Official Protocol Title:	An open-label single oral dose study to evaluate the safety, tolerability, and pharmacokinetics of MK-0518 1200 mg (600 mg tablet × 2) in healthy Japanese male participants
NCT number:	NCT03667547
Document Date:	10-Jul-2018

Post-marketing Clinical Study Protocol

Title:

An open-label single oral dose study to evaluate the safety, tolerability, and pharmacokinetics of MK-0518 1200 mg (600 mg tablet × 2) in healthy Japanese male participants

Post-marketing Clinical Study Protocol Number:

851-00

Study Drug Name:

MK-0518

Sponsor and Location:

MSD K.K. (hereinafter, Sponsor)
Refer to Appendix 7: Study Administrative Structure for the contact information for each role of the Sponsor.

Date of Preparation:

July 10, 2018

Sponsor Signatory

Typed Name: Date

Title:

Protocol-specific Sponsor contact information can be found in the Investigator Study File Binder (or equivalent).

Investigator Signatory

I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol.

Typed Name: Date

Title:

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1 Summary of the Study

1.1 Outline

Title:

An open-label single oral dose study to evaluate the safety, tolerability, and pharmacokinetics of MK-0518 1200 mg (600 mg tablet × 2) in healthy Japanese male participants

Short Title:

ISENTRESS® Tablets 600 mg post-marketing clinical study (pharmacokinetics in Japanese participants)

Acronym:

Not applicable

Hypotheses, Objectives, and Endpoints:

This study will be conducted in healthy Japanese male participants.

Objectives/hypotheses	Endpoints
Primary	
• Objective: To evaluate the safety and tolerability of MK-0518 when administered at a single oral dose of 1200 mg in healthy Japanese male participants Hypothesis (H1): None	• Physical findings • Vital signs (blood pressure, pulse rate, respiratory rate, body temperature [axillary]) • Laboratory tests (hematology, clinical chemistry, urinalysis) • 12-lead electrocardiograms (ECGs) • Adverse events (clinical symptoms/laboratory test values)
Secondary	
• Objective: To obtain plasma pharmacokinetic data (e.g. the area under the plasma concentration-time curve from time 0 to infinity [$AUC_{0-\infty}$], maximum blood concentration [C_{max}], plasma concentration at 24 hours after administration [C_{24hr}], time to reach maximum plasma concentration following drug administration [T_{max}], and apparent elimination half-life [$t_{1/2}$]) of MK-0518 1200 mg when administered as a single oral dose Hypothesis (H2): To estimate the geometric mean ratio of plasma pharmacokinetic data (the area under the plasma concentration-time curve [AUC], C_{max}, and C_{24hr}) of a single oral dose of MK-0518 1200 mg in Japanese participants retrospectively compared with non-Japanese populations	• Plasma MK-0518 concentrations and pharmacokinetic parameters ($AUC_{0-\infty}$, C_{max}, C_{24hr}, T_{max}, apparent $t_{1/2}$, apparent clearance [CL/F], and apparent distribution volume [Vz/F])

Study Design Outline:

Development phase	Phase 4 study
Primary objective	Treatment
Proposed indication	Human Immunodeficiency Virus (HIV) infection
Study population	Healthy Japanese adult male
Study type	Interventional study
Study design	Single group This study will be conducted at a single site.
Control	No control group included
Type of blinding	Open-label
Masking	Masking is not performed.
Planned study duration	The period from the first participant's signing informed consent to the last participant's last phone call or visit will be approximately 1 month in this study.

Target Sample Size: Approximately 12 participants (participants enrolled)

Type of Intervention Group and the Duration of Study Participation:

Type of intervention group	Use a tablet containing MK-0518 600 mg as a study drug. All participants will receive the study drug MK-0518 1200 mg (600 mg tablet × 2) orally under fasted condition.
Number of intervention group	1
Duration of study participation	Each participant will participate in the study for approximately 1 month from the time the participant signs informed consent to post-study examination (last phone call or visit).

Study Governance

Meeting Forms (Committees):

Steering Committee	Not established
Executive Oversight Committee	Not established
Data Monitoring Committee	Not established
Clinical Adjudication Committee	Not established
Study governance considerations are provided in Appendix 2.	

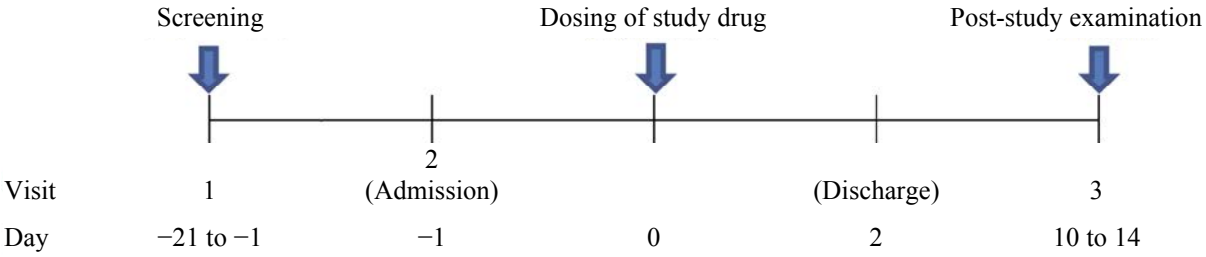
Study Accepts Healthy Volunteers: Yes

Abbreviations are described in Appendix 8: Abbreviations.

1.2 Schematic of Study Design

The study design is depicted in Figure 1.

