Title: A Phase 1, Open-Label, Randomized, Two-Way Crossover Study to Evaluate the Effect of Single-Dose Intravenous Rifampin as a Prototypic Inhibitor of OATP1B1 and OATP1B3 on the Single-Dose Pharmacokinetics of Oral TAK-906 in Healthy Adult Subjects

NCT Number: NCT04121078

Protocol Approve Date: 24 September 2019

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

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

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

Takeda submitted a protocol clarification letter for the final protocol, dated 24-September-2019, explaining the discrepancies within the protocol. The clarification letter is appended to the back of the protocol.

TAKEDA PHARMACEUTICALS

PROTOCOL

A Phase 1, Open-Label, Randomized, Two-Way Crossover Study to Evaluate the Effect of Single-Dose Intravenous Rifampin as a Prototypic Inhibitor of OATP1B1 and OATP1B3 on the Single-Dose Pharmacokinetics of Oral TAK-906 in Healthy Adult Subjects

Study Identifier:	TAK-906-1009
Compound:	TAK-906
Date:	24 September 2019
Version/Amendment Number:	Final

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LIST OF APPENDICES

1.0 STUDY SUMMARY

Name of Sponsor:	**Compound:**
Millennium Pharmaceuticals, Inc. a wholly owned subsidiary of Takeda Pharmaceutical Company, Ltd 40 Landsdowne Street Cambridge, Massachusetts USA 02139 Telephone: +1 (617) 679-7000	TAK-906
Study Identifier: TAK-906-1009	**Phase:** 1

Protocol Title: A Phase 1, Open-Label, Randomized, Two-Way Crossover Study to Evaluate the Effect of Single-Dose Intravenous Rifampin as a Prototypic Inhibitor of OATP1B1 and OATP1B3 on the Single-Dose Pharmacokinetics of Oral TAK-906 in Healthy Adult Subjects

Study Design:

This is a phase 1, open-label, randomized, two-way crossover study to evaluate the effect of single-dose intravenous (IV) rifampin on the single-dose pharmacokinetics (PK) of oral TAK-906 in healthy adult subjects.

The study will include a screening visit, two treatment periods, and a follow-up visit. Treatment will consist of a single oral dose of 25 mg TAK-906 capsule (Treatment A), and a single oral dose of 25 mg TAK-906 capsule together with a single IV dose of 600 mg rifampin (Treatment B). Eligible subjects will be randomly assigned to 1 of 2 treatment sequences (ie, AB, BA). Randomization sequences are presented below:

Table 1a Randomization Sequences

Sequence	Number of Subjects	Study Period 1	Study Period 2
AB	6	TAK-906 oral	Rifampin IV+ TAK-906 oral
BA	6	Rifampin IV + TAK-906 oral	TAK-906 oral

Treatment A = 25 mg TAK-906 capsule

Treatment B = 25 mg TAK-906 capsule together with a single IV dose of 600 mg rifampin

Each dose of TAK-906 will be separated by a washout period of at least 7 days from the time of Study Period 1 TAK-906 dose administration.

On Day 1 of Treatment A after an overnight fast of at least 10 hours, a single oral dose of TAK-906 capsule will be administered.

On Day 1 of Treatment B after an overnight fast of at least 10 hours, IV rifampin will be administered over a 30-minute period, and TAK-906 capsule will be given immediately at the end of the infusion.

In each treatment arm, subjects will be confined from the day prior to dosing (Day -1, Check-in), at the time indicated by the Clinical Research Unit (CRU), until after the 48-hour blood draw (Day 3).

Blood samples for assessment of TAK-906 concentrations will be measured from predose to 48 hours after each dose of TAK-906.

Safety will be assessed by monitoring for adverse events (AE), vital signs, electrocardiograms (ECGs), clinical laboratory results, and physical examinations throughout each study period.

There will be a washout period of at least 7 days between the TAK-906 dosing in each study period.

All subjects who received at least one dose of study drug (including subjects who terminate the study early) will return to the CRU 14 ± 2 days after the last dose of TAK-906 for follow-up procedures, and to determine if any AE has occurred since the last study visit.

Study Primary Objective:

- To evaluate the effect of single-dose IV rifampin on the single-dose PK of orally administered TAK-906.

Secondary Objective:

- To evaluate the safety and tolerability of a single oral dose of TAK-906 in the presence and absence of rifampin.

Exploratory Objective:

CCI [redacted]

Study Subject Population: Healthy male and female subjects aged 19 to 55 years inclusive. Body Mass Index (BMI) 18.0-30.0 kg/m^2.

Planned Number of Subjects:	**Planned Number of Sites:**
12	1
Dose: 25 mg TAK-906 capsule (1 x 25 mg TAK-906 capsule; Treatment A) 25 mg TAK-906 capsule (1 x 25 mg TAK-906 capsule) and a single IV dose of 600 mg rifampin (Treatment B)	**Route of Administration:** Treatment A: oral (TAK-906) Treatment B: oral (TAK-906), IV infusion (rifampin)
Duration of Treatment: On Day 1 of Treatment A, subjects will receive a single oral dose of TAK-906. On Day 1 of Treatment B, subjects will receive a 30-minute IV infusion of rifampin followed by a single oral dose of TAK-906	**Planned Study Duration:** Approximately 49 days including Screening Period and Follow-up Visit.

Criteria for Inclusion:

Subjects must fulfill all of the following inclusion criteria to be eligible for participation in the study:

1. Healthy, adult, male or female, 19-55 years of age, inclusive, at screening.
2. Continuous non-smoker who has not used nicotine-containing products for at least 3 months prior to the first dosing and throughout the study, based on screening urine cotinine test.
3. BMI ≥ 18.0 and ≤ 30.0 kg/m^2 at screening.
4. Medically healthy with no clinically significant medical history, physical examination, laboratory profiles, vital signs, or ECGs, as deemed by the investigator or designee.
5. For a male or female of non-childbearing potential, use acceptable birth control methods as indicated in Appendix D.
6. A male subject who is nonsterilized and sexually active with a female partner of childbearing potential must agree to use a barrier method of contraception from signing of the informed consent form (ICF) throughout the duration of the study and through to the follow-up visit (ie, 14 ± 2 days after the last TAK-906 dosing) (refer to Appendix D).
7. If male, must agree not to donate sperm from signing of the ICF until follow-up visit (ie, 14 ± 2 days after the last TAK-906 dosing).
8. Understands the study procedures in the ICF, and be willing and able to comply with the protocol.

Criteria for Exclusion:

Subjects must not be enrolled in the study if they meet any of the following criteria:

1. Is mentally or legally incapacitated or has significant emotional problems at the time of the screening visit or expected during the conduct of the study.
2. History or presence of clinically significant endocrine, gastrointestinal (including motility disorder and intestinal obstruction), cardiovascular, hematological, hepatic, immunological, renal, respiration, genitourinary, or major neurological (including stroke and chronic seizures) abnormalities or disease in the opinion of the investigator or designee.
3. History of any illness that, in the opinion of the investigator or designee, might confound the results of the study or poses an additional risk to the subject by their participation in the study.
4. History of cancer (malignancy).
5. History or presence of alcoholism or drug abuse within the past 2 years prior to the first dosing.
6. History or presence of hypersensitivity or idiosyncratic reaction to TAK-906, to rifampin, or to related compounds or contraindicated compounds such as antivirals [1].
7. Female subjects of childbearing potential.
8. Female subjects with a positive pregnancy test or lactating at screening or first check-in.
9. Positive urine drug or alcohol results at screening or first check-in.
10. Positive urine cotinine at screening.
11. Positive results at screening for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C virus (HCV).
12. QTcF interval is >450 msec or ECG findings are deemed abnormal with clinical significance by the investigator or designee at screening.
13. Estimated creatinine clearance <90 mL/min at screening.
14. Unable to refrain from or anticipates the use of:
    - Any drug, including prescription and non-prescription medications, herbal remedies, or vitamin supplements within 14 days prior to the first dosing and throughout the study. After first dosing, acetaminophen (up to 2 g per 24 hours) may be administered at the discretion of the investigator or designee; Sponsor must be consulted prior to administering acetaminophen to a subject.
    - Any drugs known to significantly affect the absorption, distribution, metabolism, or elimination of study drugs (TAK-906 or rifampin), including any drug that affects the function of OATP1B1 or 1B3, within 28 days prior to the first dosing and throughout the study. Appropriate sources (eg, Flockhart Table™) will be consulted to confirm lack of PK/pharmacodynamic (PD) interaction with study drugs.
15. Has been on a diet incompatible with the on-study diet, in the opinion of the investigator or designee, within the 30 days prior to the first dosing and throughout the study.
16. Donation of blood or significant blood loss (eg, approximately 500 mL) within 56 days prior to the first dosing.
17. Plasma donation within 7 days prior to the first dosing.
18. Participation in another clinical study within 30 days or 5 half-lives prior to the first dosing. The 30-day window or 5 half-lives will be derived from the date of the last blood collection or dosing, whichever is later, in the previous study to Day 1 of Study Period 1 of the current study.

