Title: A Randomized, Double-Blind, Placebo-Controlled, Single and Multiple Ascending Dose, Phase 1 Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of TAK-906 in Japanese Healthy Male Subjects

NCT Number: NCT03237156

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TAKEDA PHARMACEUTICALS

PROTOCOL

A Randomized, Double-Blind, Placebo-Controlled, Single and Multiple Ascending Dose, Phase 1 Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of TAK-906 in Japanese Healthy Male Subjects

Phase 1 TAK-906 Single and Multiple Ascending Dose Study in Japanese Healthy Male Subjects

Study Identifier: TAK-906-1004

Compound: TAK-906 (investigational ingredient code in Japan: TAK-906M)

Date: 6 June 2017

Version/Amendment Number: Initial Version

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1.0 STUDY SUMMARY

Name of Sponsor: Takeda Pharmaceutical Company Limited	**Compound:** TAK-906
Study Identifier: TAK-906-1004	**Phase:** 1
Protocol Title: A Randomized, Double-Blind, Placebo-Controlled, Single and Multiple Ascending Dose, Phase 1 Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of TAK-906 in Japanese Healthy Male Subjects	
Trial Design: This is a phase 1, randomized, double-blind, placebo-controlled, single and multiple ascending dose, parallel-group study in up to 3 cohorts of Japanese healthy male subjects, to assess the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of TAK-906. Each cohort will consist of 8 subjects where 6 subjects will be randomized to receive TAK-906 and 2 subjects will be randomized to receive matching placebo. The study population will be 24 Japanese healthy male subjects. The randomized subjects will receive a single dose of blinded study drug on Day 1 followed by multiple doses of blinded study drug twice daily (BID) for 5 days from Day 3 to Day 7, except that an evening dose of study drug will not be administered on Day 7. If a subject discontinues from the trial, a replacement subject may be enrolled, if deemed appropriate by the investigator and Sponsor. The investigational site should contact the Sponsor for the replacement subject's medication identification number. In Cohorts 1 and 2, subjects will be randomized to receive TAK-906 maleate 50 mg, 100 mg, or matching placebo. In Cohort 3, subjects will be randomized to receive TAK-906 maleate 10 mg, or matching placebo. For each cohort, follow-up assessments will occur on Day 14 which is 7 days after completion of the last treatment dose. Dose escalation to Cohort 2 will be based on a full blinded review of safety and tolerability data until follow-up assessments from Cohort 1. Cohort 3 will be conducted in parallel with Cohort 1 or 2. Dose level in Cohort 2 may be changed within the range up to 100 mg, as appropriate, based on safety and pharmacokinetic data in preceding cohorts, ie, 50 mg BID in Cohort 1 or 10 mg BID in Cohort 3 (if applicable) of this study; however, no higher dose than the proposed highest dose (100 mg BID) based on the exposures from the previous study CCI will be given without Sponsor and institutional review board (IRB) approval to revise the study protocol. In either Cohort 1, 2, or 3, each subject will be confined from Day -1 to the morning of Day 8 and discharged after the investigator's confirmation of no significant abnormality in his health through physical examination and tests on Day 8, at 24-hour after the morning dose of Day 7. A single dose and all morning doses of trial medication in multiple dose periods will be administered orally after fast of at least 10 hours that continues for at least 4 hours after dosing with restriction of water intake for at least 1 hour prior to and after dosing. The evening dose will be administered 12 hours after the morning dose and at least 2 hours after dinner. On Day 7, the trial medication will be administered only in the morning. The study drugs include TAK-906 maleate and matching placebo capsules. The capsules all have the same appearance.	
Trial Primary Objective: To evaluate safety and tolerability of single and multiple oral doses of TAK-906 in Japanese healthy male subjects. **Trial Secondary Objectives:** To evaluate PK and PD of single and multiple oral doses of TAK-906 in Japanese healthy male subjects.	
Trial Subject Population: Japanese healthy adult male subjects aged 20 to 60 years, inclusive.	
Planned Number of Subjects: Per cohort: 8 each (Cohorts 1, 2, and 3) (TAK-906: 6, placebo: 2) Estimated total: 24 (treated)	**Planned Number of Sites:** Estimated total: 1 site

Dose Levels: Single dose period: 10, 50, or 100 mg TAK-906 maleate single dose or placebo. Multiple dose period: 10, 50, or 100 mg TAK-906 maleate BID or placebo.	**Route of Administration:** Oral
Duration of Treatment: Single dosing on Day 1 and BID dosing for 5 days on Days 3 to 7 (morning dose only on Day 7), for a total of 6 dosing days.	**Planned Trial Duration:** Screening period: Days -28 to -2 Check-in: Day -1 Treatment period: Days 1 to 8 (single dose period: Days 1 and 2, multiple dose period: Days 3 to 8) Follow-up period: Days 9 to 14

Main Criteria for Inclusion:

- The subject is a Japanese healthy adult male, aged 20 to 60 years, inclusive, at the time of informed consent.
- The subject weighs at least 50 kg and has a body mass index (BMI) from 18.5 to 25 kg/m^2, inclusive at Screening.
- A male subject who is nonsterilized and sexually active with a female partner of childbearing potential agrees to use adequate contraception from the signing of informed consent to 12 weeks (84 days) after the last dose of study drug. The female partner of a male subject should also be advised to use adequate contraception.

Main Criteria for Exclusion:

- The subject has a history of any psychiatric disease that would interfere with the evaluation of study drug activity (prolactin concentration) or safety.
- The subject has a history of seizure or tardive dyskinesia.
- The subject has a history of hyperprolactinemia, pituitary adenoma, and/or hypothyroidism.
- The subject has a family history of prolonged QT.
- The subject has undergone previous gastric bypass surgery or currently has a gastric band fitted.
- The subject has dysphagia and/or inability to swallow study medication whole.
- The subject has a QT interval by the Fridericia correction method (QTcF) of >450 msec on the electrocardiogram (ECG) at Screening, at Check-in (Day -1), or prior to the first dose of study drug (Day 1 predose).
- The subject has abnormal Screening or Day -1 laboratory values that suggest a clinically significant underlying disease or any subject with the following lab abnormalities:
  - Transaminase (alanine aminotransferase and/or aspartate aminotransferase) and/or total bilirubin >1.5 × upper limit of normal.
  - Creatinine >1.2 mg/dL.

Main Criteria for Evaluation and Analyses:

The primary endpoint of the study:

- Safety and tolerability will be assessed through treatment-emergent adverse events (TEAEs) including corrected QT interval prolongation associated AE, neurologic AE, and hyperprolactinemia associated AE, physical examinations, vital signs, clinical laboratory tests, and 12-lead electrocardiogram (ECG).

The secondary endpoints will be assessed through evaluation of the following parameters:

- PK: Plasma and urine concentrations of TAK-906 and its metabolite M23.
- PD: Serum prolactin level.

Statistical Considerations:

Safety:

The following analyses will be based on the Safety Analysis Set.

A treatment-emergent AE (TEAE) is defined as an AE whose date of onset occurs on or after the start of study drug. TEAEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Frequency distribution will be provided by system organ class and preferred term for each regimen. TEAEs will be summarized by pooled placebo and each TAK-906 dose level for single dose period and combined single and multiple dose periods.

For continuous variables, the observed values and their changes from baseline will be summarized by dose over each scheduled sampling time using descriptive statistics. For categorical variables, shift tables showing the number of subjects in each category at baseline and each post-baseline visit will be provided by dose.

PK:

The following analyses will be based on the PK Analysis Set.

Plasma concentrations of TAK-906 and M23 will be summarized by dose over each scheduled sampling time using descriptive statistics. Individual plasma concentration data versus time will be presented in a data listing. Plasma PK parameters for TAK-906 and M23 will be summarized by dose over each scheduled sampling time using descriptive statistics (arithmetic mean, SD, median, minimum and maximum). In addition, geometric mean and coefficient of variation will be computed for C_{max} and AUC. Dose proportionality for TAK-906 and M23 plasma exposures (C_{max} and AUC) will be assessed statistically using a power function model.

Individual urine concentration data versus time will be presented in a data listing. The urine PK parameters for TAK-906 and M23will be summarized by dose using descriptive statistics.

PD:

The following analyses will be based on the PD Analysis Set.

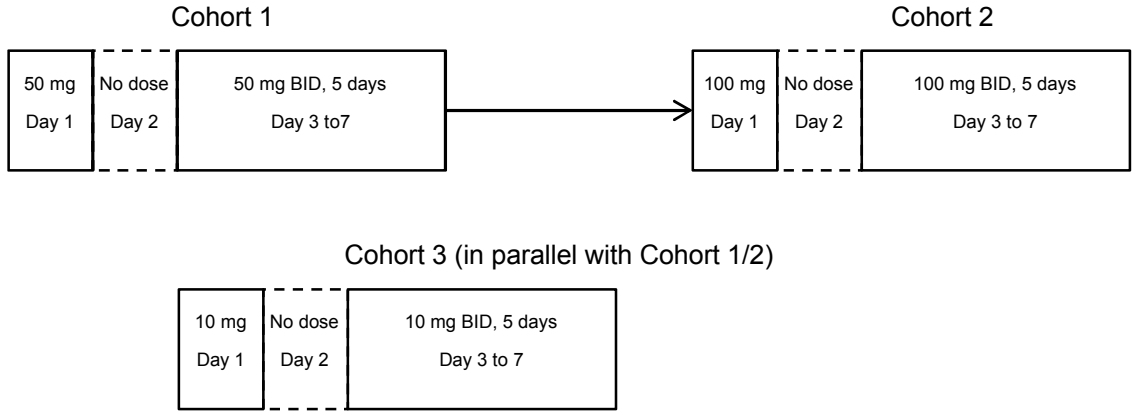
For the serum prolactin concentration, the observed values and their changes from baseline will be summarized by dose over each scheduled sampling time using descriptive statistics.

Sample Size Justification:

A sample size of 8 subjects per cohort (6 active: 2 placebo) will be used in this study, and is considered sufficient for the evaluation of TAK-906 safety, tolerability, PK and PD following oral single and multiple doses. The sample size is not based on statistical power considerations.

2.0 STUDY SCHEMATIC

Figure 2.a Schematic of Trial Design



Cohorts 1, 2, and 3

Screening Period	**Check-in**	**Single Dose Period**		**Multiple Dose Period**		**Follow-up Visit**
		Dose/Sample Collection /Safety Assessment	Sample Collection /Safety Assessment	Dose/Sample Collection /Safety Assessment	Sample Collection /Safety Assessment /Discharge	
Days -28 to -2	Day -1	Day 1	Day 2	Days 3 to 7	Day 8	Day 14
outpatient	←——— Confinement ——→					outpatient

BID=twice daily

3.0 SCHEDULE OF STUDY PROCEDURES

	Screening	Check-in	Single Dose Period			Multiple Dose Period							Follow-up
Study Day:	**Days -28 to -2**	**Day -1**	**Predose Day 1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**Early Termination Visit**	**Day 14**
Administrative Procedures													
Informed consent	X												
Inclusion/exclusion criteria	X	X	X										
Medical history/Demography	X												
Concomitant medications	----------Continuous Review----------												
Clinical Procedures/Assessments (a)													
Physical examination	X	X	X		X			X			X	X	X
Height, BMI	X												
Weight	X	X								X		X	X
Vital signs (b)	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG (c)	X	X	X	X	X			X		X	X	X	
Study drug administration (d)				X		X	X	X	X	X			
AE Monitoring	----------Continuous Monitoring----------												
Laboratory Procedures/Assessments (a)													
Hematology	X	X			X			X			X	X	X
Chemistry	X	X			X			X			X	X	X
Urinalysis	X	X			X			X			X	X	X
HBsAg, anti-HCV, HIV antibody/antigen, and syphilis screen	X												
Prolactin assessment for safety	X(i)												
Urine drug screen, urine cotinine test, and alcohol screen (urine alcohol test/alcohol breath test)	X												

	Screening	Check-in	Single Dose Period			Multiple Dose Period							Follow-up
Study Day:	**Days -28 to -2**	**Day -1**	**Predose Day 1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**Early Termination Visit**	**Day 14**
PK Evaluations													
Plasma sample for TAK-906 PK (e)			X	X	X	X	X	X	X	X	X	X (j)	
Urine sample for TAK-906 PK (f)			X	X	X					X			
PD Evaluations													
Serum sample for PD (g)			X	X	X	X	X	X	X	X	X	X	X
CCI													
				X									
Other													
Confinement		X	X	X	X	X	X	X	X	X	X	X (j)	

Footnotes are on the following page.

