day 4). The tables will include the number and percentage (N [%]) of subjects reporting any event for that term. The following is a list of TEAE summary tables to be generated.

- Overview of TEAEs (at both subject and event level).
- TEAEs by SOC and PT (at both subject and event level).
- Subject Mappings for TEAEs.
- TEAEs by PT.
- Relationship of TEAEs to Study Drug by SOC and PT.
- Drug-Related TEAEs by SOC and PT.
- Intensity of TEAEs by SOC and PT.
- Intensity of Drug-Related TEAEs by SOC and PT.

For each category and overall, subjects reporting more than 1 occurrence for a term (SOC or PT) being summarized will be counted only once using the most extreme incident (most severe for the intensity tables and related for the relationship to study drug tables).

Data listings will be provided for all TEAEs, PTEs, TEAEs that led to study drug discontinuation, TEAEs that led to abnormal liver functions, SAEs, AEs that resulted in death, and AEs occurring more than 30 days after the last dose of study medication.

7.11.2 Clinical Laboratory Evaluations

Clinical safety laboratory tests include chemistry, hematology, urinalysis, and diagnostic screening. Refer to Appendix A for scheduled clinical laboratory test measurements and to Appendix B for the list of all clinical laboratory tests.

Descriptive statistics (N, mean, median, SD, minimum and maximum) of clinical safety laboratory variables will be summarized for baseline, post-dosing, and change from baseline at each visit. Only the scheduled measurements will be included in the summary. No inferential analysis will be performed.

Individual results for hematology and chemistry laboratory tests will be evaluated against the Takeda predefined laboratory markedly abnormal value (MAV) criteria (Appendix C). All subjects that meet the MAV criteria will be presented in a data listing. If a subject has a MAV for a particular laboratory test, all visits for that subject for that parameter will be listed. The number and percentage of subjects with at least 1 post dose markedly abnormal laboratory test result will be summarized by regimen. The mapping of the subjects with post dose results which meet the MAV criteria will be listed as a table. All post dose clinical lab results within 7 days of the last

dose, including scheduled and unscheduled measurements will be included in the MAV summaries.

All clinical laboratory data will be presented in both SI and conventional units in the data listings. Laboratory data outside of the normal reference range will be flagged on the listing along with values meeting MAV criteria.

7.11.3 Vital Signs

Vital sign measurements include body temperature, pulse, respiratory rate, and blood pressure. Refer to Appendix A for scheduled vital signs measurement visits.

Descriptive statistics (N, mean, median, SD, minimum and maximum) of these vital signs will be summarized by regimen for baseline, post-dosing, and change from baseline at each scheduled time point. For each regimen (period), baseline is defined as the last non-missing vital sign measurement at or prior to predose (time relative to TAK-906 dosing) in the corresponding period. Only the vital signs collected at the scheduled visits or time points will be included in the summary. No inferential analysis will be performed for the observed vital signs.

All individual vital signs that meet Takeda's predefined criteria for markedly abnormal values (Appendix D) will be listed. The number and percentage of subjects with at least 1 post dose markedly abnormal vital sign measurement will be summarized by regimen. The mapping of the subjects with post dose results which meet the MAV criteria will be listed as a table. All post dose vital signs within 7 days of the last dose, including both scheduled and unscheduled measurements, will be included in the MAV summaries.

All vital sign data will be presented in the listings. Vital sign MAVs will be flagged in the listings.

7.11.4 12-Lead ECGs

The scheduled 12-lead ECG data will be collected according to Appendix A. The ECG parameters include heart rate, PR interval, QRS duration, QT interval, and QT interval with Fredericia's corrections (QTcF).

Quantitative triplicate ECG measurements at each time point will be averaged. Descriptive statistics (N, mean, median, SD, minimum and maximum) of quantitative ECG data will be summarized by regimen for baseline, post-dosing, and change from baseline at each scheduled time point. For each regimen (period), baseline is defined as the last non-missing ECG measurement at or prior to predose (time relative to TAK-906 dosing) in the corresponding period. Only the ECGs collected at the scheduled visits or time points will be included in the summary. No inferential analysis will be performed for the observed ECGs.

For ECG interpretation data, shift table will be provided as the number of subjects to assess interpretation status change from baseline to each scheduled post-baseline measurement by regimen. In the ECG shift table, the best value out of triplicate ECG interpretations will be used to represent baseline evaluation, and the worst value will be used to represent post baseline evaluation.