Main Criteria for Evaluation and Analyses:

Primary Endpoints

The following plasma PK parameters for TAK-906 on Day 1 in Study Period 1 and Study Period 2:

- C_{max}: maximum observed concentration
- AUC_{∞}: area under the concentration-time curve from time 0 to infinity calculated using the observed value of

the last quantifiable concentration

- AUC_{last}: area under the concentration-time curve from time 0 to time of the last quantifiable concentration

Secondary Endpoints

The safety profile for TAK-906 alone and TAK-906 + rifampin:

- TEAE assessments
- Vital signs
- 12-lead ECG
- Clinical laboratory testing (hematology, serum chemistry, and urinalysis)

Exploratory Endpoints

CCI [redacted]

Statistical Considerations:

For evaluation of potential effect of rifampin on TAK-906 PK, mixed effects model analysis will be performed on the natural log (ln)-transformed AUC_{∞}, AUC_{last}, and C_{max} to assess the potential effect of rifampin on TAK-906 PK. The mixed effects models will include sequence, treatment, and period as fixed effects, and subject nested within sequence as a random effect. Each mixed effects model will include calculation of least-squares means (LSM) as well as the difference between treatment LSM.

Ratios of LSM will be calculated using the exponentiation of the difference between treatments LSM from the analyses on the ln-transformed AUC_{∞}, AUC_{last}, and C_{max}.

Consistent with the two one-sided test [2], 90% confidence intervals (CIs) for the ratios will be derived by exponentiation of the CIs obtained for the difference between treatment LSM resulting from the analyses on the ln-transformed AUC_{∞}, AUC_{last}, and C_{max}.

The comparison of interest is as follows:

- Treatment B compared with Treatment A

CCI [redacted]

Additional statistical analyses may be performed if deemed appropriate. A more detailed description of the planned analyses will be presented in the Statistical Analysis Plan (SAP).

Sample Size Justification:

With a sample size of 12 subjects, there is an 80% probability for the 90% CIs to be within 65% and 135% of the point estimate of the geometric mean ratio for C_{max} and for AUC of TAK-906 with and without rifampin. Thus, if the observed ratios of geometric means of TAK-906 with and without rifampin is 2 for C_{max} and AUC, then the corresponding 90% CIs based on data from 12 subjects will be approximately (1.6, 2.5). This calculation assumes that log(C_{max}) and log(AUC) of TAK-906 are normally distributed with intra-subject coefficients of variation that do not

exceed 31%.

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

2.0 STUDY SCHEMATIC

<table>
<tr><th>Screening</th><th colspan="3">Treatment Study Periods 1 and 2 [a]</th><th>Follow-up Visit</th></tr>
<tr><td rowspan="4">Day -28 to Day -2</td><td>Day -1</td><td>Day 1</td><td>Days 2 and 3</td><td rowspan="4">14 ± 2 days after last TAK-906 dosing</td></tr>
<tr><td>Check-in</td><td>Dosing at Hour 0 [b]</td><td></td></tr>
<tr><td></td><td colspan="2">PK sampling and safety monitoring up to 48 hours postdose</td></tr>
<tr><td colspan="3">< - - - - - - - - - - - - confinement - - - - - - - - - - - - ></td></tr>
</table>

[a] Prior to dosing on Day 1 of Period 1, subjects will be randomized in a ratio of 1:1 to one of two treatment sequences. Subjects will receive each treatment on one occasion. Each TAK-906 dosing will be separated by at least 7 days from the time of Study Period 1 dose administration.
[b] TAK-906 administration is defined as Hour 0.

3.0 SCHEDULE OF STUDY PROCEDURES

Procedures/Assessments	**Screening**	**Study Days for Treatment A [a]**															
Study Days	**Day -28 to -2**	**-1**	**1**												**2**		**3**
Hours		**Check-in**	**Predose**	**0**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**6**	**8**	**12**	**16 [l]**	**24**	**36**	**48**
Administrative Procedures																	
Informed consent	X																
Inclusion/exclusion criteria	X	X															
Medical history/demographics	X																
Prior and concomitant medication review	X	----------Continuous Monitoring----------															
Clinical Procedures/Assessments																	
Full physical examination [m]	X		X [b]														
Height	X																
Weight	X																
BMI	X																
12-Lead Safety ECG	X		X [b] [c]			X[c]		X[c]		X[c]		X[c]					X[c]
Semi-recumbent vital signs (heart rate, systolic blood pressure and diastolic blood pressure)	X		X[b] [d]			X[d]		X[d]		X[d]		X[d]					X[d]
Vital signs (respiratory rate, oral [at the floor of the mouth]/tympanic temperature)	X		X														
Dosing of TAK-906 at the clinical research unit [e]				X													
AE monitoring	----------Continuous Monitoring----------																
Laboratory Procedures/Assessments																	
Hematology	X	X															X[i]
Urinalysis	X	X															X[i]
Chemistry	X	X															X[i]
Serum pregnancy test (♀ only)	X	X															

Procedures/Assessments	Screening	Study Days for Treatment A [a]															
Study Days	Day -28 to -2	-1	1												2		3
Hours		Check-in	Predose	0	0.5	1	1.5	2	3	4	6	8	12	16 [l]	24	36	48
Serum FSH (PMP ♀ only)	X																
Urine drug screen	X	X															
Urine cotinine screen	X																
Urine alcohol test [f]	X	X															
Hepatitis screen	X																
Human immunodeficiency virus screen	X																
Pharmacokinetics Evaluations																	
CCI [redacted]																	
CCI [redacted]																	
CCI [redacted]																	
Other																	
Confinement		X----------X															
Meals fasting [k]			X----------X														

Procedures/Assessments	**Study Days for Treatment B [a]**																	**Follow-up Visit**
Study Days	**-1**	**1**													**2**		**3**	**14 ± 2 days after last dose of TAK-906**
Hours	**Check-in**	**Predose**	**-0.5**	**0**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**6**	**8**	**12**	**16 [l]**	**24**	**36**	**48**	
Administrative Procedures																		
Inclusion/exclusion criteria	X																	
Prior and concomitant medication review	----------Continuous Monitoring----------																	
Clinical Procedures/Assessments																		
Full physical examination [m]		X [b]																X
12-Lead Safety ECG		X [b] [c]				X[c]		X[c]		X[c]		X[c]					X[c]	X
Semi-recumbent vital signs (heart rate, systolic blood pressure and diastolic blood pressure)		X [b] [d]				X[d]		X[d]		X[d]		X[d]					X[d]	X
Vital signs (respiratory rate, oral [at the floor of the mouth]/tympanic temperature)		X																
Dosing of rifampin at the clinical research unit [e]			X															
Dosing of TAK-906 at the clinical research unit [e]				X														
AE monitoring	----------Continuous Monitoring----------																	
Laboratory Procedures/Assessments																		
Hematology	X																X[i]	X
Urinalysis	X																X[i]	X
Chemistry	X																X[i]	X
Serum pregnancy test (♀only)	X																	X
Urine drug screen	X																	
Urine alcohol test [f]	X																	

Procedures/Assessments	Study Days for Treatment B [a]																Follow-up Visit
Study Days	-1	1													2		3	14 ± 2 days after last dose of TAK-906
Hours	Check-in	Predose	-0.5	0	0.5	1	1.5	2	3	4	6	8	12	16 [l]	24	36	48	
Pharmacokinetics Evaluations																		
CCI																		
CCI																		
CCI																		
CCI																		
Other																		
Confinement	X----------X																	
Meals fasting [k]		X----------X																

(a) There will be a washout period of at least 7 days between the TAK-906 dosing in each study period.

(b) Day 1 predose of Period 1 and Period 2 assessment may be done within approximately 24 hours prior to study drug administration.

(c) Triplicate measurements to be conducted at predose, and at 1, 2, 4, 8 and 48 hours postdose (times relative to TAK-906 dose [Hour 0]).

(d) Measured at predose, and at 1, 2, 4, 8 and 48 hours postdose (times relative to TAK-906 dose [Hour 0]). Subjects should have rested in a semi-recumbent position for at least 5 minutes before the measurements

(e) Dosing will occur at the CRU based on the treatment the subjects are randomized to receive within a study period. Treatment A: 25 mg TAK-906 capsule; Treatment B: 25 mg TAK-906 capsule given immediately after a single 30-minute IV dose of 600 mg rifampin.

(f) An alcohol breath test may be performed at the discretion of the investigator.

(g) CCI

(h) CCI

(i) To be performed on Day 3 of each period or prior to early termination from the study.

(j) To be collected in Period 1 only.

(k) Both doses of TAK-906 and rifampin (Day 1 of Period 1 and Day 1 of Period 2) will be administered after an overnight fast of at least 10 hours and subjects will be required to fast for at least 4 hours post TAK-906 dose.

(l) The 16-hour postdose on Day 1 will be either on Day 1 or Day 2, depending on the time of dosing on Day 1.