Figure 1 Study design



1.3 Study Schedule

Activities	Screening test[†]		Time since Study Drug Administration														Post-study Examination[‡]
			Pre-dose	0	0.5	1	1.5	2	3	4	6	8	12	16	24	48[§§]	
Visit Number	1	2 Admission														Dis-charge	3
Scheduled Visits	Day −21 to Day −1	Day −1	Day 0												Day 1	Day 2	Day 10 to Day 14
Administrative Procedures																	
Informed consent to study participation	X[§]																
Study identification card distribution	X																
Inclusion/exclusion criteria review	X		X														
Prior/concomitant medication review	X		X														
Medical history review	X																
Physical examination	X		X														X
Body weight	X																
Height	X																
Immunoserology	X																
Urine drug screen	X																
Meal[¶]										X							
Safety Measurements																	
Vital signs (blood pressure, pulse rate, and respiratory rate)[#]	X		X				X										X
Body temperature (axillary)[#]	X		X														X
Laboratory tests[††]	X		X[‖]												X		
12-lead ECGs[#]	X		X														X
Adverse events	X – X																
MK-0518-related Activities																	
Blood sampling (MK-0518)			X		X	X	X	X	X	X	X	X	X	X	X	X	
MK-0518 administration[‡‡]				X													

Activities	Screening test†		Time since Study Drug Administration													Post-study Examination‡
			Pre-dose	0	0.5	1	1.5	2	3	4	6	8	12	16	24	48§§	
Visit Number	1	2 Admission														Dis-charge	3
Scheduled Visits	Day −21 to Day −1	Day −1	Day 0												Day 1	Day 2	Day 10 to Day 14

† Screening test will be performed within 3 weeks prior to study drug administration.
‡ Post-study examination will be performed between Days 10 and 14 after study drug administration in each participant. However, adverse events will be examined until Day 14 study drug administration.
§ Written informed consent will be obtained before starting any study procedure.
‖ Predose laboratory tests will be performed within 24 hours prior to study drug administration.
¶ Participants will be provided with lunch after blood sampling performed 4 hours after study drug administration. The timing and content of subsequent meals will be determined by the principal investigator. All participants are provided with meals of the same content.
# Measurements will be performed after maintaining participants in a supine or semirecumbent position for at least 10 minutes.
†† Participants will be fasted for more than 8 hours before blood sampling for laboratory tests (hematology, clinical chemistry, and urinalysis).
‡‡ Participants will be fasted for more than 8 hours before study drug administration and for more than 4 hours after the administration. In addition, they are not permitted to drink water for 1 hour before and 1 hour after the administration.
§§ An investigator will confirm the absence of any abnormalities in tests and examinations performed before 48 hours after study drug administration in individual participants to discharge them.

2 Introduction

2.1 Rationale for the Conduct of the Study

MK-0518 (raltegravir potassium; hereinafter, raltegravir) is an HIV integrase inhibitor. The objective of this study is to evaluate the safety and pharmacokinetics of a single oral dose of MK-0518 in healthy Japanese male participants.

In Japan, raltegravir 400 mg tablet formulation (ISENTRESS® Tablets 400 mg) has been available since July 2008 with the dosing regimen of 400 mg twice daily orally. In anti-HIV treatment, it is preferable to reduce medication burden to patients to ensure better medication compliance. Accordingly, a simplified treatment regimen, i.e., the less-frequent dosing treatment regimen of raltegravir at a dose of 1200 mg (600 mg tablet × 2) once daily orally was developed. The regimen was approved in May 2018 by submitting an application for marketing approval as a drug with a new dose and as a drug with an additional dosage form using the non-Japanese application file for approval. As a condition for the approval, a pharmacokinetic study of raltegravir 600 mg tablet formulation in Japanese participants was determined to be conducted.

2.2 Background

Refer to the package insert and Pharmaceutical Interview Form of ISENTRESS® Tablets 600 mg for more details of the following background information.

- Physical, chemical and pharmaceutical properties and formulation
- Non-clinical pharmacology studies (*in vitro* pharmacology studies, *in vivo* pharmacology studies, and supplementary safety pharmacology studies)
- Animal pharmacokinetics and metabolism
- Toxicity and toxicokinetics
- Clinical efficacy

2.2.1 Background Related to the Drug and Treatment of Disease

According to the statistics from Joint United Nations Programme on HIV and AIDS (UNAIDS) in 2016, the number of patients with HIV infection and acquired immunodeficiency syndrome (AIDS) are estimated as 36.7 million in the world. In the same year, the number of new patients with HIV infection was 1.8 million. The number of new patients with HIV infection in the world was reduced by 11% compared with 2010, and the spread of HIV infection has been calming down mainly in advanced countries. Meanwhile, the number of new patients with HIV infection has still been increasing in the Eastern Europe and Central Asia.

According to the survey by the Committee of AIDS Trends, the Ministry of Health, Labour and Welfare, the number of new patients with HIV infection (nonprogressor at the time of diagnosis) in Japan was 1011 in 2016, which has been reported as more than 1000 in a year constantly since 2007 and as 18920 in total. In comparison of the number of new patients with HIV infection in Japan per 0.1 million population between populations by

age, it has been the largest in the populations in their 20's and 30's, followed by the population in their 40's, showing a high proportion of infections in the younger generation. On the other hand, the number of new patients with AIDS (those diagnosed with AIDS at the time of initial reporting) in Japan was 437 in 2016, which has been reported as more than 400 in a year constantly since 2006 and as 8523 in total.

As described above, although the number of new patients with HIV infection has been in decreasing trend mainly in advanced countries, the number of new patients with HIV infection and those with AIDS have remained unchanged in Japan. In these diseases, early diagnoses and management of treatment remain to be important.

The stages of HIV infection can be divided into 3 main stages: acute infection, asymptomatic, and AIDS stages. HIV infection causes acute infection symptoms such as pyrexia, rash, and lymph node swelling (acute infection stage). Emergence of immunological reactions specific to HIV reduces the volume of viruses in blood, not eliminating them completely. It is then followed by the long-term antagonism between the patient's immune mechanism and HIV for a long period of time (asymptomatic stage). Unless anti-HIV treatment is started during this stage, HIV continues proliferating, thereby reduces the patient's immune strength gradually, and eventually leads to vulnerability to concomitant opportunistic disease (AIDS stage). The time from the initial infection to an AIDS stage varies with patients. With no anti-HIV treatment, the time from the onset of AIDS to death is considered as approximately 2 years.