AE=adverse event, BMI=body mass index, CCI [redacted], ECG=electrocardiogram, HBsAg=hepatitis B virus surface antigen, HCV=hepatitis C virus, HIV=human immunodeficiency virus, PD=pharmacodynamics, CCI [redacted], PK=pharmacokinetics.

(a) Where applicable, all assessments will be conducted in the morning (predose on dosing days) except for Screening, Check-in, and Follow-up.
(b) Vital sign measurements will occur:
Days 1-2: Predose, 1, 2, 4, 6, and 24 hours post single dose.
Days 3-6: Before morning dose.
Days 7-8: Predose, 1, 2, 4, 6, and 24 hours post morning dose.
Day 14
(c) 12-lead ECG measurements will occur:
Days 1-2: Predose, 1, 2, 4, 6, and 24 hours post single dose.
Day 5: Predose, 1, and 2 hours post morning dose.
Days 7-8: Predose, 1, 2, 4, 6, and 24 hours post morning dose.
(d) TAK-906 or matching placebo will be administered as a witnessed dose at approximately 07:00-08:00 and at approximately 19:00-20:00. Daily study drug administration in the multiple dose period should be within ±5 minutes of nominal dosing times on Day 3. On Day 7, study drug administration time should be as close to the time of Day 3 dosing as possible. An evening dose of study drug will not be administered on Day 7.
(e) Plasma sample for TAK-906 PK and M23 will be collected:
Days 1-2: Predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hours post single dose.
Days 3-6: Just before morning dose.
Days 7-8: Predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hours post morning dose.
(f) Urine sample for TAK-906 PK and M23 will be collected:
Days 1-2: Predose (spot), 0-6, 6-12, and 12-24 hours post single dose.
Day 7: 0-6 and 6-12 hours post morning dose.
(g) Serum sample for PD will be collected:
Days 1-2: Predose, 1, 2, 4, 6, and 24 hours post single dose.
Days 3-6: Just before morning dose.
Days 7-8: Predose, 1, 2, 4, 6, and 24 hours post morning dose.
Day 14
CCI [redacted].
(i) Serum prolactin level will be measured at Screening by the local laboratory for safety assessment.
(j) For any early termination during Follow-up, outpatient assessments should be performed, and PK blood sample will not be collected.

4.0 INTRODUCTION

4.1 Background

TAK-906 is a peripherally selective dopamine (DA) D_2/D_3 receptor antagonist and being developed as a potential treatment for gastrointestinal (GI) motility disorders, such as diabetic or idiopathic gastroparesis.

Gastroparesis is a disorder of the stomach characterized by delayed gastric emptying in the absence of mechanical obstruction. After food intake, the normal stomach serves to triturate the food and to deliver it into the duodenum by peristalsis; however, this gastric motility is known to be reduced in patients with gastroparesis and the delayed gastric emptying causes gastrointestinal symptoms, such as abdominal bloating and vomiting. Idiopathic, diabetic, and postsurgical etiologies comprise the majority of gastroparesis cases [1].

The prevalence of gastroparesis in the United States (US) is 24.2 per 100,000 person [2]. In another report, the prevalence of gastroparesis is approximately 4% to 5% of the general population and higher prevalence is associated with diabetes mellitus patients; diabetic gastroparesis is present in 5% to 12% of overall diabetes mellitus population, particularly in 30% to 50% of patients with type 1 diabetes mellitus [3]. In Japan, a diagnostic procedure has not been established for gastroparesis and the prevalence has not been well described; however, considering the prevalence of gastroparesis in patients with diabetes mellitus in the US, gastroparesis seems not to be a rare disease but an infrequently diagnosed disease in Japan, where a number of potential patients are expected to be found.

Dopamine D_2 and D_3 receptors are demonstrated to be involved in the development of gastroparesis [4][5][6]. Activation of dopamine D_2 and D_3 receptors lying in the upper gastrointestinal tract and in the area postrema induces suppression of acetylcholine release, decreased muscle tension of the lower esophageal sphincter and stomach, and relaxation of stomach smooth muscle. Dopamine D_2/D_3 receptor antagonists are reported to eliminate the suppression of acetylcholine release by suppressing activation of dopamine D_2 and D_3 receptors, to increase lower esophageal sphincter and stomach muscle tension, and to promote the gastric emptying.

Currently in the US, there exists a large unmet medical need because there are no approved therapies for the chronic treatment of diabetic gastroparesis. Metoclopramide, a dopamine D_2 receptor antagonist, and domperidone, a peripherally-acting dopamine D_2/D_3 receptor antagonist, are prokinetic agents marketed in Japan. They are known to cause extrapyramidal symptoms (EPS) and cardiovascular side effects, respectively. The most notable toxicities of metoclopramide are a category of movement disorders known as EPS [7]. EPS are caused by blockade of dopamine D_2 receptors in the dorsal striatum and thus are potential side effects of all centrally-penetrant drugs that share this mechanism of action, particularly selective dopamine D_2 receptor antagonists. Of greatest concern is tardive dyskinesia, a severe and often irreversible EPS. The risk of developing tardive dyskinesia increases with dose level and duration of treatment and as such, the US package insert includes a black box warning regarding the chronic use of metoclopramide for longer than 12 weeks. Domperidone is a peripherally-acting dopamine D_2/D_3 receptor antagonist

marketed for use as an antiemetic and prokinetic agent in a number of countries worldwide including Japan, although not in the US due to its cardiovascular safety profile which includes risks for drug-induced long QT syndrome, torsades de pointes, and sudden cardiac death [8].

Nonclinical in vitro and in vivo pharmacology studies have demonstrated that TAK-906 has D_2/D_3 antagonism with a potency comparable to or greater than domperidone and metoclopramide. TAK-906 does not readily penetrate the blood brain barrier (BBB) and therefore it can block dopamine D_2/D_3 receptors in the area postrema outside of the BBB to reduce symptoms of gastroparesis, such as nausea and vomiting, but not block those inside of the BBB which are likely to cause EPS [9][10]. In addition, TAK-906 is a very weak inhibitor of the human ether-a-go-go related gene (hERG) channel, thus reducing the potential for fatal arrhythmias [8]. Therefore, TAK-906 is expected to exhibit comparable or greater prokinetic effects and less adverse effects compared with existing products on the market, which makes TAK-906 a promising drug for the treatment of gastroparesis.

CCI

4.2 Rationale for the Proposed Study

This is a phase 1, randomized, double-blind, placebo-controlled, single and multiple ascending dose, parallel-group study in Japanese healthy male subjects, to assess the safety, tolerability, PK, and PD of TAK-906.

TAK-906 is a peripherally-acting dopamine D_2/D_3 receptor antagonist belonging to a class of prokinetic drugs shown to be effective in the treatment of gastroparesis. However, chronic use of these agents has been limited due to their toxicity. Nonclinical in vitro and in vivo pharmacology studies have demonstrated that TAK-906 has D_2/D_3 antagonism with a potency comparable to or greater than domperidone and metoclopramide. In addition, TAK-906 is not expected to result in the adverse effects including EPS and cardiovascular event associated with these two agents due to its limited BBB penetration (relative to metoclopramide) and weak hERG channel affinity (relative to domperidone). As TAK-906 is expected to exhibit comparable or greater prokinetic effects and less adverse effects compared with existing dopamine D_2/D_3 receptor antagonists on the market, TAK-906 is being developed as a potential treatment for gastroparesis.

In Japan, no diagnostic procedure or criteria has not been established for gastroparesis, while a number of potential patients are expected to be found. Therefore, it is considered clinically important to promptly introduce TAK-906 in clinical settings by advancing its development simultaneously in Japan and other countries.

As described above, a foreign phase 1 study has been completed and shown that administration of single and multiple oral TAK-906 maleate doses has been well tolerated in healthy men and women and that TAK-906 is expected to have a better safety profile over existing products on the market. Based on theese results, a global phase 2 study in other countries is being contemplated. With intent to participate in the global phase 2 study from Japan, this study was planned to evaluate the safety and PK of TAK-906 in Japanese subjects and assess safety and pharmacokinetic data similarity between Japanese and non-Japanese subjects. In order to enable comparisons of non-Japanese subjects' safety and pharmacokinetic data in the foreign phase 1 study with those of the Japanese subjects in this study, this trial design, doses, and endpoints were set by referencing the foreign phase 1.

4.3 Benefit/Risk Profile

There will be no benefit to subjects in this study other than receiving physical examinations and obtaining information about their general health. Instead, patients with gastroparesis may benefit in the future from what can be learned in this study.

As for risk to subjects, clinical safety information is limited to data from the one foreign phase 1 trial.

For further information on TAK-906, please refer to the Investigator's Brochure.

5.0 TRIAL OBJECTIVES AND ENDPOINTS

5.1 Hypothesis

This study was designated based on the following hypotheses:

- TAK-906 will be safe and well tolerated in Japanese healthy male subjects in the doses to be tested.
- Following the first dose, one or more well-tolerated doses of TAK-906 will result in a 3-fold increase in serum prolactin at the maximum level of serum prolactin (C_{max}) as compared to baseline for each treatment period (single dose period, multiple dose period).

5.2 Trial Objectives

5.2.1 Trial Primary Objective

The primary objective of the study is to evaluate safety and tolerability of single and multiple oral doses of TAK-906 in Japanese healthy male subjects.

5.2.2 Trial Secondary Objective

The secondary objective of the study is to evaluate PK and PD of single and multiple oral doses of TAK-906 in Japanese healthy male subjects.

5.2.3 Trial Exploratory Objectives

CCI

5.3 Endpoints

5.3.1 Primary Endpoint

The study's primary endpoints of safety and tolerability will be assessed through TEAEs including QTc prolongation associated AE, neurologic AE, and hyperprolactinemia associated AE, physical examinations, vital signs, clinical laboratory tests, and 12-lead electrocardiogram (ECG).

5.3.2 Secondary Endpoints

Secondary endpoints include:

1. PK: Plasma and urine concentrations of TAK-906 and its metabolite, M23.
2. PD: Serum prolactin level.

6.0 TRIAL DESIGN AND DESCRIPTION

6.1 Trial Design

This is a phase 1, randomized, double-blind, placebo-controlled, single and multiple dose, parallel-group study in up to 3 cohorts of Japanese healthy male subjects, to assess the safety, tolerability, PK, and PD of TAK-906.