(m) Symptom-driven physical examination may be performed at other times, at the investigators or designee's discretion.

Abbreviations: ♀ = female, AE = Adverse events, CCI , CRU = Clinical research unit, CCI , ECG = Electrocardiogram, FSH = Follicle stimulating hormone, CCI , PMP = Postmenopausal.

4.0 INTRODUCTION

4.1 Background

The intended indication for TAK-906 is to treat patients with gastroparesis, a disorder of the stomach characterized by delayed gastric emptying in the absence of mechanical obstruction. Symptoms are chronic with episodic exacerbation [3]. These symptoms may include nausea, vomiting, early satiety, abdominal pain, and postprandial fullness. The prevalence of gastroparesis in the United States (US) is estimated to be approximately 24.2 per 100,000 [4]. In cases of chronic gastroparesis, diabetic (29%), postsurgical (13%), and idiopathic (36%) etiologies comprise the majority of cases in the tertiary referral setting [5].

TAK-906 is a peripherally selective (eg limited penetration of the blood brain barrier [BBB]) dopamine D2/D3 receptor antagonist. It has demonstrated suitable PK and pharmacodynamic (PD) activity in a phase 1 study and other completed studies. Therefore TAK-906 is expected to reduce nausea and vomiting, without the side effects which restrict the use of other D2/D3 antagonists. Because of its low BBB penetration and a weak human ether-a-go-go-related gene channel affinity indicative of a low potential cardiac risk, TAK-906 is anticipated to have an improved safety profile, compared to other D2/D3 antagonists (eg, metoclopramide and domperidone).

TAK-906 is a substrate of P-glycoprotein (P-gp) and organic anion transporting polypeptide (OATP) 1B1 and OATP1B3. Further uptake and kinetic studies using OATP1B1/1B3-expressing cells and human hepatocytes as a reference of pravastatin suggested that almost all the in vivo TAK-906 uptake into human hepatocytes is by a saturable process of transporters, not by a passive process and TAK-906 is taken up into the human hepatocytes predominantly by OATP1B1.

CCI

[redacted]

Refer to the TAK-906 Investigator's Brochure for complete information on the investigational product [6].

4.2 Rifampin

Rifampin is a semisynthetic antibiotic derivative of rifamycin SV. Rifampin inhibits deoxyribonucleic acid-dependent ribonucleic acid (RNA) polymerase activity in susceptible *Mycobacterium tuberculosis* organisms. Rifampin can be administered by oral route or by an IV infusion of 30-minutes to 3 hours. The IV doses are the same as oral doses [1].

After intravenous administration of a 300 or 600 mg dose of rifampin infused over 30 minutes to healthy male volunteers (n=12), mean peak plasma concentrations were 9.0 ± 3.0 and 17.5 ± 5.0 mcg/mL, respectively. After IV administration of 300 or 600 mg doses, rifampin plasma concentrations in these volunteers remained detectable for 8 and 12 hours, respectively

Plasma concentrations after the 600 mg dose, which were disproportionately higher (up to 30% greater than expected) than those found after the 300 mg dose, indicated that the elimination of larger doses was not as rapid.

Rifampin is widely distributed throughout the body. It is present in effective concentrations in many organs and body fluids, including cerebrospinal fluid. Rifampin is about 80% protein bound. Most of the unbound fraction is not ionized and therefore diffuses freely into tissues. Rifampin is rapidly eliminated in the bile and undergoes progressive enterohepatic circulation and deacetylation to the primary metabolite, 25-desacetyl-rifampin. This metabolite is microbiologically active. Less than 30% of the dose is excreted in the urine as rifampin or metabolites.

Rifampin, when acutely dosed, is an inhibitor of OATP 1B1/1B3 and P-gp transporters. Following multiple dosing, rifampin is a potent inducer of drug metabolism by inducing a variety of hepatic and intestinal CYP enzymes, especially CYP3A4, and hepatic P-gp.

Rifampin is classified as Food and Drug Administration (FDA) pregnancy category C.

Refer to the most recent package insert in US for complete information on rifampin [1].

4.3 Rationale for the Proposed Study

TAK-906 is a substrate of P-gp and OATP1B1 and OATP1B3. Further uptake and kinetic studies using OATP1B1/1B3-expressing cells and human hepatocytes as a reference of pravastatin suggested that almost all the in vivo TAK-906 uptake into human hepatocytes is by a saturable process of transporters, not by a passive process and TAK-906 is taken up into the human hepatocytes predominantly by OATP1B1.

Rifampin, widely known as a potent inducer of many drug metabolizing enzymes including CYP450 and UDP-glucuronosyltransferases [7, 8], is a potent inhibitor of OATP1B1 and OATP1B3 [9] when dosed acutely. Recently, Reitman et al. have demonstrated that oral rifampin, given acutely, is also an inhibitor of P-gp at the gut but not the systemic level [10]. In order to discriminate between the effect of rifampin on P-gp and on OATP1B, rifampin will be administered as an IV formulation.

This study is designed to investigate the effect of a potent inhibitor of OATP1B1 and OATP1B3 (rifampin) on the oral single-dose PK of TAK-906 in healthy adult subjects. Rifampin has been

chosen as it is recommended by the FDA and EMA as a suitable potent OATP1B1 and OATP1B3 inhibitor for use in drug-drug interaction (DDI) studies [11, 12].

4.4 Benefit/Risk Profile

The doses of TAK-906 and rifampin selected for this study are not anticipated to induce any potential risk or benefit to subjects participating in this study and are administered as outlined in the IB and product label, respectively.

The safety monitoring practices employed by this protocol (ie, AE monitoring, 12-lead ECG, vital signs, clinical laboratory tests, and physical examinations) are considered adequate to protect subjects' safety.

There will be no direct health benefit for study subjects from receipt of study drug. An indirect health benefit to the healthy subjects enrolled in this study is the free medical tests received at screening and during the study.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Hypothesis

NA

5.2 Study Objectives

5.2.1 Study Primary Objective

- To evaluate the effect of single-dose IV rifampin on the single-dose PK of orally administered TAK-906.

5.2.2 Study Secondary Objective

- To evaluate the safety and tolerability of a single oral dose of TAK-906 in the presence and absence of rifampin.

5.2.3 Study Exploratory Objective

- CCI [redacted]

5.3 Endpoints

5.3.1 Primary Endpoints

The following plasma PK parameters for TAK-906 on Day 1 in Study Period 1 and Study Period 2:

- C_{max}: maximum observed concentration
- AUC_{∞}: area under the concentration-time curve from time 0 to infinity calculated using the observed value of the last quantifiable concentration
- AUC_{last}: area under the concentration-time curve from time 0 to time of the last quantifiable concentration

5.3.2 Secondary Endpoints

The safety profile for TAK-906 alone and TAK-906 + rifampin:

- TEAE assessments
- Vital signs
- 12-lead ECG
- Clinical laboratory testing (hematology, serum chemistry, and urinalysis)

5.3.3 Exploratory Endpoints

CCI

[redacted]

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is a phase 1, open-label, randomized, two-way crossover study to evaluate the effect of single-dose IV rifampin on the single-dose PK of oral TAK-906 in healthy adult subjects.

Subjects will be screened from Day -28 to -2, to determine eligibility before randomization and eligible subjects will return to the clinic at Check-in (Day -1, Period 1).

The study will include a screening visit, two treatment periods, and a follow-up visit. Treatment will consist of a single oral dose of 25 mg TAK-906 capsule (Treatment A), and a single oral dose of 25 mg TAK-906 capsule together with a single IV dose of 600 mg rifampin (Treatment B). Eligible subjects will be randomly assigned to 1 of 2 treatment sequences (ie, AB, BA). Randomization sequences are presented below:

Table 6.a Randomization Sequences

Sequence	Number of Subjects	Study Period 1	Study Period 2
AB	6	TAK-906 oral	Rifampin IV+ TAK-906 oral
BA	6	Rifampin IV + TAK-906 oral	TAK-906 oral

Treatment A = 25 mg TAK-906 capsule

Treatment B = 25 mg TAK-906 capsule together with a single IV dose of 600 mg rifampin

Each dose of TAK-906 will be separated by a washout period of at least 7 days from the time of Study Period 1 TAK-906 dose administration.

On Day 1 of Treatment A after an overnight fast of at least 10 hours, a single oral dose of TAK-906 capsule will be administered.

On Day 1 of Treatment B after an overnight fast of at least 10 hours, IV rifampin will be administered over a 30-minute period, and TAK-906 capsule will be given immediately at the end of the infusion.

In each treatment arm, subjects will be confined from the day prior to dosing (Day -1, Check-in), at the time indicated by the CRU, until after the 48-hour blood draw (Day 3).

Blood samples for assessment of TAK-906 concentrations will be measured from predose to 48 hours after each dose of TAK-906.

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

There will be a washout period of at least 7 days between the TAK-906 dosing in each study period.