With HIV infection, the volume of viruses in blood (HIV ribonucleic acid [RNA]) and the number of CD4 lymphocytes are critical to understand the severity and course of the patient's condition. Although the level of HIV RNA is maintained at an almost constant level approximately at 6 months after HIV infection, the speed of disease progression increases with the elevated level of HIV RNA, which can therefore be used as a measure to predict progression of HIV infection. With regard to the number of CD4 lymphocytes, which is 700–1300 /mm^3 in healthy adults, a level less than 200 /mm^3 causes immunodeficiency with vulnerability to various types of opportunistic diseases. The number of CD4 lymphocytes indicates the remaining level of immunoresponsiveness in the host destroyed by HIV, providing an important measure along with the level of HIV RNA when starting anti-HIV treatment is considered .

As of March 2017, 8 types of nucleoside reverse transcriptase inhibitors, 4 types of nonnucleoside reverse transcriptase inhibitors, 8 types of protease inhibitors, and 1 type of entry inhibitor have been approved in Japan. Among these anti-HIV drugs, selecting 3 to 4 types of drugs with stronger inhibition of HIV (key drugs) and supplementary drugs that have a role of enhancing antiviral effects (backbone) as antiretroviral therapy is a standard treatment. The development of these antiretroviral therapies has changed HIV infection, previously regarded as an incurable disease, to a controllable chronic disease. Meanwhile, it is practically impossible to eliminate HIV completely out of the carrier's body even with these therapies, and once anti-HIV therapy is started in a patient with HIV infection, the level of HIV RNA in blood needs to be sustained continuously at less than detection limits. This forces HIV-infected patients to continue therapy using anti-HIV drugs throughout their lifetime, and medication adherence needs to be maintained high

during this therapy to prevent treatment failure and the development of resistance. Meanwhile, multiple drugs other than anti-HIV drugs are also often used for the treatment of disease not related to HIV. For this reason, improvement of medication adherence with a simplified antiretroviral therapy (e.g., reduced medication burden and eased dietary restriction) is considered to increase the possibility of treatment success, and is also recommended by international guidelines.

MK-0518 (raltegravir; ISENTRESS® Tablets) is an HIV integrase inhibitor developed by Merck & Co., Inc., Whitehouse Station, N.J., U.S.A., and approved in September 2007 for the first time in the world. Integrase is one of the three enzymes required for the replication of HIV, which acts on the process of incorporating deoxypentose nucleic acid (DNA) of HIV in the gene of the host cells. A series of the sequential reactions include the composition of integrase in stable complex with virus DNA, endonuclease processing of virus DNA, and transfer and ligation of DNA strands to DNA of virus and the host. The integration is required for efficient viral gene expression, as well as for stable maintenance of viral genome. The results of clinical studies demonstrated that MK-0518 is an effective integrase inhibitor with strong efficacy and safety profile. In addition, the results of non-clinical and clinical studies suggested that MK-0518 was less likely to be associated with clinically significant drug interactions. Further multiple studies evaluating efficacy, safety, and pharmacokinetics have demonstrated the properties of MK-0518.

2.2.2 Clinical Study Results

In the non-Japanese phase 3 clinical study in HIV treatment-naive patients (ONCEMRK), a randomized, double-blind, parallel-controlled study of raltegravir 400 mg twice daily + emtricitabine (FTC) + tenofovir disoproxil fumarate (TDF) was conducted to examine the safety and efficacy of raltegravir 1200 mg (600 mg tablet × 2) once daily + FTC + TDF. The results demonstrated the noninferiority of raltegravir 1200 mg once daily to raltegravir 400 mg twice daily.

2.3 Benefits/Risks

The study is planned for the purpose of collecting information related to the safety and efficacy of the study drug. Therefore, it cannot be guaranteed that the study participants will obtain benefits directly from the treatment during the study period.

Since this study is conducted in healthy participants, the administration of MK-0518 is not likely to bring benefits to their health.

Refer to the package insert and Pharmaceutical Interview Form of ISENTRESS® Tablets 600 mg for the benefits and risks of participating in this study.

3 Hypotheses, Objectives, and Endpoints

This study will be conducted in healthy Japanese male participants.

Objectives/hypotheses	Endpoints
Primary	
• Objective: To evaluate the safety and tolerability of MK-0518 when administered at a single oral dose of 1200 mg in healthy Japanese male participants Hypothesis (H1): None	• Physical findings • Vital signs (blood pressure, pulse rate, respiratory rate, body temperature [axillary]) • Laboratory tests (hematology, clinical chemistry, urinalysis) • 12-lead ECGs • Adverse events (clinical symptoms/laboratory test values)
Secondary	
• Objective: To obtain plasma pharmacokinetic data (e.g. $AUC_{0-\infty}$, C_{max}, C_{24hr}, T_{max}, and apparent $t_{1/2}$) of MK-0518 1200 mg when administered as a single oral dose Hypothesis (H2): To estimate the geometric mean ratio of plasma pharmacokinetic data (AUC, C_{max}, and C_{24hr}) of a single oral dose of MK-0518 1200 mg in Japanese participants retrospectively compared with non-Japanese populations	• Plasma MK-0518 concentrations and pharmacokinetic parameters ($AUC_{0-\infty}$, C_{max}, C_{24hr}, T_{max}, apparent $t_{1/2}$, CL/F, and Vz/F)

4 Study Design

4.1 Study Design Outline

This is an open-label single oral dose study in healthy Japanese male participants comprising a single panel. A total of 12 participants will receive 1200 mg of MK-0518 under fasting conditions.

Study procedures including visit frequency during the study period and the acceptable range of visits are outlined in "1.3 Study Schedule." Details of each procedure are provided in Section 8.

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for Endpoints

4.2.1.1 Safety Endpoints

The primary objective of this study is to evaluate the safety and tolerability of MK-0518 by giving a single oral dose of MK-0518 1200 mg in healthy Japanese male participants.

The safety and tolerability of MK-0518 will be evaluated with vital signs, clinical assessments such as physical examination, 12-lead ECGs, and laboratory tests

(hematology, clinical chemistry and urinalysis). Adverse events will be evaluated, recorded, followed up, and reported in accordance with Section 8.4 and Appendix 4.