Each cohort will consist of 8 subjects where 6 subjects will be randomized to receive TAK-906 and 2 subjects will be randomized to receive matching placebo. The study population will be 24 Japanese healthy male subjects. The randomized subjects will receive a single dose of blinded study drug on Day 1 followed by multiple doses of blinded study drug BID for 5 days from Day 3 to Day 7, except that an evening dose of study drug will not be administered on Day 7. If a subject discontinues from the trial, a replacement subject may be enrolled, if deemed appropriate by the investigator and Sponsor. The investigational site should contact the Sponsor for the replacement subject's medication identification number.

In Cohorts 1 and 2, subjects will be randomized to receive TAK-906 maleate 50 mg, 100 mg, or matching placebo. In Cohort 3, subjects will be randomized to receive TAK-906 maleate 10 mg, or matching placebo. For each cohort, follow-up assessments will occur on Day 14 which is 7 days after completion of the last treatment dose. Dose escalation to Cohort 2 will be based on a full blinded review of safety and tolerability data until follow-up assessments from Cohort 1. Cohort 3 will be conducted in parallel with Cohort 1 or 2. Dose level in Cohort 2 may be changed within the range up to 100 mg, as appropriate, based on safety and pharmacokinetic data in preceding cohorts, ie, 50 mg BID in Cohort 1 or 10 mg BID in Cohort 3 (if applicable) of this study; however, no higher dose than the proposed highest dose (100 mg BID) CCI [redacted] will be given without Sponsor and institutional review board (IRB) approval to revise the study protocol.

The planned dose levels of TAK-906 to be evaluated are outlined in Table 6.a.

Table 6.a Summary of Dose Cohorts

Cohort (a)	TAK-906 maleate Dose (a, b, c)		Subjects
	Single Dose Period	Multiple Dose Period (d)	
1	50 mg single dose on Day 1	50 mg BID for 5 days from Days 3 to 7	6 TAK-906 2 Placebo
2	100 mg single dose on Day 1	100 mg BID for 5 days from Days 3 to 7	6 TAK-906 2 Placebo
3	10 mg single dose on Day 1	10 mg BID for 5 days from Days 3 to 7	6 TAK-906 2 Placebo

BID=twice daily

(a) Dose escalation to Cohort 2 will be based on a full blinded review of safety and tolerability data until follow-up assessments from Cohort 1. Cohort 3 will be conducted in parallel with Cohort 1 or 2.

(b) A single dose and all morning doses of trial medication in multiple dose periods will be administered after fast of at least 10 hours that continues for at least 4 hours after dosing with restricted water intake for at least 1 hour prior to and after dosing. The evening dose will be administered 12 hours after the morning dose and at least 2 hours after dinner.

(c) Dose level in Cohort 2 may be changed within the range up to 100 mg, as appropriate, based on safety and pharmacokinetic data in preceding cohorts, ie, 50 mg BID in Cohort 1 or 10 mg BID in Cohort 3 (if applicable) of this study

(d) An evening dose of study drug will not be administered on Day 7.

6.2 Dose Escalation

The investigator will comprehensively examine the blinded safety results (AEs, physical examinations, vital signs, records of laboratory tests, and 12-lead ECG findings) obtained at all examinations by 14 days after the start of study drug administration in Cohort 1 and then determines the entry of Cohort 2 after discussion(s) with the Sponsor, and if appropriate, with medical experts.

Other criteria to consider discontinuation of the entry of Cohort 2 are as follows.

1. On an occasion that a SAE, of which relationship to the study drug cannot be denied, is observed.
2. At the onset of an AE for which relationship to the study drug cannot be denied and for which it is considered difficult to give medications continuously.

Furthermore, the maximum dose in this study was set at 100 mg BID for Cohort 2, based on the data from preceding studies, as described in Section 6.3.2. Dose level in Cohort 2 may be changed within the range up to 100 mg, as appropriate, based on the safety and pharmacokinetic data of preceding cohorts, ie, 50 mg BID in Cohort 1 or 10 mg BID in Cohort 3 (if applicable) of this study.

6.3 Rationale for Trial Design, Dose, and Endpoints

6.3.1 Rationale of Trial Design

In this study, a single dose period will be followed by a multiple dose period in each cohort CCI [redacted] Therefore, combining single and multiple doses in one study, with safety evaluations for at least 24 hours after the single dose is considered appropriate for the assessment of safety and PK in Japanese subjects receiving single and multiple doses of TAK-906 maleate. For each cohort, follow-up assessments will occur on Day 14 which is 7 days after completion of the last treatment dose, based on an 11 hour half-life ensuring that TAK-906 PK washout will be completed in 4 days.

Double-blind fashion using a matching placebo were selected for this first study in Japanese healthy male volunteers in order to adequately evaluate safety in Japanese subjects.

6.3.2 Rationale for Dose

CCI [redacted] The proposed starting dose is 50 mg BID and the proposed highest dose is 100 mg BID. Several considerations were given in selecting these doses: safety, tolerability, PK and PD (serum prolactin concentration).

Based on the overall nonclinical safety profile, the dog was considered the most sensitive species for TAK-906 and was used as the basis for the maximum recommended starting dose (MRSD) in the foreign phase 1 study. The TAK-906 maleate no-observed-adverse-effect level (NOAEL) in the pivotal 28-day repeat-dose study in dogs was 50 mg/kg/day, at which central nervous system (CNS)-associated pharmacological effects typical of this pharmacologic class occurred on multiple occasions in all animals, including mild sedation, mild intermittent and/or continuous tremors and ataxia. The lowest observed effect level (LOEL) for CNS effects in the dog was considered to be 10 mg/kg/day. At 1 mg/kg/day of TAK-906 mateate, a single occurrence of mild tremors was observed in 1 female dog on Day 1 and thus a 1 mg was considered an appropriately conservative dose at which to establish MRSD. The MRSD of 0.06 mg/kg/day (3.6 mg/day per 60 kg person) was calculated based on human equivalent dose converted using body surfice area and safety factor (10). Based on the results, a dose of 5 mg is considered as an safe initial clinical dose. In the foreign phase 1 study, single dose ranging from 5 to 300 mg and multiple doses of 50 and 100 mg BID for 5 days were examined. From the results, favorable safety and tolerability of TAK-906 in non-Japanese subjects was demonstrated within the range of doses studied.The proposed starting dose for this study is 50 mg BID CCI [redacted] At a dose of 50 mg BID at steady state (AUC_{24} 116 h*ng/mL; C_{max} 31.2 ng/mL), AUC and C_{max} exposure margins at the dog LOEL for CNS effects are ≥3-fold and ≥8-fold, respectively.

The proposed highest dose for this study is 100 mg BID [redacted]
There was little if any accumulation in serum prolactin concentrations with repeated dosing. As TAK-906 maleate dosing at 100 mg BID is predicted to be associated to nearly maximum prolactin production at steady state, 100 mg BID is considered an appropriate maximum dose for examination. This regimen was shown to be safe and well tolerated in non-Japanese subjects. In addition, this regimen was associated with a geometric means of AUC_{12} of 200.5 h*ng/mL and C_{max} of 71.6 ng/mL as TAK-906 exposures in non-Japanese subjects, and provides approximately 15- and 27-fold margin in daily exposure compared with the exposures in female dogs, which are lower than those in male dogs (AUC 10800 and 5880 h*ng/mL, C_{max} 4340 and 1900 ng/mL in male and female dogs, respectively) observed at the dog NOAEL of 50 mg/kg/day, respectively. Modification of this dose level may be taken into consideration depending onpreceding Cohort 1 results, in which dose level will corresponding to the 50 mg BID starting dose.

In this study, a 10 mg BID dose regimen will also examined in Cohort 3. The regimen was selected to enable safety, PK, and PD evaluations over a wider dose range than that for the multiple dose period in the foreign phase 1 study. This cohort will be conducted in parallel with the other cohorts of 50 mg BID or 100 mg BID.

6.3.3 Rationale for Endpoints

6.3.3.1 Safety Endpoints

The commonly used safety endpoints of AEs, physical examinations, vital signs, clinical laboratory tests, and 12-lead ECG assessment will be used in this study as safety endpoints. In addition, considering the mechanism of action of TAK-906 and the safety profile of existing dopamine D_2/D_3 receptor antagonists on the market, the following AEs will be monitored more carefully: QTc prolongation associated AE, neurologic AE, and hyperprolactinemia associated AE.

Consistently elevated serum prolactin levels greater than 30 ng/mL in the absence of pregnancy and postpartum lactation are indicative of hyperprolactinemia. Hyperprolactinemia can result in galactorrhea, amenorrhea, and infertility in females, and in impotence and hypogonadism in males. Serum prolactin levels measured for PD analysis will not be used for safety evaluations by the investigator or sub-investigator.

6.3.3.2 PK Endpoints

To assess the PK of TAK-906 (at single and multiple oral doses up to 100 mg and 100 mg BID, respectively) in Japanese healthy male subjects, plasma and urine concentration of TAK-906 and its metabolite, M23 will be examined, and the following PK parameters for TAK-906 will be derived:

- Single dose period (Day 1): AUC_{∞}, AUC_t, C_{max}, t_{max}, Ae_t, $f_{e,t}$, CL_R
- Multiple dose period (Day 7): $AUC_{\tau,ss}$, $C_{max,ss}$, $t_{max,ss}$, Ae_{τ}, $f_{e,\tau}$, CL_R

Other PK parameters maybe calculated if deemed necessary for the interpretation of data.

6.3.3.3 PD Endpoints

The following PD parameters for serum prolactin will be derived:

- Single dose period (Day 1): AUC_t, C_{max}
- Multiple dose period (Day 7): $AUC_{\tau,ss}$, $C_{max,ss}$

Other PD parameters maybe calculated if deemed necessary for the interpretation of data.

Serum prolactin levels will be measured as a target engagement marker. Dopamine inhibits prolactin production by pituitary lactotroph cells. When the D_2 receptor is inhibited, serum prolactin levels rise and can serve as a marker for dopamine D_2 receptor engagement.

CCI

[redacted]

6.3.4 Critical Procedures Based on Trial Objectives: Timing of Procedures

For this trial, the collection of blood samples for TAK-906 PK is the critical procedure.

- At any post-dose time point, the blood samples for TAK-906 PK need to be collected as close to the exact nominal time point as possible.
- All other procedures should be completed as close as possible, either before or after these prescribed/scheduled times.
- When ECG and/or vital signs measurements are scheduled at the same time as PK sampling, the blood draw will take priority and ECG and/or vital signs will be obtained within an acceptable time window (see Appendix C).
- The order of priority can be changed during the trial with joint agreement of the investigator and the Sponsor.
- Any nonscheduled procedures required for urgent evaluation of a safety concern will take precedence over all routine scheduled procedures.

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

Dose level in Cohort 2 may be changed within the range up to 100 mg, as appropriate, based on the safety and pharmacokinetic data of preceding cohorts, ie, 50 mg BID in Cohort 1 or 10 mg BID in Cohort 3 (if applicable) of this study.

6.5 Trial Beginning and End/Completion

6.5.1 Definition of Beginning of the Trial

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

6.5.2 Definition of End of the Trial

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

6.5.3 Definition of Trial Discontinuation

Trial discontinuation because of nonsafety reasons, such as:

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

Trial discontinuation because of safety reasons:

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

6.5.4 Criteria for Premature Termination or Suspension of the Trial

6.5.4.1 Criteria for Premature Termination or Suspension of the Trial

The study will be completed as planned unless 1 or more of the following criteria are satisfied that require temporary suspension or early termination of the study.