All subjects who received at least one dose of study drug (including subjects who terminate the study early) will return to the CRU 14 ± 2 days after the last dose of TAK-906 for follow-up procedures, and to determine if any AE has occurred since the last study visit.

6.2 Rationale for Study Design, Dose, and Endpoints

6.2.1 Rationale of Study Design

This study is designed in accordance with FDA Guidance documents for DDI studies to assess if TAK-906 is an OATP substrate.

The study design is open-label and treatments are administered in a crossover fashion, as the primary objective is to compare the PK of a single dose of TAK-906 administered alone and when administered with rifampin. Because this is an objective measurement, there is no risk of potential bias of the study results; hence, neither study blinding nor inclusion of a placebo group is required.

In healthy subjects, the biological half-life of rifampin in serum averages about 3 hours after a 600 mg dose and the half-life following a single oral dose of TAK-906 (5 mg - 300 mg) averaged approximately 4 hours when administered in the fasted state, therefore a washout period of at least 7 days between TAK-906 doses in Study Periods 1 and 2 is sufficient to prevent any carryover effects.

6.2.2 Rationale for Dose

A single oral dose of TAK-906 25 mg has been chosen as it is expected to be a clinically efficacious dose. In addition, this dose is well below the maximum single dose (300 mg) that has been investigated to date and was shown to be well tolerated in healthy subjects, to allow for any increases in exposure that may be observed with transporter inhibition.

The recommended single IV dose of 600 mg rifampin was selected to ensure maximal selectivity for inhibiting the hepatic transporters, OATP1B1 and OATP1B3, and to avoid effects on gut transporters (eg, P-gp) as well as to not result in enzyme and transporter induction [13, 14].

6.2.3 Rationale for Endpoints

6.2.3.1 Pharmacokinetic Endpoints

The primary PK endpoints will include C_{max}, AUC_{∞}, and AUC_{last}, as these parameters describe the exposure and bioavailability of TAK-906 and are the most relevant PK parameters for the purpose of evaluating an interaction.

6.2.3.2 Safety Endpoints

TEAEs, vital signs, ECG findings, and laboratory test results are commonly used safety endpoints.

6.2.3.3 Exploratory Endpoints

CCI

[redacted]

6.2.4 Critical Procedures Based on Study Objectives: Timing of Procedures

For this study, the collection of blood [redacted] is the critical parameter and is required to be collected as close to the scheduled times defined in this protocol as possible. All other procedures should be completed as close to the prescribed/scheduled time as possible, but can be performed prior or after the prescribed/scheduled time.

6.3 Study Design/Dosing/Procedures Modifications Permitted Within Protocol Parameters

No design or dosing modifications are allowed. Modifications to study procedures are permitted as required for management/treatment of AE's.

6.4 Study Beginning and End/Completion

6.4.1 Definition of Beginning of the Study

The beginning of the study will be defined as the beginning of screening (ie, signing of the ICF) of the first subject.

6.4.2 Definition of End of the Study

The end of study for each sequence is defined as the date of the last scheduled study procedure (ie, the follow-up visit on Day 14 ± 2 days for all subjects including those who received at least one dose of study drug and withdrawn early as outlined in the Schedule of Study Procedures (Section 3.0).

6.4.3 Definition of Study Completion

The end of the study is scheduled after completion of the evaluations in the follow-up visit for the last subject in the study.

This time period may change in the event that the study is terminated early or the last subjects is lost to follow-up.

6.4.4 Definition of Study Discontinuation

In consultation with the Sponsor, Celerion reserves the right to terminate the study in the interests of subject welfare.

The Sponsor reserves the right to suspend or terminate the study at any time and not allow additional enrollment, but to continue the study safety monitoring procedures for subjects that have already dosed for abnormalities as required.

6.4.5 Criteria for Premature Termination or Suspension of the Study

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.

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

6.4.6 Criteria for Premature Termination or Suspension of a Site

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

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

In the event that the Sponsor, an institutional review board (IRB)/independent ethics committee (IEC), or regulatory authority elects to terminate or suspend the study or the participation of a study site, a study-specific procedure for early termination or suspension will be provided by the Sponsor; the procedure will be followed by applicable study sites during the course of termination or study suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

7.1 Inclusion Criteria

Subjects must fulfill all of the following inclusion criteria to be eligible for participation in the study:

1. Healthy, adult, male or female, 19-55 years of age, inclusive, at screening.
2. Continuous non-smoker who has not used nicotine-containing products for at least 3 months prior to the first dosing and throughout the study, based on screening urine cotinine test.
3. BMI $\geq$ 18.0 and $\leq$ 30.0 kg/m^2 at screening.
4. Medically healthy with no clinically significant medical history, physical examination, laboratory profiles, vital signs, or ECGs, as deemed by the investigator or designee.
5. For a male or female of non-childbearing potential, use acceptable birth control methods as indicated in Appendix D.
6. A male subject who is nonsterilized and sexually active with a female partner of childbearing potential must agree to use a barrier method of contraception from signing of the ICF throughout the duration of the study and through to the follow-up visit (ie, 14 ± 2 days after the last TAK-906 dosing) (refer to Appendix D).
7. If male, must agree not to donate sperm from signing of the ICF until follow-up visit (ie, 14 ± 2 days after the last TAK-906 dosing).
8. Understands the study procedures in the ICF, and be willing and able to comply with the protocol.

7.2 Exclusion Criteria

Subjects must not be enrolled in the study if they meet any of the following criteria:

1. Is mentally or legally incapacitated or has significant emotional problems at the time of the screening visit or expected during the conduct of the study.
2. History or presence of clinically significant endocrine, gastrointestinal (including motility disorder and intestinal obstruction), cardiovascular, hematological, hepatic, immunological, renal, respiration, genitourinary, or major neurological (including stroke and chronic seizures) abnormalities or disease in the opinion of the investigator or designee.
3. History of any illness that, in the opinion of the investigator or designee, might confound the results of the study or poses an additional risk to the subject by their participation in the study.
4. History of cancer (malignancy).
5. History or presence of alcoholism or drug abuse within the past 2 years prior to the first dosing.
6. History or presence of hypersensitivity or idiosyncratic reaction to TAK-906, to rifampin, or to related compounds or contraindicated compounds such as antivirals [1].

7. Female subjects of childbearing potential.
8. Female subjects with a positive pregnancy test or lactating at screening or first check-in.
9. Positive urine drug or alcohol results at screening or first check-in.
10. Positive urine cotinine at screening.
11. Positive results at screening for HIV, HBsAg, or HCV.
12. QTcF interval is >450 msec or ECG findings are deemed abnormal with clinical significance by the investigator or designee at screening.
13. Estimated creatinine clearance <90 mL/min at screening.
14. Unable to refrain from or anticipates the use of:
    - Any drug, including prescription and non-prescription medications, herbal remedies, or vitamin supplements within 14 days prior to the first dosing and throughout the study. After first dosing, acetaminophen (up to 2 g per 24 hours) may be administered at the discretion of the investigator or designee; Sponsor must be consulted prior to administering acetaminophen to a subject.
    - Any drugs known to significantly affect the absorption, distribution, metabolism, or elimination of study drugs (TAK-906 or rifampin) including any drug that affects the function of OATP1B1 or 1B3, within 28 days prior to the first dosing and throughout the study. Appropriate sources (eg, Flockhart Table™) will be consulted to confirm lack of PK/PD interaction with study drugs.
15. Has been on a diet incompatible with the on-study diet, in the opinion of the investigator or designee, within the 30 days prior to the first dosing and throughout the study.
16. Donation of blood or significant blood loss (eg, approximately 500 mL) within 56 days prior to the first dosing.
17. Plasma donation within 7 days prior to the first dosing.
18. Participation in another clinical study within 30 days or 5 half-lives prior to the first dosing. The 30-day window or 5 half-lives will be derived from the date of the last blood collection or dosing, whichever is later, in the previous study to Day 1 of Study Period 1 of the current study.

7.3 Excluded Medications, Supplements, Dietary Products

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

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

Category	Between Screening and First Dosing (Days -28 to predose [Day 1])	After First Dosing (Day 1) to Follow-Up
Alcohol	Prohibited from 48 hours prior to first dosing.	Prohibited until end of PK collection in Period 2.
Xanthine and/or caffeine	Prohibited from 24 hours prior to first dosing in each period [a]	Prohibited until end of PK collection in each period [a].
Medications [b]	See Sections 7.2 and 7.3	See Sections 7.2 and 7.3
Food substance		
Grapefruit/Seville orange	Prohibited from 14 days prior to first dosing	Prohibited until end of PK collection in Period 2.
Other Fruit Juice	Prohibited from 72 hours prior to first dosing	Prohibited until end of PK collection in Period 2.
Vegetables from the mustard green family (eg, kale, broccoli, watercress, collard greens, kohlrabi, Brussels sprouts, mustard), and charbroiled meats	Prohibited from 7 days prior to first dosing	Prohibited until end of PK collection in Period 2.