4.2.1.2 Pharmacokinetic Endpoints

The secondary objective of this study is to obtain plasma pharmacokinetic parameters ($AUC_{0-\infty}$, C_{max}, C_{24hr}, T_{max}, apparent $t_{1/2}$, CL/F, and Vz/F) of a single oral dose of MK-0518 1200 mg in healthy Japanese male participants.

Samples for drug concentration measurements will be collected at points shown in "1.3 Study Schedule." Pharmacokinetic parameters ($AUC_{0-\infty}$, C_{max}, C_{24hr}, T_{max}, apparent $t_{1/2}$, CL/F, and Vz/F) will be calculated using MK-0518 concentrations in plasma obtained at each collection point.

4.2.2 Rationale for the Use of Comparator/Placebo

No comparator/placebo is used in this study.

4.3 Justification for Dosing Regimen of the Study Drug

4.3.1 Starting Dose for This Study

Following the non-Japanese phase 1 clinical study that had demonstrated an improvement in the bioavailability of newly formulated raltegravir 600 mg tablets, a non-Japanese phase 3 clinical study in HIV treatment-naive patients (ONCEMRK) demonstrated the noninferiority of raltegravir 1200 mg (600 mg tablet × 2) once daily to raltegravir 400 mg twice daily. On the basis of these study results and data from 3 drug interaction studies, the dosage and administration of raltegravir 1200 mg (600 mg tablet × 2) once daily was approved in Japan. The approved dose of 1200 mg (600 mg tablet × 2) was selected as the dose for this study.

4.3.2 Maximum Dose/Expected Exposure for This Study

A single dose of raltegravir 1200 mg (600 mg tablet × 2) in fasted healthy non-Japanese adult participants showed an $AUC_{0-\infty}$ (mean) of 50.1 μM•hr, a C_{max} (mean) of 15.7 μM, a C_{24hr} (mean) of 41.6 nM, a T_{max} (median) of 1.50 hours, and an apparent $t_{1/2}$ (mean) of 8.95 hours. Population pharmacokinetics showed no clinically meaningful effect of the differences in race on the pharmacokinetics of raltegravir 1200 mg (600 mg tablet × 2) repeatedly administered once daily. In addition, the pharmacokinetics of a single oral dose of raltegravir 400 mg in fasted healthy Japanese adult male participants were similar to those in non-Japanese. The exposures for this study are expected to be almost the same as those of a single dose of raltegravir 1200 mg (600 mg tablet × 2) in fasted healthy non-Japanese adults.

4.3.3 Rationale for Dose Interval and Dose Design

Exposure-response analysis related to the efficacy of raltegravir has revealed that plasma trough concentrations (C_{trough}) are important for demonstrating the efficacy of raltegravir. Repeated once-daily dosing with raltegravir 1200 mg (600 mg tablet × 2) for 5 days in healthy non-Japanese adults showed no plasma raltegravir accumulation. Therefore, since the efficacy and exposures of repeat dosing can be fully predicted from the pharmacokinetic profile for a single dosing, the safety, tolerability, and pharmacokinetics of a single oral dose of ISENTRESS® Tablets 600 mg in healthy Japanese male participants was planned to be evaluated in the same design as that for the studies normally conducted as post-marketing clinical studies of an anti-HIV drug.

4.4 Beginning and End-of-Study Definition

This study begins when the first participant signs the Informed Consent Form (ICF). The study ends when the last participant completes the last follow-up (the last study-related telephone-call or visit), withdraws from the study, or is lost to follow-up (i.e., the participant is unable to be contacted by an investigator).

Prior to a final decision on continuation or termination of the study, a study may be paused during review of newly available preclinical/clinical safety, pharmacokinetic, pharmacodynamic, efficacy, or biologic data or other data of interest. It may also be necessary to keep the study open for gathering and reviewing of additional supportive data to complete the objectives of the study. If necessary, appropriate amendment(s) to the protocol or appropriate communication(s) will be generated. The study end will then not be identified until the Sponsor has made the decision to end the study following the completion of this review. The relevant regulatory authority(ies) and Institutional Review Board(s) (IRB[s])/Independent Ethics Committee(s) (IEC[s]) will be apprised of the maximum duration of the study beyond the last participant completion and the justification for keeping the study open.

4.4.1 Criteria for Early Study Termination

There are no prespecified criteria for terminating the study early.

5 Study Population

Healthy Japanese male participants between the ages of 20 and 45 will be enrolled in this study.

Prospective approval of protocol deviations related to inclusion criteria (e.g., waivers or exemptions) is not permitted.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Type of participant/target disease

1) Is a Japanese male between the ages of 20 and 45 at the time of signing informed consent.

Participant Demographics

2) Has a Body Mass Index (BMI)[†] between 18.5 kg/m^2 and 32.0 kg/m^2 at the time of screening test.
   [†] BMI = weight (kg)/height (m)^2
   Note: BMI values will be rounded to one decimal place.

Informed Consent

3) Has understood the methodology of the study and voluntarily signed written informed consent to study participation.

Others

4) Is considered to be in good health by an investigator based on the medical history, physical findings, vital signs, and the results of 12-lead ECG noted at the screening test and before study drug administration. Refer to Appendix 5 for criteria for ECG abnormalities.
5) Is considered to be in good health based on the results of laboratory tests performed at the screening test and before study drug administration. A list of laboratory tests performed for this study is attached in Appendix 3. Refer to Appendix 6: Algorithm for Assessing Abnormal Laboratory Values for algorithm related to the assessment of abnormal laboratory values.
6) Has been a nonsmoker and has not used nicotine-containing products for over 3 months at the time of screening test.
7) Is willing to comply with the study restrictions (refer to Section 5.3 for a summary of study restrictions).

5.2 Exclusion criteria

Participants are excluded from the study if any of the following criteria apply:

Medical History

1) Have a history of clinically significant endocrine, gastrointestinal, cardiovascular, hematological, hepatic, immunological, renal, respiratory, genitourinary, or neurological (including cerebrovascular stroke and epilepsy) abnormalities or diseases.
2) Has significant emotional problem at the time of screening test or suspected to occur during the conduct of the study, or has a history of clinically significant psychiatric disorder within the last 5 years.
3) Has a history of malignancy.
4) Has a history of clinically significant allergies to multiple antigens or severe allergies (e.g., food, drug, and latex [natural rubber] allergies), or has had an

anaphylactic reaction or significant intolerability (e.g., systemic allergic reaction) to prescription or non-prescription drugs or food.