All individual ECGs that meet Takeda's predefined criteria for markedly abnormal values (Appendix E) will be listed. The number and percentage of subjects with at least 1 markedly abnormal ECG measurement will be summarized by regimen. The mapping of the subjects who meet the MAV criteria will be listed as a table. All post dose ECGs within 7 days of the last dose, including both scheduled and unscheduled measurements, will be included in the MAV summaries.

All ECG data will be presented in the listings. ECG MAVs will be flagged in the listings.

7.11.5 Other Observations Related to Safety

Physical examination findings and all cases of overdose will be presented in data listings. No summary tables will be provided.

7.12 Interim Analysis

Not applicable.

7.13 Changes in the Statistical Analysis Plan

None.

8.0 REFERENCES

1. A Single-Sequence, Open-Label, 2-Period, Crossover Trial to Evaluate the Effect of the Potent CYP3A4 Inhibitor Itraconazole on the Single-Dose Pharmacokinetics of Oral TAK-906 in Healthy Adult Subjects, Takeda Development Center Americas, Inc., Protocol No. TAK-906-1003, dated 25 May, 2017.

Appendix A Schedule of Trial Procedures

	Screening	Period 1 (a)					Period 2						Follow-up/Early Termination
		Day					Day						10-14 days after last dose of TAK-906
Procedures/Assessments	**Day -28 to -2**	**-1**	**Pre-dose (Day 1)**	**1**	**2**	**3**	**1**	**2**	**3**	**4**	**5**	**6**	
Administrative Procedures													
Informed consent	X												
Inclusion/exclusion criteria	X	X	X										
Medical history/demographics	X												
Prior and concomitant medication review		----------Continuous Monitoring----------											
Clinic Procedures/Assessments													
Full physical examination	X	X (b)											X
Height	X												
Weight	X												
BMI	X												
12-Lead ECG	X		X(c)	X(c)		X				X(c)		X	X
Semirecumbent vital signs (heart rate [HR], systolic blood pressure and diastolic blood pressure	X		X(d)	X(d)		X		X		X(d)		X	X
Vital signs (respiratory rate, oral [at the floor of the mouth]/tympanic temperature) rate	X		X	X		X		X		X		X	X
TAK-906 administration				X						X			
Itraconazole administration (e)							X	X	X	X	X		
AE monitoring		---------Continuous Monitoring--------											
Laboratory Procedures/Assessments													
Hematology	X	X (b)					X (b)					X	X
Urinalysis	X	X (b)					X (b)					X	X
Chemistry	X	X (b)					X (b)					X	X
Serum follicle stimulating hormone (FSH)	X												
β-human chorionic gonadotropin (hCG)	X	X											X

Procedures/Assessments	Screening	Period 1 (a)					Period 2						Follow-up/Early Termination
		Day					Day						10-14 days after last dose of TAK-906
	Day -28 to -2	-1	Pre-dose (Day 1)	1	2	3	1	2	3	4	5	6	
Urine drug screen	X	X					X						
Urine alcohol test/alcohol breath test (f)	X	X					X						
Hepatitis screen	X												
Human immunodeficiency virus (HIV)	X												
Pharmacokinetics Evaluations													
CCI [redacted]													
CCI [redacted]													
Pharmacogenomic (PGx) Evaluations													
PGx DNA collection			X										
PGx RNA collection			X										
Other													
Confinement			X----------X							X----------X			
Meals fasting (i)				X						X	X		

(a) There will be a minimum 4 day washout between Periods 1 and 2, starting from administration of TAK-906 maleate on Day 1 of Period 1.
(b) Day 1 predose assessment may be done within approximately 24 hours prior to trial drug administration.
(c) Triplicate measurements to be conducted at 0 (predose), 1, 2, 4, 8 and 48 hours postdose (times relative to TAK-906 maleate dose).
(d) Measured at 0 (predose), 1, 2, 4, 8 and 48 hours postdose (times relative to TAK-906 maleate dose).
(e) Itraconazole will be administered once daily at the same time each day and 1 hour prior to TAK-906 maleate on Day 4.
(f) An alcohol breath test may be performed at the discretion of the investigator.
(g) CCI [redacted]
(h) CCI [redacted]
(i) Subjects will fast overnight at least 8 hour before dose of TAK-906 maleate on Day 1 of Period 1 and at least 8 hours before itraconazole and TAK-906 maleate doses on Day 4 of Period 2.