[a] small amounts of caffeine derived from normal foodstuffs e.g., 250 mL/8 oz./1 cup decaffeinated coffee or other decaffeinated beverage, per day, with the exception of espresso; 45 g/1.5 oz. chocolate bar, per day, would not be considered a deviation to this restriction.

[b] Occasional use of acetaminophen, up to 2 g per 24 hours, as approved by the investigator or designee is allowed following approval by the Sponsor.

If deviations occur, the investigator will decide on a case-by-case basis whether the subject may continue participation in the study based on the time the drugs were administered and their pharmacology.

7.3.1 Tobacco or Nicotine-Containing Products Usage

Subjects will not have used nicotine-containing products for at least 3 months prior to the first dosing and will not use throughout the study.

7.4 Diet, Fluid, Activity

7.4.1 Diet and Fluid

Water (except water provided with each oral dosing) will be restricted 1 hour prior to and 1 hour after each oral study drug administration, but will be allowed *ad libitum* at all other times, when dosing occurs at the CRU. Other fluids may be given as part of meals and snacks but will be restricted at all other times throughout the confinement period.

On Day 1 of each Study Period, subjects will fast overnight for at least 10 hours prior to TAK-906 administration and will continue to fast for at least 4 hours postdose of TAK-906. Water may be consumed without restrictions beginning 1 hour after dosing. Lunch will be provided approximately 4 hours after dosing of TAK-906. Dinner will be provided approximately 9 to 10 hours after dosing of TAK-906. An evening snack will be permitted at the appropriate time. The meals and snacks served will be similar across study days, periods, and subjects.

If a blood draw or any study procedure coincides with a meal, the blood draw/study procedures will take precedence to the meal.

7.4.2 Activity

Subjects will be seated for oral administration of TAK-906 capsule and will be in a semi-recumbent position for IV administration of rifampin. When rifampin and TAK-906 are dosed together subjects will be seated upright just after IV administration of rifampin for the TAK-906 dosing.

Subjects will remain ambulatory or seated upright for the first 4 hours post TAK-906 dose, except when they are required to be in a different position for other study procedures. However, should AEs occur at any time, subjects may be placed in an appropriate position or will be permitted to lie down on their right side.

Subjects will be instructed to refrain from strenuous physical activity which could cause muscle aches or injury, including contact sports at any time from screening until discharge from the clinic on Day 3 of Period 2.

7.5 Criteria for Discontinuation or Withdrawal of a Subject

Subjects are free to withdraw from the study at any time for any reason.

In addition, subjects may be withdrawn from the study by the investigator or designee for the following reasons:

- AEs.
- A positive pregnancy test for females.
- Positive drug or alcohol results.
- Difficulties in blood collection.

- Interruption of IV infusion.

A subject may be withdrawn by the investigator (or designee) or the Sponsor if enrollment into the study is inappropriate, the study plan is violated, or for administrative and/or other safety reasons.

7.6 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.5. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator. In addition, efforts should be made to perform all procedures scheduled for the Early Termination Visit and the Follow-up Visit.

7.7 Subject Replacement

Discontinued subjects may be replaced at the discretion of the Sponsor and the investigator. Subjects who drop out for safety reasons will not be replaced.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

8.1 Clinical Study Drugs

8.1.1 TAK-906 Capsule

Oral dose of TAK-906 drug product is a nonsterile, capsule dosage form, supplied in a hard gelatin capsule of TAK-906 maleate. TAK-906 maleate is the active pharmaceutical ingredient.

No other active ingredients are included in the drug product.

8.1.2 Rifampin IV

IV rifampin drug product is a solution for infusion; containing rifampin 600 mg, sodium formaldehyde sulfoxylate 10 mg, and sodium hydroxide to adjust pH. Rifampin is the active pharmaceutical ingredient.

No other active ingredients are included in the drug product.

8.1.3 Study Drug Administration

Treatments will consist of a single oral dose of 25 mg TAK-906 capsule (Treatment A), and a single oral dose of 25 mg TAK-906 capsule administered immediately after completion of a single IV dose of 600 mg rifampin (Treatment B).

TAK-906 will be administered orally following an overnight fast with approximately 240 mL of water. Subjects will be instructed not to crush, split or chew the oral study drug.

The IV rifampin will be administered in a 30-minute infusion, prior to administration of TAK-906.

The pharmacy at the CRU will provide each dose in individual unit dose containers for each subject and for each study period, as per the randomization scheme.

The exact clock time of oral dosing will be recorded; the start and end of infusion for the IV dose will be recorded. Each TAK-906 administration is defined as Hour 0.

8.1.4 Clinical Study Drug Labeling

TAK-906 capsule containers will be affixed with a clinical label in accordance with local regulatory requirements.

Rifampin will be provided with the commercially available package and labeling in accordance with local regulatory requirements.

8.1.5 Clinical Study Drug Inventory and Storage

The Sponsor will supply sufficient quantities of TAK-906 and the CRU will provide sufficient quantities of rifampin (the same lot number will be used throughout the study) to allow completion of this study.

The lot numbers and expiration dates (where available) of the study drugs supplied will be recorded in the final report.

Investigational drugs must be kept in an appropriate, limited-access, secure place until it is used, destroyed or returned to the Sponsor or designee for destruction. Investigational drugs must be stored under the conditions specified on the label, and remain in the original container until dispensed.

A temperature log of the drug storage area must be maintained every working day.

Records will be made of the receipt, preparation, dispensing, and final disposition of the study drugs supplied. All study products will be prepared and labeled by licensed pharmacy staff according to the procedures outlined in the pharmacy manual.

8.1.6 Clinical Study Drug Blinding

This is an open-label study.

8.1.7 Randomization Code Creation and Storage

Eligible subjects will be randomly assigned to 1 of 2 treatment sequences ie, AB or BA according to a randomization schedule generated by Celerion where Treatment A is 25 mg TAK-906 capsule and Treatment B is 25 mg TAK-906 capsule given immediately after a single 30-minute IV dose of 600 mg rifampin.

8.1.8 Clinical Study Blind Maintenance/Unblinding Procedure

NA.

8.1.9 Accountability and Destruction of Celerion-Supplied Drugs

At the conclusion of the study, any unused TAK-906 study drug will be retained by Celerion, returned to the Sponsor or designee, or destroyed, as per Sponsor instructions. At the conclusion of the study, any unused rifampin will be destroyed. If no supplies remain, this fact will be documented in the pharmacy product accountability records.

9.0 STUDY PROCEDURES

9.1 Administrative Procedures

9.1.1 Informed Consent Procedure

The purpose of the study, the procedures to be carried out and the potential hazards will be described to the subjects in non-technical terms. Subjects will be required to read, sign and date an ICF summarizing the discussion prior to screening, and will be assured that they may withdraw from the study at any time without jeopardizing their medical care.

Subjects will be given a copy of their signed ICF.

9.1.1.1 Assignment of Screening and Randomization Numbers

Each subject will be assigned a unique identification number upon screening. Subjects who complete the study screening assessments and meet all the eligibility criteria will be assigned a unique randomization identification number at the time of the first dosing, different from the screening number, and will receive the corresponding product at the corresponding site of administration.

If replacement subjects are used, the replacement subject number will be 100 more than the original (eg, Subject No. 101 will replace Subjects No. 1).

9.1.1.2 Study Drug Assignment

This is a 2-way, crossover study. Subjects will receive each treatment in 2 periods as detailed in Section 6.1.

9.1.2 Inclusion and Exclusion

Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0.

9.1.3 Medical History/Demography

Medical history and demographic data, including name, sex, age, race, ethnicity, and history of tobacco use will be recorded.

9.1.4 Concomitant Medications

Concomitant medications will be prohibited as listed in Section 7.2 and in Section 7.3. All medications taken by subjects during the course of the study will be recorded.

9.2 Clinical Procedures and Assessments

The Schedule of Study Procedures (Section 3.0) summarizes the clinical procedures to be performed at each visit. Individual clinical procedures are described in detail below. Additional

evaluations/testing may be deemed necessary by the investigator or designee and/or the Sponsor for reasons related to subject safety.

For this study, the collection of blood for plasma concentrations for TAK-906 is the critical parameter and is required to be collected as close to the scheduled times defined in this protocol as possible. All other procedures should be completed as close to the prescribed/scheduled time as possible, but can be performed prior or after the prescribed/scheduled time.

9.2.1 Physical Examination

Physical examinations will be performed as outlined in the Schedule of Study Procedures (Section 3.0).

Symptom-driven physical examinations may be performed at other times, if deemed necessary by the investigator or designee.

9.2.2 Height and Weight

Body height (cm) and weight (kg) will be reported as outlined in the Schedule of Study Procedures (Section 3.0).

9.2.3 BMI

BMI will be calculated based on the height and weight measured at screening.

9.2.4 Vital Signs

Single measurements of body temperature, respiratory rate, blood pressure, and heart rate, will be measured as outlined in the Schedule of Study Procedures (Section 3.0). Additional vital signs may be taken at any other times, if deemed necessary.