1. 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 TAK-906, such that the risk is no longer acceptable for subjects participating in the study.
2. Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.
3. Two or more subjects in any single cohort or across more than 1 cohort experience any of the Takeda Medically Significant List events (as outlined in Table 10.a).
4. Two or more subjects in any single cohort experience a QTcF of >500 msec or an increased QTcF of >60 msec relative to baseline.
5. Abnormal liver function:

a. Two or more subjects in any single cohort or across more than 1 cohort experience alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) elevations of >5 × upper limit of normal (ULN) in the absence of a concomitant bilirubin increase.

b. One or more subjects in any single cohort experience ALT and/or AST elevations of >3 ×ULN in the presence of a total bilirubin increase of >2 ×ULN or an international normalized ratio (INR) of >1.5 without findings of cholestasis or other alternate etiology to explain the elevations (ie, "Hy's Law cases").

c. Two or more subjects in any single cohort or across more than 1 cohort experience ALT and/or AST elevations of >3 ×ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).

6.5.4.2 Procedures for Premature Termination or Suspension of the Trial

In the event that the Sponsor, an IRB, or a 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.

6.5.5 Criteria for Premature Termination or Suspension of an Investigational Site

6.5.5.1 Criteria for Premature Termination or Suspension of an Investigational Site

An investigational 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.

6.5.5.2 Procedures for Premature Termination or Suspension of an Investigational Site

In the event that the Sponsor, an IRB, or a 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 the first dose of study drug.

7.1 Inclusion Criteria

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

1. In the opinion of the investigator or sub-investigator, the subject is capable of understanding and complying with protocol requirements.
2. The subject signs and dates a written, informed consent form prior to the initiation of any study procedures.
3. The subject is a Japanese healthy adult male, aged 20 to 60 years, inclusive, at the time of informed consent.
4. The subject weighs at least 50 kg and has a body mass index (BMI) from 18.5 to 25 kg/m^2, inclusive at Screening.
5. A male subject who is nonsterilized and sexually active with a female partner of childbearing potential agrees to use adequate contraception* from the signing of informed consent to 12 weeks (84 days) after the last dose of study drug. The female partner of a male subject should also be advised to use adequate contraception*.

* Definitions and procedures for adequate contraception and pregnancy avoidance, and reporting responsibilities are defined in Appendix B.

[Justification for inclusion criteria]

Criteria 1, 2, 3 and 5 are set as standard criteria for the conduct of clinical pharmacological studies in healthy adults.

Criterion 4

Since whole blood collections of 400 mL from individuals weighing less than 50 kg is harmful to health according to the Act on Securing a Stable Supply of Safe Blood Products (Ministry of Health and Welfare [MHW] ordinance No. 22 in 1956) [11], the lower weight limit is set at 50 kg.

For BMI, Japanese subjects are to be within range of the standard weight according to the Criteria for Obesity Disease proposed by the Japan Society for the Study of Obesity [12].

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 16 weeks (112 days) prior to the first dose of study drug.
2. The subject has received TAK-906 in a previous clinical study or as a therapeutic agent.

3. The subject is an immediate family member of or an investigational site employee, or is in a dependent relationship with an investigational 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 neurologic, cardiovascular, pulmonary, hepatic, renal, metabolic, gastrointestinal, or endocrine disease or other abnormality, which may impact the ability of the subject to participate in the study or potentially confound its results.
5. The subject has a history of any psychiatric disease that would interfere with the evaluation of study drug activity (prolactin concentration) or safety.
6. The subject has a history of seizure or tardive dyskinesia.
7. The subject has a history of hyperprolactinemia, pituitary adenoma, and/or hypothyroidism.
8. The subject has a family history of prolonged QT.
9. The subject has undergone previous gastric bypass surgery or currently nad a gastric band fitted.
10. The subject has dysphagia and/or inability to swallow study medication whole.
11. The subject has a known hypersensitivity to any component of the TAK-906 formulation or related compounds.
12. The subject has a history of drug abuse (defined as any illicit drug use) or a history of alcohol abuse within 2 years prior to the Screening visit, or is unwilling to agree to abstain from alcohol and drugs throughout the study, or has a positive urine test result for drugs of abuse or a positive alcohol screen (urine alcohol test/breath test) result for alcohol at Screening.
13. The subject has taken any excluded medication, supplements, or dietary products during the time periods listed in the Excluded Medications, Supplements, and Dietary Products table in Section 7.3.
14. If male, the subject intends to donate sperm during the course of this study or for at least 12 weeks (84 days) after the last dose of study drug.
15. The subject has current or recent (within 24 weeks [168 days]) gastrointestinal disease that would be expected to influence the absorption of drugs (ie, a history of malabsorption, esophageal reflux, peptic ulcer disease, erosive esophagitis, frequent [more than once per week] occurrence of heartburn, or any surgical intervention).
16. The subject has a history of cancer, except basal cell carcinoma which has been in remission for at least 5 years prior to Day 1.
17. The subject has a positive test result for hepatitis B virus surface antigen (HBsAg), hepatitis C virus (HCV) antibody, human immunodeficiency virus (HIV) antibody/antigen, or serological reactions for syphilis at Screening.

18. The subject has used nicotine-containing products (including but not limited to cigarettes, pipes, cigars, chewing tobacco, nicotine patch or nicotine gum) within 4 weeks (28 days) prior to the first dose of study drug. Cotinine test is positive at Screening.
19. The subject has poor peripheral venous access.
20. The subject has undergone whole blood collection of at least 200 mL within 4 weeks (28 days) or at least 400 mL within 12 weeks (84 days) prior to the start of study drug administration.
21. The subject has undergone whole blood collection of at least 800 mL in total within 52 weeks (364 days) prior to the start of study drug administration.
22. The subject has undergone blood component collection within 2 weeks (14 days) prior to the start of study drug administration.
23. The subject has a Screening or Check-in (Day -1) ECG that was abnormal (clinically significant).
24. The subject has a QTcF of >450 msec on the ECG at Screening, at Check-in (Day -1), or prior to the first dose of study drug (Day 1 predose).
25. The subject has abnormal Screening or Day -1 laboratory values that suggest a clinically significant underlying disease or any subject with the following lab abnormalities:

- Transaminase (ALT and/or AST) and/or total bilirubin >1.5 ×ULN.
- Creatinine >1.2 mg/dL.

26. The subject who, in the opinion of the investigator or sub-investigator, is unlikely to comply with the protocol or is unsuitable for any other reason.

[Justification for exclusion criteria]

Criterion 1 is set to specify a minimum interval not affected by any previous clinical trial in order to ensure the safety of subjects, in reference to “General Considerations for Clinical Trials” [13].

Criteria 2, 3, 4, 12, 13, 14, 16,17, 18, 19, and 26 are set as standard criteria for clinical pharmacological studies in healthy adults and in consideration of subjects’ safety.

Criterion 5 is set due to the possibility of effects on safety and PD evaluations.

Criterion 6, 7, 8, 9, 11, 23, 24, and 25 are set in consideration of subjects’ safety.

Criterion 10 is set due to the possibility of effects on PK evaluations.

Criterion 13 is set as a standard criterion for clinical pharmacological studies in healthy adults and in consideration of subjects’ safety, and also due to the possibility of effects on PK evaluations.

Criterion 15 is set in consideration of subjects’ safety and also due to the possibility of effects on PK evaluations.

Criteria 20 to 22 are set in accordance with the Act on Securing a Stable Supply of Safe Blood Products (MHW ordinance No. 22 in 1956) [11].

7.3 Excluded Medications, Supplements, Dietary Products

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

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

28 days prior to treatment (Day 1) to Follow-up	7 days prior to treatment (Day 1) to Follow-up	7 days prior to treatment (Day 1) to Discharge (Day 8)	24 hours prior to treatment (Day 1) to Discharge (Day 8)
• Prescription medications • OTC medications • Neutraceuticals (St. John's wort, ginseng, kava kava, ginkgo biloba, and melatonin) • Chinese herbals • Immunization/Vaccines • Nicotine-containing products	• Grapefruit/ grapefruit juice • Brassica vegetables (eg, kale, broccoli, watercress, collard greens, kohlrabi, Brussels sprouts, and mustard) • Charbroiled meats	• Vitamin supplements • Alcohol-containing products	• Caffeine-containing products • Fruit juice

OTC=over-the-counter.
Note: If required to treat an AE, certain medications may be allowed after discussion and agreement between the Sponsor and the investigator.

Subjects must be instructed not to take any medications including over-the-counter (OTC) products, without first consulting with the investigator or sub-investigator.

7.4 Diet, Fluid, Activity

7.4.1 Diet and Fluid

Subjects must abstain from all food and drink (except water) at least 8 hours before any clinical laboratory evaluations. On a day of study drug administration, subjects must not drink water, with the exception of water (240 mL) to take medication, between 1 hour prior to and 1 hour after dosing.

On the day of Check-in (Day -1), dinner will be consumed by 21:00. On Days 3 through 7, dinner will be taken at least 2 hours before evening doses (no evening dose on Day 7).

Breakfast must not be taken on the all days of study drug administration. The subjects must fast for 10 hours or more prior to and 4 hours after a single dose and all morning doses of trial medication in multiple dose periods.

An overview of the diet/meal considerations is presented in Table 7.b.

Table 7.b Overview of Diet/Meal Considerations

Cohorts 1, 2, and 3		
Day 1		
Approximate Time	Dose	Meal
08:00-09:00	X	No breakfast
12:00-13:00		Standard Lunch
19:00-20:00		Standard Dinner
Day 2		
Approximate Time	Dose	Meal
08:00-09:00		Standard Breakfast
12:00-13:00		Standard Lunch
19:00-20:00		Standard Dinner
Days 3 through 7		
Approximate Time	Dose	Meal
08:00-09:00	X	No breakfast
12:00-13:00		Standard Lunch
17:00-18:00		Standard Dinner (at least 2 hours before evening dose)
20:00-21:00	X (No evening dose on Day 7)	

During hospitalization, subjects will take given meals and will not be allowed to take any other food. The caloric content and meal composition will be the same for each cohort.

After discharge, excessive eating or drinking should be avoided until all follow-ups are completed.

7.4.2 Activity

Supine positions are not allowed for 1 hour after dosing, unless irequired for examinations, etc.

Excessive exercise is not allowed during the study period. Subjects should do 15 minutes of light exercise a day during the hospitalization.

Blood donations are not allowed for at least 12 weeks (84 days) after the final examination in this study.

If a subject visits another medical institution during the study period, the investigator or sub-investigator should be informed of the visit in advance whenever possible, and should be reported the circumstances and therapy after visit. The investigator should communicate that medical institution about the subject's participation in the study.

No photosafety assessment has been performed to date with TAK-906; therefore, subjects should be cautioned to avoid exposure to direct sunlight during hospitalization.

7.5 Documentation of Subjects Failure

The investigator or sub-investigator must account for all subjects who sign informed consent. If a subject is withdrawn from the study before the first study drug administration, the investigator or sub-investigator should complete the electronic case report form (eCRF).

Primary reasons for subject failure are to be recorded in the eCRF using the following categories:

- Death.
- AE.
- Screen Failure (failed inclusion criteria or did meet exclusion criteria) <specify reason>.
- Protocol deviation.
- Lost to follow-up.
- Withdrawal by subject <specify reason>.
- Study terminated by Sponsor.
- Sample size sufficient.
- Other <specify reason>.

Subject identification numbers assigned to subjects who fail screening should not be reused. However if a reserve subject is to participate in another cohort, the same subject identification number may be used.