5) Is positive for hepatitis B virus surface antigen, hepatitis C virus antibodies, syphilis, or HIV antigen or antibody on the screening test.
6) Had surgery, donated or lost blood within 4 weeks prior to the screening test.

Prior and Concomitant Medications

7) Requires the use or anticipates the required use of prescription or non-prescription drugs or herbal products beginning 14 days prior to study drug administration through the post-study examination (or cytochrome P450 [CYP], uridine diphosphate [UDP] glucuronic acid transferase, and/or P-glycoprotein [P-gp] inducers including St. John's wort beginning 28 days prior to study drug administration through the post-study examination). There may be certain medications that are permitted (see Section 6.4).

Prior Study (Clinical Trial) Experience

8) Has participated in another study (clinical trial) within 4 months prior to the screening test. The interval between studies (clinical trials) will be derived from the last procedure (e.g., post-study examination, follow-up of adverse events) for the last study (clinical trial) to the screening test for this study.

Diagnostic Assessments

9) Has a systolic blood pressure < 90 mmHg or > 140 mmHg, or a diastolic blood pressure < 50 mmHg or > 90 mmHg on the screening test or predose blood pressure measurement. Blood pressure measurements will be performed after maintaining a supine or semirecumbent position for at least 10 minutes.

Others

10) Consumes greater than 3 glasses of alcoholic beverages (definition of 1 glass: 354 mL for beer, 118 mL for wine, 29.5 mL for distilled spirits) per day.
11) Consumes greater than 6 servings (definition of 1 serving: equivalent to 120 mg of caffeine) of coffee, tea, cola, energy drinks, or other caffeinated beverages per day.
12) Is a regular user of cannabis, any illicit drugs, or has a history of drug or alcohol abuse within 2 years at the time of the screening test. Participants must have a negative predose urine drug screen.
13) Is unable to consent to refrain from the consumption of citrus beverages and foods (e.g., grapefruits) beginning 2 weeks prior to administration of the study drug until the end of post-study examination, and the consumption of all fruit beverages and foods for 24 hours predose and postdose.
14) Is or has an immediate family member (e.g., spouse, parent/legal guardian, sibling, or child) who is study site or Sponsor staff directly involved with this study.

5.3 Lifestyle Considerations

5.3.1 Dietary Restrictions

5.3.1.1 Meals

Fasting requirements for study procedures, such as laboratory tests are specified in Section 8.

Participants will fast from all food and drinks, except water, for at least 8 hours prior to study drug administration. Participants will fast from all food and drinks except water between study drug administration and the first scheduled meal. Meals will be provided at time points specified in the study schedule. Between these meals, participants will fast from all food and drinks except water. After the 24-hour postdose tests and observations have been completed, subsequent meals and snacks will be unrestricted in caloric content, composition and timing.

Water will be provided at the time of study drug administration. Water will be restricted 1 hour prior to and 1 hour after study drug administration.

The study drug will be taken with approximately 240 mL (± approximately 10 mL) of water.

5.3.1.2 Fruit Juice

Participants will refrain from the consumption of citrus beverages and foods (e.g., grapefruits) beginning approximately 2 weeks until the post-study examination.

Participants will also refrain from the consumption of all fruit beverages and food beginning 24 hours prior to study drug administration until 24 hours after the administration. At all other times, the consumption of fruits beverages and foods (excluding citrus [e.g., grapefruits] beverages and foods) is allowed.

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

5.3.2.1 Caffeine

Participants will refrain from the consumption of caffeinated beverages and xanthine-containing products for 12 hours prior to the screening test and 12 hours prior to post-study examination, and beginning 12 hours prior to study drug administration until 12 hours after the administration. At all other times, caffeinated beverages and xanthine-containing products will be limited to no more than 6 units per day (definition of 1 unit: equivalent to 120 mg of caffeine).

5.3.2.2 Alcohol

Participants will refrain from the consumption of alcohol beginning 24 hours prior to study drug administration until 24 hours after the administration. Participants will also

refrain from the consumption of alcohol for 24 hours prior to the screening test and 24 hours prior to post-study examination. At all other times, alcohol beverages are allowed but limited to no more than 3 glasses per day (definition of 1 glass: 354 mL for beer, 118 mL for wine, 29.5 mL for distilled spirits).

5.3.2.3 Tobacco

Smoking (and the use of nicotine and nicotine-containing products) is not permitted from the screening test through the post-study examination.

5.3.3 Daily Living Activities

Participants are instructed to avoid strenuous physical activities (e.g., excessive weight lifting, running, bicycling) from the screening test through the post-study examination.

5.4 Screen failures

Screen failures are defined as participants who have consent to participate in this study but are not subsequently enrolled in the study. A minimal set of information will be collected on screen failures as well. Minimal information includes the following information specified in the "Data Handling Guidelines": participant demography, details of the reasons for screen failures, inclusion/exclusion criteria, and adverse events/serious adverse events meeting reporting requirements.

5.5 Criteria Related to Participant Replacement

If a participant withdraws from the study, a new participant (reserve participant) can participate in the study if deemed appropriate by an investigator and Sponsor. The new participant will be assigned a unique treatment/randomization number. The study site will contact the Sponsor for the new participant's treatment/randomization number.

6 Intervention in the Study

An intervention in the study is defined as the use of any study drug, marketed product or medical device in accordance with the protocol.

6.1 Dosage Schedule of the Study Drug

Table 1 shows the study drug for this study.