Blood pressure and heart rate measurements will be performed with subjects in a semi-recumbent position (at least 5 minutes), except when they are required to be in a different position because of other study procedures and/or AEs (eg, nausea, dizziness) or if deemed necessary by the investigator or designee.

9.2.5 12-Lead ECG

Triplicate 12-lead ECGs will be performed as outlined in the Schedule of Study Procedures (Section 3.0). Additional ECGs may be taken at any other times, if deemed necessary by the investigator or designee.

ECGs will be performed with subjects in a semi-recumbent position. All ECG tracings will be reviewed by the investigator or designee.

9.2.6 Study Drug Administration

Single dose of oral TAK-906 or single dose of oral TAK-906 coadministered with IV rifampin will be provided as described in Section 8.1.3.

Study drugs will be administered on Day 1 of each period per the randomization.

The pharmacy at the CRU will provide all doses for each subject, as per the randomization (Section 8.1.7).

9.2.7 AE Monitoring

Subjects will be monitored throughout the study for adverse reactions to the study drugs and/or procedures as described in Section 10.0.

9.2.8 Laboratory Procedures and Assessments

All tests listed below will be performed as outlined in the Schedule of Study Procedures (Section 3.0). In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the investigator or designee.

9.2.8.1 Clinical Laboratory Tests

Hematology

Hematology will consist of the following tests:

Hemoglobin	Red blood cell count
Hematocrit	Platelet count
Total and differential leukocyte count	

Chemistry

Serum chemistry tests will be performed after at least an 8-hour fast; however, in case of dropouts or rechecks, subjects may not have fasted for 8 hours prior to the serum chemistry sample being taken.

Chemistry evaluations will consist of the following standard chemistry panel:

Blood Urea Nitrogen	Sodium
Bilirubin (total and direct)	Potassium
Alkaline phosphatase	Glucose
Aspartate aminotransferase (AST)	Chloride
Alanine aminotransferase (ALT)	Total protein
Albumin	
Creatinine*	

* At Screening, creatinine clearance will be calculated using Cockcroft-Gault formula.

Urinalysis

Urinalysis will consist of the following tests:

pH	Bilirubin
Specific gravity	Blood *
Protein *	Nitrite *
Glucose	Urobilinogen
Ketones	Leukocyte esterase *

*If urinalysis is positive for protein, blood, nitrite and/or leukocyte esterase, a microscopic examination (for red blood cells, white blood cells, bacteria, casts, and epithelial cells) will be performed.

Other

HIV test	Urine drug screen – Opiates (includes morphine, heroin (diacetylmorphine), codeine, 6-acetylmorphine, dihydrocodeine, hydrocodone, thebaine, and hydromorphone) – Amphetamines – Barbiturates – Benzodiazepines – Cocaine – Cannabinoids
HBsAg	
HCV	
Urine alcohol screen	
Urine cotinine screen	
Serum pregnancy test (human chorionic gonadotropin [hCG]) (a)	
FSH if menopause is suspected (b)	

(a) Serum hCG pregnancy test will be done on all female subjects at Screening, Check-in (Day -1) and at Follow-up Visit Day /Early Termination.
(b) FSH level will be obtained for female subjects at Screening if they are postmenopausal by history (ie, defined as no menses for 12 months without an alternative medical cause; a high FSH level in the postmenopausal range (FSH >40 IU/L) may be used to confirm a post-menopausal state in younger women [eg, those <45 year old] or women who are not using hormonal contraception or hormonal replacement therapy) and not surgically sterile. The FSH result must be >40 IU/L for the subject to be permitted not to use highly effective contraception.

9.3 PK Sample Collection

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

For all subjects, blood samples for the determination of plasma TAK-906 CCI [redacted] will be collected at scheduled time points as delineated in the Schedule of Study Procedures (Section 3.0) in 4 mL blood collection tubes containing the appropriate anticoagulant, respectively. The actual time of sample collection will be recorded on the source document in the case report form (CRF).

Instruction for blood sampling, collection, processing, and sample shipment will be provided separately.

Table 9.a Primary Specimen Collections

Specimen Name	Primary Specimen	Primary Specimen Derivative	Description of Intended Use	Sample Collection
Plasma sample for PK	Blood	Plasma	Plasma sample for PK analysis	Mandatory

If a subject experiences an SAE, a blood sample for PK analysis should also be obtained at the unscheduled visit. PK samples will be collected at Early Termination at the discretion of the investigator.

9.3.1 PK Measurements

The PK parameters of TAK-906 will be determined from the concentration-time profiles for all evaluable subjects using a noncompartmental analysis method. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. A more detailed description will be given in the clinical pharmacology analysis plan.

The following PK parameters will be calculated from plasma concentrations of TAK-906 CCI [redacted] as appropriate, unless otherwise specified:

AUC_{last}: The area under the concentration-time curve from time 0 to time of the last quantifiable concentration.

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

$AUC_{extrap\%}$: The area under the curve from the last quantifiable concentration to infinity calculated using the observed value of the last quantifiable concentration, expressed as a percentage of AUC_{∞}.

C_{max}: Maximum observed concentration.

CCI [redacted]

CCI [redacted]

No PK parameters will be calculated for subjects with 2 or fewer consecutive time points with detectable concentrations.

The actual date and time of sample collection will be recorded on the source document and CRF. Samples collected 10% from the nominal time will not be considered a protocol deviation as long as the exact date and time of PK sampling collection is recorded in the CRF.

The decision as to which plasma samples collected will be assayed for evaluation of PK will be determined by the Sponsor. CCI [redacted].

CCI [redacted]

CCI

[redacted]

9.3.3 Blood Volume

Total blood sampling volume for an individual subject is shown in Table 9.c.

Table 9.c Approximate Blood Volume

Sample Type	Sample Volume (mL)	Number of Samples: Screening and Day -1	Number of Samples: Days 1-3 + FU	Total Volume (mL)
Clinical laboratory tests (Screening)	12.5	1	NA	12.5
Clinical laboratory tests (Non screening)	12.5	2	3	62.5
CCI [redacted]				
Total Approximate Blood Sampling Volume				**305***

NA=not applicable.
*Total blood volume collections for the study may increase if additional assessments are needed for AE/SAE occurrence, or at the investigator's discretion.

9.3.4 Confinement

In each treatment period, subjects will be housed on Day -1, at the time indicated by the CRU until after the 48-hour blood draw and/or study procedures on Day 3. Subjects will return for study procedures as indicated in the Schedule of Study Procedures (Section 3.0).

At all times, a subject may be required to remain at the CRU for longer at the discretion of the investigator or designee.

10.0 ADVERSE EVENTS

10.1 Definitions and Elements of AEs

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

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

An untoward finding generally may:

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

Diagnoses versus signs and symptoms:

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

Laboratory values and ECG findings:

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

Pre-existing conditions:

- A pre-existing condition (present at the time of signing of informed consent) is considered a concurrent medical history condition and should NOT be recorded as an AE. A baseline evaluation (eg, laboratory test, ECG, X-ray, 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 history condition, the worsening or complication should be recorded appropriately as an AE (worsening or complication occurs after informed consent is signed). Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of…").

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

Worsening of AEs:

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

Changes in severity of AEs:

- 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 CRF, 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 10.2.8.
- In the event of drug overdose, the subject should be treated symptomatically.

10.1.1 SAEs

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

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

Table 10.a Takeda Medically Significant AE List

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

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

10.1.2 Special Interest AEs

There are no AEs of Special Interest for this study.

10.2 AE Procedures

10.2.1 Assigning Severity/Intensity of AEs

The PI or designee will review each AE and assess its relationship to drug treatment (refer to Section 10.2.2). All AEs, including signs, symptoms, or clinically significant treatment-emergent laboratory abnormalities will be graded on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 toxicity grading scale.

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on the following general guideline [15]:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
Grade 3	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

A Semi-colon indicates 'or' within the description of the grade.
Note: Not all grades are appropriate for all AEs. Therefore, some AEs are listed within the CTCAE with fewer than 5 options for grade selection. Grade 5 (death) is not appropriate for some AEs and therefore is not an option.
ADL=Activities of Daily Living
* Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
** Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

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, i.e., the relationship cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant drugs and concurrent treatments, may also be responsible.

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

10.2.3 Start Date

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

10.2.4 End Date

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

10.2.5 Pattern of Adverse Event (Frequency)

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

10.2.6 Action Taken With Study Treatment

- Drug withdrawn – a study 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.
- Dose reduced – the dose was reduced due to the particular AE.
- Dose increased – the dose was increased due to the particular AE.
- Drug interrupted – the dose was interrupted due to the particular AE.

10.2.7 Outcome

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

subject died from another cause with the particular AE state remaining "Not recovered/not resolved."