7.6 Criteria for Discontinuation or Withdrawal of a Subject

Primary reasons for discontinuation or withdrawal of a subject from the study or study drug should be recorded in the eCRF using the following categories. For subject failure, refer to Section 7.5.

1. Death. The subject died on study.

   Note: If the subject dies on study, the event will be considered as SAE. See Section 10.2.9.3 for the reporting procedures.

2. AE. The subject has experienced an AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the AE.

   In multidose studies, study drug should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until the subject's laboratory profile has returned to normal/baseline status, see Section 9.2.8), if the following circumstances occur at any time during study drug treatment:

   - Liver Function Test (LFT) Abnormalities
     - ALT or AST >8×ULN, or
     - ALT or AST >5×ULN and persists for more than 2 weeks, or

- ALT or AST >3×ULN in conjunction with elevated total bilirubin >2×ULN or INR >1.5, or
- ALT or AST >3×ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).

- QT prolongation
  - QTcF >500 msec or ΔQTcF (change from baseline in QTcF) >60 msec.

3. Protocol deviation. The discovery post-dose that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.
4. Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented in the subject's source documentation.
5. Withdrawal by subject. The subject 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).
6. Study terminated by the Sponsor. The Sponsor terminates the study.
7. Other

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

7.7 Procedures for Discontinuation or Withdrawal of a Subject

The investigator or sub-investigator may discontinue a subject's study participation at any time during the study if the subject meets the study termination criteria described in Section 7.6. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator or sub-investigator. In addition, efforts should be made to perform all procedures scheduled for the Early Termination Visit.

7.8 Subject Replacement

If a subject discontinues from the trial, a replacement subject may be enrolled, if deemed appropriate by the investigator and Sponsor. The investigational site should contact the Sponsor for the replacement subject's medication identification number.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

8.1 Clinical Study Drug

[Compound]

Code name: TAK-906

The study drugs include TAK-906 maleate and matching placebo capsules. The capsules all have the same appearance.

Dosage form and strength:

Category of study drug	Dosage Form	Strength
TAK-906 maleate 5 mg capsules	Capsule	One capsule containing 5 mg of TAK-906 maleate.
TAK-906 maleate 25 mg capsules	Capsule	One capsule containing 25 mg of TAK-906 maleate.
Placebo capsules	Capsule	One capsule containing microcrystalline cellulose NF in place of TAK-906 maleate.

[Package]

TAK-906 maleate and matching placebo capsules are packaged in high density polyethylene (HDPE) bottles with polypropylene caps and induction seals.

[Manufacturing]

TAK-906 maleate capsules and placebo capsules were manufactured by Takeda Pharmaceutical Company Limited (and formerly by Altos Therapeutics, LLC).

8.1.1 Clinical Study Drug Labeling

The labels affixed to the HDPE bottles give a description of the study drug (drug name, count, strength, storage conditions, manufacturing number, and expiration date), the study number, the name and address of the Sponsor, and state that the drug is for study use only.

8.1.2 Clinical Study Drug Inventory and Storage

TAK-906 maleate and matching placebo capsules may be stored at controlled room temperature (20°C to 25°C, with excursions allowed between 15°C to 30ºC) conditions per United States Pharmacopeia (USP).

Study drug must be kept in an appropriate, limited-access, secure place until it is used or returned to the Sponsor or designee for destruction. Study drugs must be stored under the conditions specified on the label, and remain in their original container until dispensed bottle containing one dose of study drug. A daily temperature log of the drug storage area must be maintained every working day.

8.1.3 Clinical Study Drug Blinding

Randomization personnel designated by the investigational site and it's assistant will retain the blind according to the randomization schedule and procedure, by affixing a label with a medication identification number on each dispensing bottle containing one dose of TAK-906 maleate 5 mg, TAK-906 maleate 25 mg or matching placebo; this should be done in the room where the other site personnel or the Sponsor employees are kept out.

8.1.4 Randomization Code Creation and Storage

Randomization responsible personnel designated by the Sponsor will prepare the randomization schedule and procedure prior to the start of the study. All randomization information will be stored in a secured area, accessible only by authorized personnel.

8.1.5 Clinical Trial Blind Maintenance/Unblinding Procedure

The investigator must store the emergency key until the time of an emergency blind break or the end of the trial.

Since maintenance of the blind may be compromised because of results from drug concentrations and PD assessments, such results should not be disclosed prior to blind breaking. In the event that results must be reported to the investigator prior to breaking the blind, all efforts should be made to maintain the blind (eg, by changing a medication identification number in order to avoid identification of subjects by laboratory site personnel). Detailed procedures for measuring subject drug concentration levels and PD assessments are provided in the separately created procedure for directions on the handling of biological samples for measuring drug concentrations and PD assessments.

To unblind a subject, the study drug blind can be obtained by opening a sealed envelope.

The Sponsor must be notified as soon as possible if the study drug blind is broken. The date, time, and reason the blind is broken must be recorded in the document called Record of Early Blind-Breaking and the same information (except the time) must be recorded in the (e)CRF.

If any site personnel are unblinded to a subject, study drug must be stopped immediately and that subject must be withdrawn from the study.

No change should be made to any subject assessment after unblinding.

8.1.6 Accountability and Destruction of Sponsor-Supplied Drugs

The on-site pharmacist (a site designee) will receive the pharmacy manual created by the Sponsor, and follow the procedures for manageing the Sponsor-supplied drug supplies. A copy of these procedures will be provided to the investigator as well. The manual will provide instructions on ensuring appropriate receipt, handling, storage, management, and dispensation of the Sponsor-supplied drug. The manual will also describe procedures for the collection of unused medications from the subject and their return to the Sponsor, or the destruction of any unused supplies.

The on-site pharmacist (a site designee) will immediately return any unused study drugs in a sealed package to the Sponsor after the study is closed at the investigational site.

9.0 STUDY PROCEDURES

The investigator or sub-investigator should collect data according to the procedures described in the following sections. For each procedure, subjects are to be assessed by the same investigator, sub-investigator or site designee whenever possible. The Schedule of Study Procedures is located in Section 3.0.

9.1 Administrative Procedures

9.1.1 Informed Consent Procedure

Informed consent must be obtained prior to the initiation of any study procedures. The requirements of informed consent are described in Section 13.2.

A separate informed consent form pertaining to the collection, storage, and analysis of samples must be obtained prior to collecting any blood sample for pharmacogenomic research for this study.

9.1.1.1 Assignment of Subject Identification Numbers

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

9.1.1.2 Study Drug Assignment

Subjects will be assigned, sequential in ascending order of their subject identification number, to receive study drug according to the randomization schedule for each cohort.

Subjects will be assigned to receive a 4-digit medication identification number. The number will be assigned by the investigational site personnel in sequential order beginning with 1001 and ending with 1008 in Cohort 1, beginning with 2001 and ending with 2008 in Cohort 2, and beginning with 3001 and ending with 3008 in Cohort 3. The 4-digit number will be used by the investigational site to facilitate the prelabeling of PK and PD samples, and will be the only subject identifier used on all PK and/or PD sample collections. It should also be contained on the PK and PD transport vials shipped to the bioanalytical laboratory, and will be used by the laboratory to report the subject data results. The 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. Furthermore, if treatment is given to a reserve subject, the study drug with the medication identification number for the initial subject who fails screening will be used. And if a subject is replaced, the study drug with a different medication identification number from that for the withdrawn subject will be used for the replacement subject.

9.1.2 Inclusion and Exclusion

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

9.1.3 Medical History/Demography

Demographic information to be obtained will include date of birth, sex, race as described by the subject, height, weight, caffeine use, alcohol use, and smoking classification of the subject.

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases that resolved within 1 year prior to the signing of informed consent. Ongoing conditions will be considered concurrent medical conditions. This includes clinically significant laboratory, ECG, or physical examination abnormalities noted at screening/baseline examination. Any conditions (ie, diagnoses) should be described.

Medication history information to be obtained includes any medication relevant to eligibility criteria and safety evaluations stopped at or within 4 weeks (28 days) prior to the signing of informed consent.

9.1.4 Concomitant Medications

Concomitant medication is any drug given in addition to the study drug. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by the Sponsor. Subjects will be asked whether they have taken any medication other than the study drug (used from the signing of informed consent through the end of the study), and all medication including vitamin supplements, OTC medications, and oral herbal preparations, must be recorded in the eCRF. Documentation will include generic medication names, route of administrations, start and end dates, and reasons for use.

9.2 Clinical Procedures and Assessments

9.2.1 Full Physical Exam

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.

9.2.2 Height and Weight

Each subject should have a height and weight measured. Height will be recorded in centimeters without decimal places (rounding off the first decimal place). Weight will be collected in kilograms (kg) with the first decimal place (rounding off the second decimal place).

9.2.3 BMI

BMI should be derived as:

Metric: BMI=weight (kg)/height $(m)^2$

The values should be calculated to the first decimal place (rounding off the second decimal place). When the BMI is used as entry criteria, then this determination must be made after rounding.

9.2.4 Vital Signs

Vital signs will include body temperature (axilla measurement), respiratory rate, supine blood pressure (systolic and diastolic, after resting more than 5 minutes), and pulse (beats per minute).

The same method (eg, the same and appropriately sized cuff, manual or automated) must be used for all measurements for each individual subject and should be the same for all subjects. All measurements will be recorded on the source documents and in the eCRF.

When vital signs are scheduled at the same time as blood draws, the blood draw will take priority and vital signs will be obtained within an acceptable time window (see Appendix C).

9.2.5 12-Lead ECG

A standard 12-lead ECG will be recorded. Subjects should be resting in a recumbent position for at least 5 minutes before each ECG measurement. The investigator or sub-investigator (or a qualified observer at the investigational site) will interpret the ECG using 1 of the following categories: normal or abnormal. If an ECG is abnormal, the investigator or sub-investigator (or a qualified observer at the investigational site) will judge clinical significance of the abnormality. The time that the ECG was performed will be recorded. The following parameters will be recorded on the eCRF from the subject's ECG trace: heart rate, RR interval, PR interval, QT interval, QRS interval, and QTcF.

When 12-lead ECG measurements are scheduled at the same time as blood draws, the blood draw will take priority and 12-lead ECGs will be obtained within an acceptable time window (see Appendix C).

9.2.6 Study Drug Administration

The subjects will receive a single dose of blinded study drug on Day 1 followed by multiple doses of blinded study drug BID for 5 days from Day 3 to Day 7, except that an evening dose of study drug will not be administered on Day 7.

Daily study drug administration in the multiple dose period should be within ±5 minutes of nominal dosing times on Day 3. On Day 7, study drug administration time should be as close to the time of Day 3 dosing as possible.

The number of capsules per dose is presented in Table 9.a.

Table 9.a Number of Capsules per Dose

Cohort	Treatment	TAK-906 maleate 5 mg Capsule	TAK-906 maleate 25 mg Capsule	Placebo Capsule
1	TAK-906 maleate 50 mg	0	2	0
	Placebo	0	0	2
2	TAK-906 maleate 100 mg	0	4	0
	Placebo	0	0	4
3	TAK-906 maleate 10 mg	2	0	0
	Placebo	0	0	2

All subjects will take study drug during each period with 240 mL of water.

A single dose and all morning doses of trial medication in multiple dose periods will be administered orally after fast of at least 10 hours that continues for at least 4 hours after dosing with restricted of water intake for at least 1 hour prior to and after dosing. The evening dose will be administered 12 hours after the morning dose and at least 2 hours after dinner.

9.2.7 AE Monitoring

AE monitoring begins after the signing of informed consent. A complete description of AE collections and procedures is provided in Section 10.2.