Table 1 Study Drug

Treatment Group	Type of Group	Drug Name	Type	Dosage Form	Strength	Dose	Route	Regimen	Use	IMP/ NIMP	Supply
	Investigational product	ISENTRESS® Tablets 600 mg	Drug	Tablet	600 mg	2 tablets (1200 mg) once	Oral	Single-dosing	Investigational product	NIMP	Marketed product
The definitions of Investigational Medicinal Product (IMP) and Non-Investigational Medicinal Product (NIMP) will be in accordance with the guidance issued by the European Commission. The definitions of IMP/NIMP may vary with countries and regions. In such cases, applicable local laws and regulations will be followed.											

As study drug shown in Table 1, the marketed product (ISENTRESS® Tablets 600 mg) will be purchased by the study site and used for the study.

Refer to Section 8.1.8 for the details of study drug administration.

6.2 Preparation/Handling/Storage/Accountability of the Study Drug

6.2.1 Preparation of the Study Drug

There are no specific calculations or evaluations required to be performed in order to determine the dose to each participant for this study. The rationale for selection of the dose of the study drug is provided in Section 4.3.

6.2.2 Handling, Storage, and Accountability of the Study Drug

Refer to the package insert and Pharmaceutical Interview Form of ISENTRESS® Tablets 600 mg for the handling/storage/accountability of the study drug.

Only authorized site staff may administer the study drug. Only participants enrolled in the study will receive study drug administration. All study drugs will be stored in a secure, manually or automatically monitored and controlled area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The study drug storage manager will be responsible for study drug accountability, reconciliation, and record keeping (i.e., receipt, reconciliation, and final disposition records).

Where study drug disposition at the site is appropriate, the study drug storage manager will ensure that disposition procedure is documented.

For the marketed products purchased for this study by the study site, the study site will record the lot numbers, the manufacturers, and expiry dates in accordance with local guidelines unless otherwise instructed by the Sponsor.

The study drug storage manager is responsible for appropriate recording, appropriate supply, storage, handling, distribution, and use of the study drug in accordance with the protocol and applicable laws and regulations, and will take all measures required.

6.3 Method to Minimize Bias: Randomization and Blinding

6.3.1 Assignment Procedure

Participants will be allocated to the treatment group by nonrandom assignment in this study.

6.3.2 Stratification

No stratification based on age, gender, or other factors will be performed.

6.3.3 Blinding

This is an open-label study; therefore, the treatment detail is open to the investigator, participants, and the Sponsor.

6.4 Concomitant Therapy

Even if a participant does not discontinue prior medications for 14 days prior to study drug administration (or CYP, UDP glucuronic acid transferase, and/or P-gp inducers including St. John's wort for 28 days prior to study drug administration), he may be included in the study if the investigator can rationalize that the use of the prior medication(s) has no clinically significant effect on the study.

Concurrent use of any medication prescribed or obtained during the study period, or concurrent vaccination must be discussed between the investigator and Sponsor prior to administration, unless treatment needs to be started before their discussion. The participant will be allowed to continue in the study if both the Sponsor and the investigator agree.

6.4.1 Rescue and Supportive Therapies

No rescue or supportive therapies are specified for this study.

6.5 Dose Modification for the Study Drug (Titration/Adjustment/Other)

No dose modification is specified for this study.

6.6 Intervention After the End of the Study

There is no intervention specified to be performed after the end of this study.

6.7 Disclosure of Treatment Assignments

This is an open-label study; therefore, the participants, the study site personnel, the Sponsor, or its delegate are not blinded. The drug information (name, strength, or potency) is included in the package insert, and no emergency key containing treatment assignments will be provided.

7 Discontinuation of Study Drug Administration and Participant Withdrawal From the Study

7.1 Discontinuation of Study Drug Administration

Participants may discontinue study drug administration at any time for any reason or be discontinued from the administration at the discretion of the investigator should any untoward event occurs. In addition, a participant may be discontinued from study drug

administration by the investigator or the Sponsor if study drug administration is inappropriate, the protocol is violated, or for administrative or other safety reasons. Specific procedures to be performed at the time of discontinuation of study drug administration are provided in Section 8.1.9.

7.2 Participant Withdrawal From the Study

A participant must be withdrawn from the study if the participant or his legally acceptable representative withdraws consent.

If a participant withdraws from the study, they will no longer receive study drug administration or be followed at protocol-specified visits.

Specific procedures to be performed at the time of withdrawal from the study are provided in Section 8.1.9. The procedures to be performed should a participant repeatedly fail to return for protocol-specified visits and/or if the study site is unable to contact the participant are specified in Section 7.3.

7.3 Lost to Follow-up

If a participant fails to return to the study site for a specified study visit or if the site is unable to contact the participant, the following procedures will be performed.

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant will be explained about the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee must make every effort to regain contact with the participant at each missed visit (e.g., telephone calls and/or a certified letter to the participant's last known mailing address or equivalent methods). These contact attempts will be documented in the participant's medical record.
- Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be handled in accordance with the prespecified statistical data handling and analysis guidelines.

8 Study Assessments and Procedures

- Study procedures and their timing are outlined in "1.3 Study Schedule."
- Adherence to the protocol-specified requirements, including those specified in "1.3 Study Schedule," is essential and required for study conduct.
- The principal investigator is responsible for ensuring that the study procedures are conducted by appropriately qualified or trained staff. Delegation of study site personnel responsibilities will be documented and stored in the Investigator Study File Binder (or equivalent).
- Study-related medical (or dental) decisions will be made by an investigator who is a qualified physician (or dentist only when appropriate).

- The investigator must perform and evaluate all screening items to confirm that potential participants meet all inclusion criteria. The investigator will record the details of all participants screened, and manage the records of confirming their eligibility or reasons for screening failures, as applicable.
- Procedures conducted as part of the participant's routine clinical care (e.g., hematology) before signing informed consent may be utilized for screening or baseline evaluations provided the procedure met the protocol-specified criteria and were performed within the time frame specified in "1.3 Study Schedule."
- Additional evaluations/testing may be deemed necessary by the investigator and/or the Sponsor for reasons related to participant safety. In some cases, such evaluations/testing may be potentially sensitive in nature (e.g., HIV infection, hepatitis C), and thus local laws and/or regulations may require that additional informed consent be obtained from the participant. In these cases, such additional evaluations/testing will be performed in accordance with those local laws and/or regulations.