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

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

10.2.8.1 Collection Period

Collection of AEs (ie, AEs, SAEs, Special Interest AEs, and Abnormal LFTs) will commence at the time the subject signs the informed consent. Routine collection of AEs will continue until the follow-up visit 14 ± 2 days after last TAK-906 dosing in Period 2. For subjects who discontinue prior to the administration of study medication, AEs will be followed until the subject discontinues study participation.

10.2.8.2 Reporting AEs

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

All subjects experiencing AEs, whether considered associated with the use of the study 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 CRF, whether or not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

- Event term.
- Start and end date and time.
- Pattern of AE (frequency).
- Severity/Intensity.

- Causality (investigator's opinion of the causal relationship between the event and administration of study drug[s]).
- Action taken with study drug.
- Outcome of event.
- Seriousness.

10.2.8.3 Reporting SAEs

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

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

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

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

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

Reporting of SAEs that begin before first administration of investigational product will follow the same procedure for SAEs occurring on treatment.

SAE Follow-Up

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

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

10.2.8.4 Reporting Special Interest AEs

There are no AEs of Special Interest for this study.

10.2.8.5 Reporting of Abnormal LFTs

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

If a subject is noted to have ALT or AST >3×ULN and total bilirubin >2×ULN for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 10.2.8.3. The investigator must contact the Medical Monitor for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease. Follow-up laboratory tests as described in Section 9.2.8 must also be performed. In addition, an LFT Increases CRF must be completed and transmitted with the Takeda SAE form (as per Section 10.2.9).

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

The Sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, investigators and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the Sponsor or Sponsor's designee, SUSARs will be submitted within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The Sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the study. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

11.0 STATISTICAL METHODS

11.1 Statistical and Analytical Plans

All statistical analysis of the study will be performed using the statistical software, SAS version 9.3 or higher Details concerning the standards for precision, decimals, descriptive statistics will be in the SAP.

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a SAP. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives. Additional statistical analyses other than those described in this section may be performed if deemed appropriate.

11.1.1 Analysis Sets

11.1.1.1 PK Set

The PK set will consist of all subjects who received study drug and have at least 1 measurable plasma concentration.

11.1.1.2 Safety Set

The safety analysis set will consist of all subjects who are enrolled and received at least 1 dose of study drug.

11.1.2 Analysis of Demography and Other Baseline Characteristics

Continuous demographic data (ie, age, weight, height, and BMI) will be listed and summarized using appropriate summary statistics. Categorical demographic data (ie, gender, race, and ethnicity) will also be listed and tabulated.

11.1.3 PK Analysis

TAK-906 concentrations will be listed and summarized descriptively by PK sampling time. Summary will be done by treatment. Individual subject and arithmetic mean profiles of the concentration time data will be plotted by treatment on linear and semi-log scales. For summary statistics and arithmetic mean plots by sampling time, the nominal PK sampling times will be used, and for individual subject plots by PK sampling time, the actual PK sampling times will be used.

TAK-906 PK parameters for each subject will be listed and summarized by treatment using descriptive statistics.

If applicable, descriptive statistics will be provided for the plasma CCI concentrations using appropriate summary statistics to be fully specified in the SAP. PK parameters for plasma CCI concentrations may be calculated as described in Section 9.3.1 as available.

For evaluation of potential effect of rifampin on TAK-906 PK, mixed effects models will be performed on the ln-transformed AUC_{∞}, AUC_{last}, and C_{max} to assess the potential effect of rifampin on TAK-906 PK. The mixed effects models will include sequence, treatment, and period

as fixed effects, and subject nested within sequence as a random effect. Each mixed effects model will include calculation of LSM as well as the difference between treatment LSM.

Ratios of LSM will be calculated using the exponentiation of the difference between treatments LSM from the analyses on the ln-transformed AUC_{∞}, AUC_{last}, and C_{max}.

Consistent with the two one-sided test [2], 90% CIs for the ratios will be derived by exponentiation of the CIs obtained for the difference between treatment LSM resulting from the analyses on the ln-transformed AUC_{∞}, AUC_{last}, and C_{max}.

The comparison of interest is as follows:

- Treatment B compared with Treatment A

Additional statistical analyses may be performed if deemed appropriate. A more detailed description of the planned analyses will be presented in the SAP.

CCI

Summary statistics for the parameters of CCI will be tabulated. Results, if any, may be summarized in a report separate from the main clinical study report.

11.1.5 Safety Analysis

All safety data will be populated in the individual CRFs and listed by subject.

11.1.5.1 AEs

AEs will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA®) available at Celerion. Data will be summarized using preferred term and primary system organ class.

The number and percentage of subjects with TEAEs, defined as any AEs, regardless of relationship to study drug and SAEs, which occur on or after dosing in subjects, will be summarized by MedDRA® system organ class, and preferred term, by severity, and by relationship to study drug. Separate summaries will also be generated for AEs by treatment-relationship and severity. Data listings will be provided for all AEs (including PTEs for enrolled subjects), AEs leading to study drug discontinuation, AEs leading to study visit discontinuation, SAEs, and AEs resulting in death.

11.1.5.2 Clinical Laboratory Evaluation

Baseline, postbaseline, and change from Baseline in clinical laboratory tests will be summarized. Individual results for clinical laboratory tests will be listed. A shift table describing out of normal range shifts will be provided.

11.1.5.3 Vital Signs

Baseline, postbaseline, and change from Baseline in vital signs will be summarized. Individual results for vital signs will be listed.

11.1.5.4 ECGs

Baseline, postbaseline, and change from Baseline in ECG results will be summarized. Individual results for ECG measures will be listed.

11.1.5.5 Other Safety Parameters

Physical examination findings will be presented in the data listings.

Medical history, and concurrent conditions will be coded using the MedDRA® and concomitant medications will be coded using the World Health Organization (WHO) drug dictionary and will be listed by subject.

11.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned. There is no predetermined criteria for early termination.

11.3 Determination of Sample Size

With a sample size of 12 subjects, there is an 80% probability for the 90% CIs to be within 65% and 135% of the point estimate of the geometric mean ratio for C_{max} and for AUC of TAK-906 with and without rifampin. Thus, if the observed ratios of geometric means of TAK-906 with and without rifampin is 2 for C_{max} and AUC, then the corresponding 90% CIs based on data from 12 subjects will be approximately (1.6, 2.5). This calculation assumes that log(C_{max}) and log(AUC) of TAK-906 are normally distributed with intra-subject coefficients of variation that do not exceed 31%.

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

12.0 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Study-Site Monitoring Visits

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

All aspects of the study and its documentation will be subject to review by the Sponsor or the Sponsor's 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 CRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

12.2 Protocol Deviations

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

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

12.3 Quality Assurance Audits and Regulatory Agency Inspections

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

13.0 ETHICAL ASPECTS OF THE STUDY

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

13.1 IRB and/or IEC Approval

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

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

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

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

13.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The informed consent form and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The informed consent form will detail the requirements of the subjects and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

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

The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC.

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 or she will participate in the study, then the informed consent form and subject authorization form (if applicable) must be signed and dated by the subject at the time of consent and prior to the subject entering into the study. The subject should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the informed consent form and subject authorization (if applicable) at the time of consent and prior to subject entering into the study; however, the Sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

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

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

Subjects who consented and provided a PGx sample for DNA and RNA analysis can withdraw their consent and request disposal of a stored sample at any time prior to analysis. Notify Sponsor of consent withdrawal.

13.3 Subject Confidentiality

The Sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the Sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

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

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

13.4 Publication, Disclosure, and Clinical Study Registration Policy

13.4.1 Publication and Disclosure

The investigator is obliged to provide the Sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the Sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the Sponsor.

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

13.4.2 Clinical Study Registration

In order to ensure that information on clinical studies 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 studies it Sponsors anywhere in the world on ClinicalTrials.gov and/or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with investigator's city, state (for America's investigators), country, and recruiting status will be registered and available for public viewing.

For some registries, Takeda will assist callers in locating study sites closest to their homes by providing the investigator name, address, and phone number to the callers requesting study information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the study. The investigative sites are encouraged to handle the study inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of study enrollment, they should be referred to the Sponsor.

Any investigator who objects to the Sponsor providing this information to callers must provide the Sponsor with a written notice requesting that their information not be listed on the registry site.

13.4.3 Clinical Study Results Disclosure

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

13.5 Insurance and Compensation for Injury

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

14.0 ADMINISTRATIVE AND REFERENCE INFORMATION

14.1 Administrative Information

14.1.1 Study Contact Information

Contact Type / Role	Contact
Serious adverse event and pregnancy reporting	PPD

14.1.2 INVESTIGATOR AGREEMENT

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

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation, E6(R2) Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.2.9 of this protocol.
- Terms outlined in the study site agreement.
- Responsibilities of the Investigator (Appendix B).