9.2.8 Laboratory Procedures and Assessments

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

9.2.8.1 Clinical Laboratory Tests

Hematology

Hematology will consist of the following tests:

Erythrocytes (red blood cells [RBCs])	Leukocytes (white blood cells [WBCs]) with absolute differential
Hemoglobin	Mean corpuscular hemoglobin (MCH)
Hematocrit	Mean corpuscular hemoglobin concentration (MCHC)
Platelets	Mean corpuscular volume (MCV)

Chemistry

Chemistry evaluations will consist of the following standard chemistry panel:

Albumin	Potassium
Alkaline phosphatase	Protein (total)
ALT	Sodium
AST	C-reactive protein
Bilirubin (total)	Total cholesterol
Blood urea nitrogen	Lactate dehydrogenase
Calcium	Magnesium
Chloride	Phosphorus
Creatinine	Triglycerides
Gamma-glutamyl transferase (GGT)	Uric acid
Glucose	

Urinalysis

Urinalysis will consist of the following tests:

Protein	Ketones	Urine microscopy
Glucose	pH	RBC
Blood	Specific gravity	WBC
Nitrite	Urobilinogen	Squamous epithelial cells

Other

Diagnostic Screening:	
Serum	**Urine**
Immunology Hepatitis panel (HBsAg and anti-HCV) HIV antibody/antigen Syphilis screen (serological reactions for syphilis)	Drug screen (phencyclidines, benzodiazepines, cocaines, amphetamines, cannabinoids, morphines, barbiturates, and tricyclic antidepressants)
Prolactin	Cotinine screen
	Alcohol screen (urine alcohol test/alcohol breath test)

Note: The investigator or sub-investigator will report the results of immunology, urine drug screen, cotinine screen, and alcohol screen directly to subjects. The Sponsor will confirm the overall test results (as "Positive" or "All negative"), rather than detailed results, for subjects (including reserve subjects) to be administered the study drug.

The local laboratory will perform laboratory tests for hematology, chemistry, urinalysis, and prolactine assessment for safety (at Screening). The results of laboratory tests will be returned to the investigator or sub-investigator, who is responsible for reviewing and filing these results.

If subjects experience an ALT or AST of >3 ×ULN, 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 noted. (Refer to Section 7.6 and Section 10.2.9.5 for the appropriate guidance on reporting abnormal LFTs.)

The investigator will maintain a copy of the reference ranges for the laboratory used.

9.3 PK, PD, and CCI

Samples for PK, PD, and CCI will be collected as specified in the Schedule of Study Procedures (Section 3.0). Please refer to the separately created procedure for information on the collection, processing, and shipment of samples to the central laboratory. The actual time of sample collection for PK and PD analyses will be recorded on the source documents and eCRF.

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

Table 9.b Primary Specimen Collections

Specimen Name	Primary Specimen	Primary Specimen Derivative	Description of Intended Use	Sample Collection
Plasma sample for TAK-906 PK	Plasma		PK measurement	Mandatory
Urine sample for TAK-906 PK	Urine		PK measurement	Mandatory
Serum sample for PD (prolactin)	Serum		PD measurement	Mandatory
CCI				

PK=pharmacokinetics, PD=pharmacodynamics. CCI

9.3.1 PK Measurements

The PK parameters of TAK-906 and M23 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 PK parameters will be calculated for plasma concentration values of TAK-906 and M23, unless otherwise specified:

Symbol/Term	Definition
Plasma	
$AUC_{\tau,ss}$	Area under the plasma concentration-time curve during a dosing interval, at steady state.
AUC_t	Area under the plasma concentration-time curve from time 0 to time t.
AUC_∞	Area under the plasma concentration-time curve from time 0 to infinity, calculated using the observed value of the last quantifiable concentration.
C_{max}	Maximum observed plasma concentration.
$C_{max,ss}$	Maximum observed plasma concentration during a dosing interval, at steady state.
t_{max}	Time of first occurrence of C_{max}.
$t_{max,ss}$	Time of first occurrence of C_{max}, at steady state.

The following urine PK parameters of TAK-906 and M23 will be derived from urine concentrations of TAK-906, unless otherwise specified:

Symbol/Term	Definition
Urine	
Ae_t	Amount of drug excreted in urine from time 0 to time t.
Ae_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.
$f_{e,\tau}$	Fraction of administered dose of drug excreted in urine during a dosing interval. Molecular weight adjustment needed for metabolites.
CL_R	Renal clearance.

9.3.1.1 Plasma for PK Measurements

Blood samples (one 4-mL sample per scheduled time) for PK analyses of TAK-906 and M23 will be collected into Vacutainers [redacted]

Serial blood samples for PK analyses of TAK-906 and M23 will be collected according to Table 9.c.

Table 9.c Collection of Blood Samples for PK Analysis

Analyte	Matrix	Study Day	Scheduled Time
TAK-906 and M23	Plasma	1-2	Predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hours post single dose
TAK-906 and M23	Plasma	3-6	Just before morning dose
TAK-906 and M23	Plasma	7-8	Predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hours post morning dose

Blood samples for subjects randomized to placebo will not be analyzed.

If a subject is prematurely terminating from the study between the first dose of study drug and the completion of procedures on Day 8, a final PK blood sample needs to be drawn from that subject in confinement; however, for any early termination during Follow-up, a PK blood sample will not be collected.

9.3.1.2 Urine for PK Measurements

Serial urine samples for PK analyses of TAK-906 and M23 will be collected according to Table 9.d.

Table 9.d Collection of Urine Samples for PK Analysis

Analyte	Matrix	Study Day	Scheduled Time
TAK-906 and M23	Urine	1-2	Predose (spot), 0-6, 6-12, and 12-24 hours post single dose
TAK-906 and M23	Urine	7	0-6 and 6-12 hours post morning dose

Urine samples for subjects randomized to placebo will not be analyzed.

9.3.1.3 Bioanalytical Methods

Plasma and urine concentrations of TAK-906 and M23 will be measured by high-performance liquid chromatography with CCI [redacted]

9.3.2 PD Measurements

The following PD parameters will be calculated for serum concentration values of prolactin, unless otherwise specified:

Symbol/Term	Definition
Serum	
$AUC_{\tau,ss}$	Area under the serum concentration-time curve from time 0 to time t, at steady state.
AUC_t	Area under the serum concentration-time curve from time 0 to time t.
C_{max}	Maximum observed serum concentration.
$C_{max,ss}$	Maximum observed serum concentration during a dosing interval, at steady state.

9.3.2.1 Serum for PD Measurements

Serial blood samples (one 5-mL sample per scheduled time) for PD analysis will be collected according to Table 9.e. In addition, serum prolactin level will be measured in a laboratory test at Screening for safety assessment by local laboratory.

Table 9.e Collection of Blood Samples for PD Analysis

Analyte	Matrix	Study Day	Scheduled Time
Prolactin	Serum	1-2	Predose, 1, 2, 4, 6, and 24 hours post single dose
Prolactin	Serum	3-6	Just before morning dose
Prolactin	Serum	7-8	Predose, 1, 2, 4, 6, and 24 hours post morning dose
Prolactin	Serum	14	–

9.3.2.2 Bioanalytical Methods

Serum prolactin levels for PD analysis will be measured using an in vitro diagnostic assay CCI [redacted]

9.3.3 CCI [redacted]

9.3.3.1 CCI [redacted]

CCI [redacted]

9.3.3.2 CCI [redacted]

Not applicable.

9.3.4 Confinement

In either Cohort 1, 2, or 3, each subject will be confined from Day -1 to the morning of Day 8 and discharged after the investigator's or sub-investigator's confirmation of no significant abnormality in his health through physical examination and tests on Day 8, at 24-hour post morning dose of Day 7.

10.0 ADVERSE EVENTS

10.1 Definitions and Elements of AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study; it does not necessarily have to have a causal relationship with the treatment or study participation.

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

An untoward finding generally may:

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

Diagnoses versus signs and symptoms:

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

Laboratory values and ECG findings:

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

Pre-existing conditions:

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

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

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

Worsening of AEs:

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

Changes in severity of AEs:

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

Preplanned surgeries or procedures:

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

Elective surgeries or procedures:

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

Overdose:

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

database. AEs associated with an overdose will be documented on AE CRF(s) according to Section 10.0.

- Serious adverse events (SAEs) of overdose should be reported according to the procedure outlined in Section 10.2.9.
- In the event of drug overdose, the subject should be treated symptomatically.

10.1.1 SAEs

An SAE is defined as any untoward medical occurrence that:

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

Note: Terms identified on the Medically Significant AE List represent the broad medical concepts to be considered as "Important Medical Events" satisfying SAE reporting requirements.

10.2 AE Procedures

10.2.1 Assigning Severity/Intensity of AEs

The different categories of severity/intensity are:

Mild: The event is transient and easily tolerated by the subject.

Moderate: The event causes the subject discomfort and interrupts the subject's usual activities.

Severe: The event causes considerable interference with the subject's usual activities.

10.2.2 Assigning Causality of AEs

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

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

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

10.2.3 Assigning Causality of AEs to Study Procedures

The causality of each AE to study procedures will be assessed.

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

10.2.4 Start Date

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

10.2.5 End Date

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

10.2.6 Pattern of Adverse Event (Frequency)

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

10.2.7 Action Taken With Study Treatment

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

10.2.8 Outcome

- Recovered/resolved – subject returned to first assessment status with respect to the AE.
- Recovering/resolving – the intensity is lowered by one or more stages: the diagnosis has or signs/symptoms have almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to the baseline value; the subject died from a cause other than the particular AE with the condition remaining "recovering/resolving."
- Not recovered/not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/symptoms or laboratory value on the last day of the observed study period has become worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE state remaining "Not recovered/not resolved."

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

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

10.2.9.1 Collection Period

Collection of AEs (ie, AEs, SAEs, and Abnormal LFTs) will commence at the time the subject signs the informed consent. Routine collection of AEs will continue until the follow-up visit on Day 14.

10.2.9.2 Reporting AEs

At each study visit, the investigator or sub-investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study. Subjects experiencing an SAE prior to the first exposure to study drug 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. Nonserious AEs that begin prior to the first exposure to study drug, whether related or unrelated to study procedure, need not be followed-up for the purposes of the protocol.

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

- Event term.
- Start and end date and time.
- Pattern of AE (frequency).
- Severity/Intensity.
- Investigator's or sub-investigator's opinion of the causality between the event and administration of study drug(s) (related or not related).
- Investigator's or sub-investigator's opinion of the causality to study procedure(s), including the details of the suspected procedure.
- Action taken with trial drug.

- Outcome of event.
- Seriousness.
- Timing of occurrence (after administration of study drug).
- QTc prolongation associated AEs, neurologic AEs or hyperprolactinemia associated AEs, or not.

10.2.9.3 Reporting SAEs

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

An SAE should be reported by the investigator or sub-investigator to the Sponsor (see Protocol Annex 1) within 1 business day of the first onset or notification of the SAE, along with any relevant information. The investigator should submit a detailed SAE Form to the Sponsor within 10 calendar days. 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 or sub-investigator's name.
- Name of the study medication(s).
- Causality assessment.

Any SAE spontaneously reported to the investigator or sub-investigator following the AE collection period should be reported to the Sponsor if considered related to study participation.

SAE Follow-Up

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

All SAEs should be followed up until resolution or a permanent outcome for the event.