The amount of blood collected from each participant over the duration of the study will amount to approximately 73 mL.

Repeat or unscheduled blood samples may be taken for safety reasons or for technical issues with the samples.

Sample	Blood collected per time (mL)	Number of blood collections	Total amount of blood collected (mL)
Laboratory tests	7	3	21
Samples for the measurement of MK-0518 concentrations	4	13	52
Total amount of blood collected per participant			73 mL

8.1 Study Administrative Procedures

8.1.1 Informed Consent and Information

The investigator will obtain written consent from each participant or his legally acceptable representative prior to participating in the study. If there are changes to the participant's status during the study period (e.g., health condition or age category), the investigator will ensure the appropriate consent has been obtained.

8.1.1.1 Informed Consent and Information Related to Participating in This Study

Consent to participation in the study must be documented by the participant's dated signature or by his legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form will be given to the participant before participation in the study.

The initial ICF, any subsequent revised ICF, and any written information provided to the participant must receive the IRB/IEC's approval in advance of use. The participant or his legally acceptable representative will be informed immediately if new information becomes available that may affect the participant's willingness to continue participation in the study. The communication of the new information will be provided via a revised ICF or an addendum to the original consent form that captures the participant's dated signature or his legally acceptable representative's dated signature.

Information about the study and the study population will be added to the ICF template at the protocol level.

The ICF will fulfill IRB/IEC requirements, applicable laws and regulations, and the Sponsor requirements.

8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator to ensure that the participant qualifies for study participation.

8.1.3 Study Identification Card

All participants will be given a study identification card identifying them as a participant in the study. The card will contain study site contact information (including telephone numbers) that can be used in the event of an emergency. The investigator or qualified designee will provide the participant with a study identification card immediately after the participant provides written consent to study participation. At the time of the provision of the participant's treatment/randomization number, the number will be added to his study identification card.

The study identification card also contains contact information for the MSD K.K. Clinical Study Emergency Center so that a health care provider can obtain information about the participant's study drug in emergency situations where the investigator is not available.

8.1.4 Medical History

Medical history will be reviewed by the investigator.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

There are no planned medications other than the study drug in this study. Participants are not permitted to use prescription or non-prescription drugs or herbal products beginning 14 days prior to study drug administration through the end of post-study examination.

Participants are not permitted to use CYP, UDP glucuronic acid transferase, or P-gp inducers including St. John's wort beginning 28 days prior to study drug administration through the post-study examination.

The investigator will review the presence or absence of prior medication use, including any protocol-specified washout requirement, and record prior medications used by the participant within 14 days prior to study drug administration.

8.1.5.2 Concomitant Medications

There are no planned medications other than the study drug in this study.

The use of all medications other than the study drug will be discussed with the Sponsor prior to administration, unless emergency treatment is necessary.

The investigator will record medication used by participants during the study.

8.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures performed prior to the allocation to treatment group. Each participant will be assigned only 1 screening number. One screening number must not be assigned to different participants.

Any participant who is screened multiple times will retain the original screening number assigned at the initial screening visit. Refer to Section 8.11.1 for specific details on the screening-related requirements (screening/re-screening).

8.1.7 Assignment of Treatment/Randomization Number

All eligible participants will be allocated to the treatment group without randomization. The allocated participants will receive a treatment/randomization number each. The treatment/randomization numbers will be used to identify the individual participants for all procedures performed after treatment allocation. The screening number assigned to a participant will be used as his treatment/randomization number. Once a treatment/randomization number is assigned to a participant, it can never be re-assigned to another participant.

A single participant will be assigned 1 treatment/randomization number.

8.1.8 Study Drug Administration

Participants will be given 2 tablets of MK-0518 600 mg with approximately 240 mL (± approximately 10 mL) of water in the morning under fasting conditions. The exact time of administration will be recorded.

Study drug administration will be witnessed by the investigator or designee.

Study drug administration will be performed on the day of the allocation to the treatment group.

8.1.8.1 Timing of Study Drug Administration

Tests and observations will be performed in accordance with "1.3 Study Schedule"(for further details, refer to "4.2.1.2 Pharmacokinetic Endpoints" and "4.2.1.1 Safety Endpoints"). At a point where multiple tests and blood collections are scheduled (e.g., 24 hours after study drug administration), the collection of samples for the measurement of MK-0518 concentrations will be adjusted to a point as close as possible to the specified point.

8.1.9 Study Discontinuation and Withdrawal of Consent

If a participant withdraws his consent, all appropriate procedures among those specified for the post-study examination will be performed at the time of discontinuation. Adverse events occurring at the time of consent withdrawal will be followed up in accordance with the safety requirements specified in Section 8.4.

8.1.10 Participant Blinding/Unblinding

This is an open-label study; therefore, there is no blinding for this study.

8.1.11 Admission

Participants will visit the study site on the day before scheduled study drug administration and be admitted to the site until 48 hours after study drug administration. The absence of protocol violations in terms of health condition after the screening test and compliance related to the requirements for medications, meals, activities, etc. will be confirmed.

The investigator will review the participant's eligibility in terms of all criteria including his health condition before study drug administration. Refer to "1.3 Study Schedule" for specific activities to be performed before study drug administration.

After admission, participants are not permitted to go out of the study site unless permitted by the investigator. The investigator will discharge each participant after confirming the absence of any abnormalities on tests and observations performed before 48 hours after study drug administration. The duration of admission may be extended at the discretion of the investigator.

If a participant develops an adverse event(s) during admission, the investigator will investigate whether the event requires admission. Stay at the study site beyond the protocol-specified admission period (see "1.3 Study Schedule"), though admission is not required, will be handled as "extended stay." Conditions requiring admission will be treated as "serious adverse events" that will follow the reporting procedures specified in "8.4.4 Regulatory Reporting Requirements for SAEs."

8.1.12 Calibration of Equipment

The investigator or designee has the responsibility to ensure that any equipment used for a clinical evaluation/test during the study (device or instrument that provides information about inclusion/exclusion criteria or safety or efficacy parameters) is suitably calibrated and maintained, and that the data obtained is reliable and reproducible. Documentation of equipment calibration will be retained as source documentation at the study site.