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

_____

Signature of Investigator Date

_____

Investigator's Name (print or type)

_____

Investigator's Title

_____

Location of Facility (City, State/Provence)

_____

Location of Facility (Country)

14.1.3 Study-Related Responsibilities

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

14.1.4 List of Abbreviations

CCI [redacted]	
AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC_{last}	The area under the concentration-time curve from time 0 to time of the last quantifiable concentration.
AUC_{∞}	Area under the concentration-time curve from time 0 to infinity, calculated using the observed value of the last quantifiable concentration.
CCI [redacted]	[redacted]
BBB	Blood brain barrier
BMI	Body mass index
CFR	Code of Federal Regulations
CI	Confidence interval
CCI [redacted]	[redacted]
C_{max}	Maximum observed concentration
CC [redacted]	[redacted]
CCI [redacted]	[redacted]
CRF	Case report form
CRU	Clinical Research Unit
DDI	Drug-drug interaction
ECG	Electrocardiogram
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
FU	Follow-up
g	Gram
GCP	Good Clinical Practice
HBsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IB	Investigator's Brochure

ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	Intravenous
kg	Kilogram
L	Liters
LFT	Liver function test
ln	Natural log
LSM	Least-squares means
m^2	Meters squared
MedDRA®	Medical Dictionary for Regulatory Activities®
mg	Milligram
min	Minute
mL	Milliliter
mmHg	Millimeter of mercury
msec	Millisecond
NA	Not applicable
OATP	Organic anion transporting polypeptide
P-gp	P-glycoprotein
PD	Pharmacodynamic
PK	Pharmacokinetic(s)
PTE	Pretreatment event
RCF	Relative centrifugal force
RNA	ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SUSARs	Suspected unexpected serious adverse reactions
CCI [redacted]	
TEAE	Treatment-emergent adverse event
CCI [redacted]	
ULN	Upper limit of normal
US	United States
USA	United States of America
CCI [redacted]	
WBC	White blood cell
WHO	World Health Organization

15.0 DATA HANDLING AND RECORDKEEPING

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

15.1 CRFs (Electronic and/or Paper)

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

Celerion standard CRFs will be supplied. CRFs are produced, stored electronically, and are available to the designated study team members. Each CRF is reviewed and signed by the PI. The final signed CRFs are provided to the Sponsor on a compact disc.

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

Corrections are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change. Reasons for significant corrections should additionally be included.

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

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

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

15.2 Record Retention

The investigator agrees to keep the records stipulated in Section 15.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), electronic copy of CRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the Sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site

and filed with the original in the subject's chart to ensure long-term legibility. Furthermore, ICH E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and Sponsor.

Refer to the Clinical Study Site Agreement for the Sponsor's requirements on record retention. The investigator and the head of the institution should contact and receive written approval from the Sponsor before disposing of any such documents.

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17.0 APPENDICES

Appendix A Responsibilities of the Investigator

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

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

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff that will assist in the protocol.
3. If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.
4. Ensure that study related procedures, including study specific (nonroutine/nonstandard panel) screening assessments are NOT performed on potential subjects, prior to the receipt of written approval from relevant governing bodies/authorities.
5. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
6. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 CFR Part 56, ICH, and local regulatory requirements.
7. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
8. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
9. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each informed consent form should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an informed consent form does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
10. Prepare and maintain adequate case histories of all persons entered into the study, including CRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of

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

11. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
12. Maintain current records of the receipt, administration, and disposition of Sponsor-supplied drugs, and return all unused Sponsor-supplied drugs to the Sponsor.
13. Report adverse reactions to the Sponsor promptly. In the event of an SAE, notify the Sponsor within 24 hours.

Appendix B Elements of the Subject Informed Consent

In seeking informed consent, the following information shall be provided to each subject:

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the subject's participation.
4. A description of the procedures to be followed, including invasive procedures.
5. The identification of any procedures that are experimental.
6. The estimated number of subjects involved in the study.
7. A description of the subject's responsibilities.
8. A description of the conduct of the study.
9. A statement describing the treatment(s) and the probability for random assignment to each treatment.
10. A description of the possible side effects of the treatment that the subject may receive.
11. A description of any reasonably foreseeable risks or discomforts to the subject and, when applicable, to an embryo, fetus, or nursing infant.
12. A description of any benefits to the subject or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
13. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject and their important potential risks and benefits.
14. A statement describing the extent to which confidentiality of records identifying the subject will be maintained, and a note of the possibility that regulatory agencies, auditor(s), IRB/IEC, and the monitor may inspect the records. By signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.
15. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
16. The anticipated prorated payment(s), if any, to the subject for participating in the study.
17. The anticipated expenses, if any, to the subject for participating in the study.
18. An explanation of whom to contact for answers to pertinent questions about the research (Investigator), subject's rights, and IRB/IEC and whom to contact in the event of a research-related injury to the subject.
19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject otherwise is entitled, and that the subject or the subject's

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

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

25. Female subjects of childbearing potential (eg, nonsterilized, premenopausal female subjects) who are sexually active must use highly effective contraception (as defined in the informed consent) from signing the informed consent and throughout the duration of the study, and for 18 weeks after the dose of study drug. Regular pregnancy tests will be performed throughout the study for all female subjects of childbearing potential. If a subject is found to be pregnant during study, study drug will be discontinued and the investigator will offer the subject the choice to receive unblinded treatment information.
26. Male subjects must use highly effective contraception (as defined in the informed consent) from signing the informed consent throughout the duration of the study and for 18 weeks after the dose of study drug. If the partner or wife of the subject is found to be pregnant during the study, the investigator will offer the subject the choice to receive unblinded treatment information.
27. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix C Investigator Consent to the Use of Personal Information

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

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

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

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

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

Investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

Appendix D Pregnancy and Contraception

Contraception and Pregnancy Avoidance Procedure

Male Subjects

From signing of informed consent, throughout the duration of the study, and through to the follow-up visit, nonsterilized** male subjects who are sexually active with a female partner of childbearing potential* must use barrier contraception (eg, condom with spermicidal cream or jelly). In addition, they must be advised not to donate sperm during this period.

Female Subjects and Their Male Partners

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

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

1. Unacceptable methods of contraception are:
    - Spermicides only.
    - Withdrawal.
    - No method at all.
    - Use of female and male condoms together.
    - Cap/diaphragm/sponge without spermicide and without condom.
    - Sexual abstinence is NOT an acceptable method of contraception.
2. Subjects will be provided with information on highly effective/effective methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy, donation of ova, and sperm donation during the course of the study.
3. During the course of the study, regular serum human chorionic gonadotropin (hCG) pregnancy tests will be performed for all women only and all subjects (male and female) will receive continued guidance with respect to the avoidance of pregnancy and sperm donation as part of the study procedures. Such guidance should include a reminder of the following:

a) contraceptive requirements of the study
b) reasons for use of barrier methods (ie, condom) in males with pregnant partners
c) assessment of subject compliance through questions such as
    i. Have you used the contraception consistently and correctly since the last visit?
    ii. Have you forgotten to use contraception since the last visit?
    iii. Is there a chance for a female partner who could become pregnant?

Pregnancy

Women of childbearing potential will not be included in this study.

Any pregnancies in the partner of a male subject during the study and until the follow-up visit, should be recorded following authorization from the subject's partner.

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

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

A Phase 1, Open-Label, Randomized, Two-Way Crossover Study to Evaluate the Effect of Single-Dose Intravenous Rifampin as a Prototypic Inhibitor of OATP1B1 and OATP1B3 on the Single-Dose Pharmacokinetics of Oral TAK-906 in Healthy Adult Subjects

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical Science Approval	24-Sep-2019 15:10 UTC
	Clinical Pharmacology Approval	24-Sep-2019 15:20 UTC
	Biostatistics Approval	24-Sep-2019 15:26 UTC

celerion
Translating Science to Medicine

Protocol Clarification Letter for Celerion Study No.: CA28400
Takeda Study No.: TAK-906-1009
Date of Final Protocol: 24-Sep-2019
Date of Protocol Clarification Letter: 03-Oct-2019

Phase 1, Open-Label, Randomized, Two-Way Crossover Study to Evaluate the Effect of Single-Dose Intravenous Rifampin as a Prototypic Inhibitor of OATP1B1 and OATP1B3 on the Single-Dose Pharmacokinetics of Oral TAK-906 in Healthy Adult Subjects

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This protocol clarification letter is written to correct an inconsistency between items # 25 and # 26 of Appendix B entitled Elements of the Subject Informed Consent and other sections of the protocol.

Item 25 should be ignored since only women of nonchildbearing potential will be enrolled in this study as correctly depicted in Section 7.2 – Exclusion Criteria and as per Appendix D - Pregnancy and Contraception.

Item 26 should indicate that nonsterilized male subjects who are sexually active with a female partner of childbearing potential must agree to use barrier method of contraception from signing of the informed consent form throughout the duration of the study and through to the follow-up visit (ie, 14 ± 2 days after the last TAK-906 dosing) as correctly written in Section 7.1 – Inclusion Criteria and as per Appendix D - Pregnancy and Contraception.

The final protocol dated 24-Sep-2019 was not amended to incorporate this change, therefore, this protocol clarification letter is written.

PPD

07-Oct-2019
Date

09 oct 2019
Date

oct 3 2019
Date