10.2.9.4 Reporting QTc prolongation associated AEs, neurologic AEs, and hyperprolactinemia associated AEs

Considering the mechanism of action of TAK-906 and the safety profile of existing dopamine D_2/D_3 receptor antagonists on the market, the following AEs (treatment-emergent only, serious or non-serious) are considered to be ones for which ongoing monitoring and rapid communication by the investigator to Takeda may be appropriate, and may require further investigation in order to characterize and understand in this study.

QTc prolongation associated AEs:

- Torsade de pointes, Sudden death, Ventricular tachycardia, Ventricular fibrillation and flutter, Syncope, and Seizure.

Neurologic AEs:

- Extrapyramidal disorder, Tardive dyskinesia, Akathisia, and Parkinsonian like disorder.

Hyperprolactinemia associated AEs.

- Hyperprolactinemia, Libido decreased, Sexual dysfunction, Gynecomastia, and Galactorrhoea.

If these AEs are considered to be clinically significant, it should be reported to the Sponsor immediately or within 1 business day of onset or subject's notification of the event. An AE Form specified to these AEs or an SAE Form should be completed, signed, or signed and sealed by the investigator and reported to the Sponsor within 10 business days.

The investigator should record these AEs as AEs in the eCRF, and submit the original copy of the AE Form or the SAE Form along with all other required documentation to the Sponsor.

10.2.9.5 Reporting of Abnormal LFTs

If a subject is noted to have ALT or AST >3 ×ULN and total bilirubin >2 ×ULN for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 10.2.9.3. The investigator or sub-investigator must report to the monitor and evaluate relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease or medical history/concurrent medical conditions. Follow-up laboratory tests as described in Section 9.2.8 must also be performed.

10.2.10 Safety Reporting to Investigators, IRBs, 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, IRBs, and the head of the investigational site. Relative to the first awareness of the event by/or further provision to the Sponsor or its designee, SUSARs will be submitted to the regulatory authorities as expedited report 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 study drug or that would be sufficient to consider changes in the study drug 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.

11.0 STATISTICAL METHODS

11.1 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 definitions of analysis variables, and analysis methodologies to address all study objectives.

11.1.1 Analysis Sets

In this study, three analysis sets are defined: the Safety Analysis Set, the PK Analysis Set, and the PD analysis Set. The definition of each analysis set will be described in the SAP.

11.1.1.1 Safety Analysis Set

The Safety Analysis Set will be defined as all subjects who received at least one dose of study drug.

11.1.1.2 PK Analysis Set

The PK Analysis Set will consist of subjects who received at least one dose of study drug, completed the minimum protocol-specified procedures with no significant protocol deviations, and who were evaluable for the PK.

11.1.1.3 PD Analysis Set

The PD Analysis Set will consist of subjects who received at least one dose of study drug, completed the minimum protocol-specified procedures with no significant protocol deviations, and who were evaluable for the PD.

11.1.2 Analysis of Demography 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.

11.1.3 PK Analysis

Plasma concentrations of TAK-906 and M23 will be summarized by dose over each scheduled sampling time using descriptive statistics. Individual plasma concentration data versus time will be presented in a data listing.

Plasma PK parameters for TAK-906 and M23 will be summarized by dose over each scheduled sampling time using descriptive statistics (arithmetic mean, SD, median, minimum and maximum). In addition, geometric mean and coefficient of variation will be computed for C_{max} and AUC.

Dose proportionality for TAK-906 and M23 plasma exposures (C_{max} and AUC) will be assessed statistically using a power function model.

Individual urine concentration data versus time will be presented in a data listing.

The urine PK parameters for TAK-906 and M23 will be summarized by dose using descriptive statistics.

A more detailed analysis will be presented in the SAP.

11.1.4 PD Analysis

For the serum prolactin concentration, the observed values and their changes from baseline will be summarized by dose over each scheduled sampling time using descriptive statistics.

A more detailed analysis will be presented in the SAP.

11.1.5 Safety Analysis

11.1.5.1 AEs

A TEAE is defined as an AE whose date of onset occurs on or after the start of study drug. TEAEs will be coded using Medical Dictionary for Refulatory Activities (MedDRA) dictionary. Frequency distribution will be provided by system organ class and preferred term for each regimen. TEAEs will be summarized by pooled placebo and each TAK-906 dose level for single dose period and combined single and multiple dose periods. All TEAE data will be provided in the data listings.

11.1.5.2 Clinical Laboratory Evaluation

For continuous variables, the observed values and their changes from baseline will be summarized by dose over each scheduled sampling time using descriptive statistics. For categorical variables, shift tables showing the number of subjects in each category at baseline and each post-baseline visit will be provided by dose. All clinical laboratory data will be provided in the data listings.

11.1.5.3 Vital Signs

The observed values and their changes from baseline will be summarized by dose over each scheduled sampling time using descriptive statistics. All vital sign data will be provided in the data listings.

11.1.5.4 Other Safety Parameters

ECG parameters are summarized as follows: for continuous variables, the observed values and their changes from baseline will be summarized by dose over each scheduled sampling time using descriptive statistics. For categorical variables, shift tables showing the number of subjects in each category at baseline and each post-baseline visit will be provided by dose. All ECG data will be provided in the data listings.

Physical examination findings will be presented in the data listings.

11.2 Interim Analysis and Criteria for Early Termination

No formal interim analysis is planned.

11.3 Determination of Sample Size

A sample size of 8 subjects per cohort (6 active: 2 placebo) will be used in this study, and is considered sufficient for the evaluation of TAK-906 safety, tolerability, PK and PD following oral single and multiple doses. The sample size is not based on statistical power considerations.

12.0 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Investigational Site Monitoring Visits

Monitoring visits to the investigational 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 the head of investigational site guarantee access to source documents by the Sponsor or its designee (CRO) and by the IRB.

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

12.2 Protocol Deviations

The investigator or sub-investigator can deviate and change from the protocol for any medically unavoidable reason, for example, to eliminate an immediate hazard to study subjects, without a prior written agreement with the Sponsor or a prior approval from IRB. In the event of a deviation or change, the investigator should notify the Sponsor and the head of the investigational site of the deviation or change as well as its reason in a written form, and then retain a copy of the written form. When necessary, the investigator may consult and agree with the Sponsor on a protocol amendment. If the protocol amendment is appropriate, the amendment proposal should be submitted to the head of the investigational site as soon as possible and an approval from IRB should be obtained.

The investigator or sub-investigator should document all protocol deviations.

12.3 Quality Assurance Audits and Regulatory Agency Inspections

The investigational site also may be subject to quality assurance audits by the Sponsor or designees. In this circumstance, the Sponsor-designated auditor will contact the investigational 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 Food and Drug Administration [FDA], the United Kingdom Medicines and Healthcare products Regulatory Agency [MHRA], the Pharmaceuticals and Medical Devices Agency of Japan [PMDA]). If the investigational site is contacted for an inspection by a regulatory body, the Sponsor should be notified immediately. The investigator and the head of investigational site guarantee access for quality assurance auditors to all study documents as described in Section 12.1.

13.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix A.

13.1 IRB Approval

IRBs 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. If any member of the IRB has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained.

The Sponsor or designee will supply relevant documents for submission to the respective IRB 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 for approval. The IRB'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. The IRB 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 notify investigational site once the Sponsor has confirmed the adequacy of investigational site regulatory documentation. Until the investigational site receives notification, no protocol activities, including screening, may occur.

Investigational Sites must adhere to all requirements stipulated by their respective IRB. This may include notification to the IRB 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, and submission of the investigator's final status report to IRB. All IRB 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 and Sponsor.

Regarding pharmacogenomic investigation using collected and stored specimens, analysis will be carried out at the time when details for this analysis are determined. The Sponsor will create a research protocol for pharmacogenomics investigations.

13.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form describes 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 further explains 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 is free to withdraw at any time without giving a reason and without prejudice to his further medical care.

The investigator is responsible for the preparation, content, and IRB approval of the informed consent form. The informed consent form must be approved by both the IRB and the Sponsor prior to use.

The informed consent form must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator or sub-investigator to explain the detailed elements of the informed consent form to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB.

The subject 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 determines he will participate in the study, then the informed consent form must be signed and dated by the subject at the time of consent and prior to the subject entering into the study. The subject should be instructed to sign using his legal name, not nicknames, using blue or black ballpoint ink. The investigator or sub-investigator must also sign and date the informed consent form at the time of consent and prior to subject entering into the study.

Once signed, the original informed consent form will be stored in the investigator's site file. The investigator or sub-investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form shall be given to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects 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.

CCI [redacted]

13.3 Subject Confidentiality

The Sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the Sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth 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, MHRA, PMDA), the Sponsor's designated auditors, and the appropriate IRBs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 13.2).

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

13.4 Publication, Disclosure, and Clinical Trial Registration Policy

13.4.1 Publication and Disclosure

The investigator is obliged to provide the Sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the Sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results 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. The investigator or sub-investigator needs to obtain a prior written approval from the Sponsor to publish any information from the study externally such as to a professional association.

13.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum register all interventional clinical trials it Sponsors anywhere in the world on ClinicalTrials.gov and/or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with facility name, investigator's city, country, and recruiting status will be registered and available for public viewing.

13.4.3 Clinical Trial Results Disclosure

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

13.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the investigational site where the subject is participating. If a local underwriter is required, then the

Sponsor or its designee will obtain clinical study insurance against the risk of injury to study subjects. Refer to the clinical study site agreement regarding the Sponsor's policy on subject compensation and treatment for injury. If the investigator or sub-investigator has questions regarding this policy, he or she should contact the Sponsor or its designee.

14.0 ADMINISTRATIVE AND REFERENCE INFORMATION

14.1 Administrative Information

14.1.1 Study Contact Information

A separate contact information list (Protocol Annex 1) will be provided to the investigational site.

14.1.2 INVESTIGATOR AGREEMENT

A separate agreement will be provided to the investigational site.

14.1.3 Study-Related Responsibilities

A separate contact information list (Protocol Annex 1) will be provided to the investigational site.

14.1.4 List of Abbreviations

Term	Definition
AE	adverse event
Ae	amount of drug excreted in urine
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BBB	blood brain barrier
BID	twice daily
BMI	body mass index
CL_R	renal clearance
C_{max}	maximum observed concentration
CNS	central nervous system
DA	dopamine
CCI	[redacted]
eCRF	electronic case report form
ECG	electrocardiogram
EPS	extrapyramidal symptoms
FDA	Food and Drug Administration
fe	fraction of administered dose of drug excreted in urine
FIH	first-in-human
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GI	gastrointestinal
HBsAg	hepatitis B virus surface antigen
HCV	hepatitis C virus
HDPE	high density polyethylene

Term	Definition
hERG	human ether-á-go-go related gene
HIV	human immunodeficiency virus
ICH	International Conference on Harmonisation
INR	international normalized ratio
IRB	institutional review board
LFT	liver function test
LOEL	lowest observed effect level
MAD	multiple-ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MHW	Ministry of Health and Welfare
MRSD	maximum recommended starting dose
NOAEL	no-observed-adverse-effect level
OTC	over-the-counter
PD	pharmacodynamics
PK	pharmacokinetics
CCI	[redacted]
PMDA	Pharmaceuticals and Medical Devices Agency of Japan
RBC	red blood cell
SAD	single-ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SUSAR	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event
t_{max}	time of first occurrence of C_{max}
$t_{1/2}$	half-life period
ULN	upper limit of normal
US	United States
WBC	white blood cell

15.0 DATA HANDLING AND RECORDKEEPING

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

15.1 eCRFs

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

The Sponsor or its designee will supply investigational sites with access to eCRFs. The Sponsor will make arrangements to train appropriate investigational site staff in the use of the eCRF. These forms are used to transmit 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 investigational site.