Appendix B Clinical Laboratory Tests and Screening

Chemistry

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

Hematology

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

Urinalysis

Protein	Glucose
Blood	Nitrite

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

Urine Drug Screen

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

Alcohol Screen

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

Screening - Serum

β–human chorionic gonadotropin (women only)	FSH (women only).
HIV test	Hepatitis panel, including hepatitis B surface antigen and anti-hepatitis C virus.

Appendix C Criteria for Identification of Markedly Abnormal Laboratory Values

Hematology—Criteria for Markedly Abnormal Values

Parameter	Unit	Low Abnormal	High Abnormal
Hemoglobin	Both	<0.8 × LLN	>1.2 × ULN
Hematocrit	Both	<0.8 × LLN	>1.2 × ULN
RBC count	Both	<0.8 × LLN	>1.2 × ULN
WBC count	Both	<0.5 x LLN	>1.5 x ULN
Platelet count	Conventional SI	<75 x 10^3/μL <75 x 10^9/L	>600 x 10^3/μL >600 x 10^9/L

LLN=lower limit of normal, RBC=red blood cell, ULN=upper limit of normal, WBC=white blood cell.

Serum Chemistry—Criteria for Markedly Abnormal Values

Parameter	Unit	Low Abnormal	High Abnormal
ALT	Both	--	>3x ULN
AST	Both	--	>3x ULN
GGT	Both	--	>3x ULN
Alkaline phosphatase	Both	--	>3x ULN
Total bilirubin	Conventional SI	-- --	>2.0 mg/dL >34.2 μmol/L
Albumin	Conventional SI	<2.5 g/dL <25 g/L	-- --
Total protein	Both	<0.8x LLN	>1.2x ULN
Creatinine	Conventional SI	--	>2.0 mg/dL >177 μmol/L
Blood urea nitrogen	Conventional SI		>30 mg/dL >10.7 mmol/L
Sodium	Conventional SI	<130 mEq/L <130 mmol/L	>150 mEq/L >150 mmol/L
Potassium	Conventional SI	<3.0 mEq/L <3.0 mmol/L	>6.0 mEq/L >6.0 mmol/L
Glucose	Conventional SI	<50 mg/dL <2.8 mmol/L	>350 mg/dL >19.4 mmol/L
Chloride	Conventional SI	<75 mEq/L <75 mmol/L	>126 mEq/L >126 mmol/L
Calcium	Conventional SI	<7.0 mg/dL <1.75 mmol/L	>11.5 mg/dL >2.88 mmol/L
Carbon dioxide	Conventional SI	<8.0 mEq/L <8.0 mmol/L	

ALT=alanine aminotransferase, AST=aspartate aminotransferase, GGT=γ-glutamyl transferase, LLN=lower limit of normal, ULN=upper limit of normal.

Appendix D Criteria for Abnormal Changes from Baseline of Vital Signs

Parameter	Unit	Lower Criteria	Upper Criteria
Pulse	bpm	<50	>120
Systolic blood pressure	mm Hg	<85	>180
Diastolic blood pressure	mm Hg	<50	>110
Body temperature	^{o}C	<35.6	>37.7

Appendix E Criteria for Markedly Abnormal Values for the 12-Lead ECG Parameters

Parameter	Lower Criteria	Upper Criteria
Heart rate	<50 beats per minute	>120 beats per minute
PR	≤120 milliseconds	≥200 milliseconds
QT Interval	≤300 milliseconds	≥460 milliseconds
QTcF Interval	≤300 milliseconds	≥500 milliseconds OR ≥30 milliseconds change from baseline and ≥450 milliseconds
QRS	≤60 milliseconds	≥120 milliseconds

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Pharmacovigilance Approval	07-Aug-2017 13:57 UTC
	Clinical Pharmacology Approval	07-Aug-2017 14:00 UTC
	Clinical Approval	07-Aug-2017 14:05 UTC
	Statistical Approval	07-Aug-2017 14:05 UTC
	Statistical Approval	07-Aug-2017 19:20 UTC