Corrections are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was madeThe investigator must review the eCRFs for completeness and accuracy and must e-sign appropriate eCRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy, and authenticity of all data entered on the eCRFs.

The following data will not be recorded into the eCRFs:

- CCI [redacted]
- Laboratory results
- Measurement results of drug concentrations
- PD analysis result

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

eCRFs will be reviewed for completeness and acceptability at the investigational 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.

15.2 Record Retention

The investigator and the head of the investigational site agree to keep the records stipulated in Section 15.1 and those documents that include (but are not limited to) the study-specific documents, the identification log for all participating subjects, medical records, all original signed and dated informed consent forms, electronic copy of eCRFs, including their audit trail, and detailed records of drug disposition that will enable evaluations or audits by regulatory authorities, the Sponsor or its designees. The investigator and the head of the investigational site are required to retain relevant essential documents until the day specified as 1 or 2 below, whichever comes later. However, if the Sponsor requests a longer time period for retention, the head of the investigational site should discuss how long and how to retain those documents with the Sponsor.

1. The day on which marketing approval for the study drug is obtained (or the day 3 years after the date of notification in the case that the investigation is discontinued.)
2. The day 3 years after the date of early termination or completion for the study.

In addition, the investigator and the head of the investigational site should retain the relevant essential documents until the receipt of a Sponsor-issued notification that states the retention is no longer required.

16.0 REFERENCES

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13. General Considerations for Clinical Trials (PMSB/ Examination and Licensing Division Nortification No.380, 21/Apr/1998).

17.0 APPENDICES

Appendix A Responsibilities of the Investigator

1. Conduct the appropriate study in accordance with the protocol and GCP considering the rights, safety and wellbeing of human subjects.
2. When a part of the important activities related to the study are delegated to a sub-investigator or the study collaborator, prepare the lists of activities to be delegated and responsible personnel, submit the lists to the head of the investigational site in advance to get them accepted.
3. Prepare a written informed consent form and other written information, and update as appropriate.
4. Confirm the contents of the clinical study agreement.
5. Provide necessary information on the protocol, medications and responsibilities of individual personnel to the sub-investigator and study collaborator, and provide guidance and supervision.
6. Screen subjects who meet the requirements of the protocol, provide the explanation of the study in writing and obtain the written consent.
7. Assume responsibility for all the medical judgement related to the study.
8. Ensure in collaboration with the head of the investigational site that sufficient medical care for all clinically significant AEs related to the study are provided to subjects throughout and beyond the period when subjects participate in the study, upon obtaining consent from the subject.
9. If a subject consults other medical institution or other department, notify the physician of the medical institution or department of the subject's participation in the study, as well as the end and termination of the study in writing, and document such records.
10. In case of urgent report of a SAE, immediately notify the head of the investigational site and the Sponsor in writing.
11. Determine the need of emergency key code blinding of a subject in case of emergency.
12. Prepare correct and complete eCRFs, and submit them to the Sponsor with electronic signature.
13. Check and confirm the contents of eCRFs prepared by the sub-investigator or transcribed from the source data by the study collaborator, and submit them to the Sponsor with electronic signature.
14. Discuss any proposal from the Sponsor including update of the protocol.
15. Notify the head of the investigational site of the end of the study in writing.

Appendix B Pregnancy and Contraception

Contraception and Pregnancy Avoidance Procedure

Male Subjects and Their Female Partners

From the signing of informed consent, throughout the duration of the study, and for 12 weeks (84 days) after last dose of study drug, any nonsterilized** male subjects who are sexually active with a female partner of childbearing potential* must use adequate contraception. In addition, they must be advised not to donate sperm during this period. Females of childbearing potential who are partners of male subjects are also advised to use additional contraception as shown in the table on containing adequate contraception below.

* 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 2 years since last regular menses with an FSH of >40 IU/L).

** Sterilized males should be at least 1 year post-bilateral vasectomy and have confirmed that they have obtained documented absence of sperm in the ejaculate, or have had a bilateral orchidectomy.

An acceptable method of contraception is defined as one that has no higher than a 1% failure rate.

Barrier methods (each time the subject has intercourse)	Intrauterine devices (IUDs)	Hormonal contraceptives
Male condom with spermicide.	Copper T PLUS condom. Progesterone T PLUS condom.	Combined pill.

Subjects will be provided with information on acceptable methods of contraception for 12 weeks (84 days) after last dose of study drug, as part of their informed consent process, and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy in partners and of sperm donations for 12 weeks (84 days) after their last dose of study drug.

Pregnancy

If any pregnancies in the partner of a male subject, during the study or for 12 weeks (84 days) after the last dose, should be recorded following authorization from the subject's partner.

If the pregnancy in the partner of a male subject occurs during or after administration of blinded drug, the investigator or sub-investigator must inform the subject of his right to receive treatment information. If the subject chooses to receive unblinded treatment information, that individual's blind should be broken by the investigator or sub-investigator. Any subjects randomized to placebo need not be followed.

If the female partner of a male subject agrees to have her primary care physician informed, the investigator or sub-investigator should notify the primary care physician that her partner was participating in a clinical study at the time she became pregnant and provide details on the study drug that the subject has received (blinded or unblinded, as applicable).

All pregnancies in the female partners of male subjects will be followed to final outcome, using the pregnancy form, with the consent of the female partners of those male subjects. The outcome, including any premature termination, must be reported to the Sponsor. An evaluation after any birth of a child will also be conducted.

Appendix C Acceptable Time Window for Study Procedure

Variables	Timing of procedures (standard)		Acceptable window
Examinations only for diagnostic screening (a)	Screening period	Days -28 to -2	Not applicable
Physical examination	Screening period	Days -28 to -2	Not applicable
	Check-in	Day -1	Not applicable
	Treatment period	Day 1: Predose. Day 5: Before morning dose.	From awakening to immediately prior to (morning) dose
		Days 2 and 8: 24 hours postdose of Days 1 and 7, respectively.	Within ±1 hour
	Follow-up	Day 14	Within ±2 days
Weight	Screening period	Days -28 to -2	Not applicable
	Check-in	Day -1	Not applicable
	Treatment period	Day 7: Predose.	From awakening to immediately prior to dose
	Follow-up	Day 14	Within ±2 days
Vital signs	Screening period	Days -28 to -2	Not applicable
	Check-in	Day -1	Not applicable
	Treatment period	Days 1 and 7: Predose. Days 3 to 6: Before morning dose.	From awakening to immediately prior to (morning) dose
		Days 1 and 7: 1, 2, 4, and 6 hours postdose.	Within ±30 minutes
		Days 2 and 8: 24 hours postdose of Days 1 and 7, respectively.	Within ±1 hour
	Follow-up	Day 14	Within ±2 days
12-lead ECG	Screening period	Days -28 to -2	Not applicable
	Check-in	Day -1	Not applicable
	Treatment period	Days 1 and 7: Predose. Day 5: Predose.	From awakening to immediately prior to (morning) dose
		Days 1 and 7: 1, 2, 4, and 6 hours postdose.	Within ±30 minutes
		Days 2 and 8:24 hours postdose of Days 1 and 7, respectively.	Within ±1 hour
		Day 5: 1 and 2 hours postdose.	Within ± 30 minutes

Variables	Timing of procedures (standard)		Acceptable window
Hematology and chemistry for safety assessments (b)	Screening period	Days -28 to -2	Not applicable
	Check-in	Day -1	Not applicable
	Treatment period	Days 2 and 8: 24 hours postdose of Days 1 and 7, respectively.	Within ±1 hour
		Day 5: Before morning dose.	From awakening to immediately prior to morning dose
	Follow-up	Day 14	Within ±2 days
Urinalysis for safety assessments	Screening period	Days -28 to -2	Not applicable
	Check-in	Day -1	Not applicable
	Treatment period	Days 2 and 8: 24 hours postdose of Days 1 and 7, respectively.	From awakening to 1 hour post-scheduled time
		Day 5: Before morning dose.	From awakening to immediately prior to morning dose
	Follow-up	Day 14	Within ±2 days
Plasma sample for TAK-906 PK	Treatment period	Day 1: Predose.	From awakening to immediately prior to dose
		Day 1: 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 16 hours postdose.	Within ±5 minutes
		Day 2: 24 hours postdose of Day 1.	Within ±15 minutes
		Days 3 to 6: Just before morning dose.	From 15 minutes predose to immediately prior to morning dose
		Day 7: Predose.	Immediately prior to dose
		Day 7: 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 16 hours postdose.	Within ±5 minutes
		Day 8: 24 hours postdose of Day 7.	Within ±15 minutes
Urine sample for TAK-906 PK	Treatment period	Day 1: Predose (spot).	From awakening to immediately prior to dose
		Days 1 to 2: 0-6, 6-12, and 12-24 hours postdose.	Not applicable
		Day 7: 0-6 and 6-12 hours postdose.	Not applicable

Footnotes are on the following page.

Variables	Timing of procedures (standard)		Acceptable window
Serum sample for PD (prolactin)	Treatment period	Day 1: Predose.	From awakening to immediately prior to dose
		Day 1: 1, 2, 4, and 6 hours postdose.	Within ±5 minutes
		Day 2: 24 hours postdose of Day 1.	Within ±15 minutes
		Days 3 to 6: Just before morning dose.	From 15 minutes predose to immediately prior to morning dose
		Day 7: Predose.	Immediately prior to dose
		Day 7: 1, 2, 4, and 6 hours postdose..	Within ±5 minutes
		Day 8: 24 hours postdose of Day 7.	Within ±15 minutes
	Follow-up	Day 14	Within ±2 days
CCI [redacted]			

BMI=body mass index, ECG=electrocardiogram, HBsAg=hepatitis B virus surface antigen, HCV=hepatitis C virus, HIV=human immunodeficiency virus, CCI [redacted]
PK=pharmacokinetics, PD=pharmacodynamics.

(a) Including height measurement, BMI calculation, immunological test (HBsAg, anti-HCV, HIV antibody/antigen, and syphilis screen), prolactin assessment for safety, urine drug screen, urine cotinine test, and alcohol screen (urine alcohol test/alcohol breath test).
(b) Serum prolactin level will be measured at Screening for safety assessment.

Total blood sampling volumes for an individual subject is shown below:

Sample Type	Sample Volume (mL)	Number of Samples					Total Volume (mL)
		Screening	Day -1	Days 1-2	Days 3-8	Follow-up	
Hematology	2	1	1	1	2	1	**12**
Chemistry	5	1 (a)	1	1	2	1	**30**
Blood for TAK-906 PK	4	0	0	12	16	0	**112**
Blood for PD	5	0	0	6	10	1	**85**
CCI [redacted]							

PK=pharmacokinetics, PD=pharmacodynamics, CCI [redacted]
HBsAg=hepatitis B virus surface antigen, HCV=hepatitis C virus, HIV=human immunodeficiency virus.

(a) One 5-mL sample collected for blood chemistry test at Screening will be also used for immunological test (HBsAg, anti-HCV, HIV antibody/antigen, and syphilis screen), and prolactin assessment for safety.

A Randomized, Double-Blind, Placebo-Controlled, Single and Multiple Ascending Dose, Phase 1 Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of TAK-906 in Japanese Health Male Subjects

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical Pharmacology Approval	07-Jun-2017 04:42 UTC
	Biostatistics Approval	07-Jun-2017 07:38 UTC
	Clinical Approval	07-Jun-2017 11:20 UTC