8.2 Efficacy Assessments

There are no direct efficacy assessment parameters specified in this study.

8.3 Safety Assessments

Specific procedures and assessments related to laboratory tests to be performed in this study are provided below. The total amount of blood to be collected over the course of the study, including blood volumes collected by visit and by sample per participant, is shown in Section 8.

Planned time points for individual safety assessments are provided in "1.3 Study Schedule."

8.3.1 Physical Examinations

Whole-body examination findings will be evaluated by the investigator as per institutional standard procedures. Height and weight will also be measured and recorded at the time of the screening test.

Physical findings will be evaluated per institutional standard procedures.

The investigator will pay special attention to clinical signs related to previous serious illnesses.

Body Mass Index (BMI):

BMI equals a person's weight (kg) divided by height (m) squared (BMI = kg/m^2). Document the BMI to one decimal place.

Measure the participant's weight after an overnight fast, after voiding, without a jacket or coat, without shoes, on an accurate scale. Document the measured weight (kg) to one decimal place.

Measure the participant's height on an accurate stadiometer, without shoes. Document the measured height (m) to the nearest 0.01 meter (1 cm).

8.3.2 Resting Vital Signs

Vital Sign Measurements (Blood Pressure, Pulse Rate, and Respiratory Rate):

Participants will be kept supine or semirecumbent (head elevated at an angle of 45°) for at least 10 minutes prior to having vital sign measurements obtained. Supine or semirecumbent vital signs will include blood pressure, pulse rate, and respiratory rate. Blood pressure shall be measured using a correct size of blood pressure cuff on a correct position on the participants' arm to obtain accurate measurements.

A measurement before study drug administration will be used as the baseline to calculate the change for safety evaluations (and for rechecks, if needed). Postdose vital sign measurements will be single measurements.

Participants will be instructed to rest seated or semi-recumbent until 4 hours postdose except for the time of study-related procedures.

Body Temperature:

Body temperature will be measured. The same method shall be used for all measurements for all participants.

8.3.3 Electrocardiograms

A 12-lead electrocardiogram (ECG) (single measurement) will be obtained by the investigator or medically qualified designee as specified in "1.3 Study Schedule" using an ECG machine that automatically measures heart rate, PR, QRS, and QT and QTc intervals.

Qualified personnel will place each lead to a proper position. Skin will be clean and dry prior to lead placement. Participants will be shaved as needed to ensure proper lead placement. Participants may also need to remove garments interfering lead placement.

Participants will be kept supine or semirecumbent for at least 10 minutes prior to each ECG measurement.

The correction formula to be used for QTc interval is Fridericia.

8.3.4 Safety Laboratory Tests

- Refer to Appendix 3 for the list of clinical laboratory tests to be performed for this study, and to "1.3 Study Schedule" for the timing and frequency of tests.
- The investigator will review laboratory reports, document this review, and record any clinically meaningful changes occurring during the study in the adverse event form in the case report form (CRF). Laboratory reports will be filed with the source documents. Clinically significant abnormal laboratory findings are abnormal findings which are not associated with the participant's underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- If laboratory results from non-protocol-specified laboratory assessments performed at the study site require a change in study participant management or are considered clinically significant by the investigator (e.g., serious adverse event, adverse event, or dose modification of the study drug), the results will be recorded in the appropriate CRF (e.g., SLAB).
- For any clinically significant abnormal laboratory findings during the study or within 14 days after study drug administration, every attempt will be made to perform repeat assessments until the values return to normal or baseline, or until a new baseline is established as determined by the investigator.

8.4 Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Reportable Safety Events

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for preparing and transmitting AE, SAE, and other reportable safety event reports are shown in Appendix 4.

AEs, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator will detect, document, and report events that meet the definition of an AE or SAE as well as other reportable safety events. The investigator will also continue to follow up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3.

The investigator will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/Grade and causality with the study drug.

8.4.1 Time Period and Frequency of Reporting AEs, SAEs, and Other Reportable Safety Events

All AEs, SAEs, and other reportable safety events that fall under any of the following criteria occurring after the consent form is signed but before treatment allocation will be reported by the investigator for only participants assigned to treatment: the event led to study withdrawal; and the event is the result of a protocol-specified medical intervention (e.g., washout or discontinuation of usual therapy, diet, or a procedure).

From the time of treatment allocation through 14 days after study drug administration, all AEs, SAEs and other reportable safety events occurring will be reported by the investigator.

Additionally, any SAE brought to the attention of the investigator any time outside of the time period specified in the previous paragraph will also be reported immediately to the Sponsor if the event is considered “related” to the study drug.

The investigator is not obligated to actively seek AE or SAE or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the causality between the event and the study drug (or study participation) to be a reasonable possibility (related), the investigator must promptly report to the Sponsor.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 2.

Table 2 Reporting Time Periods and Time Frames for Adverse Events, Serious Adverse Events and Other Reportable Safety Events

Type of Event	Time Period			Time Frame to Report Event and Follow-up Information to the Sponsor:
	Consent to Allocation	Allocation through Protocol-Specified Follow-up Period	After the Protocol-Specified Follow-up Period	
Non-Serious Adverse Event	Report if: – Due to protocol-specified medical intervention – Led to study withdrawal	Report all	Reporting not required	See the data handling guidelines
Serious Adverse Event including Cancer and Overdose	Report if: – Due to protocol-specified medical intervention – Led to study withdrawal	Report all	Report if: – considered "related" to the study drug Follow-up ongoing events for outcome	Within 24 hours of learning of event
Pregnancy/ Lactation Exposure	Report if: – Due to medical intervention – Led to study withdrawal	Report all	Follow-up all reported pregnancies until completion/termination and report outcome	Within 24 hours of learning of event
Event of Clinical Interest (ECI) (Require regulatory reporting)	Report if: – Due to medical intervention – Led to study withdrawal	Report if: – Potential drug-induced liver injury (DILI) – Require regulatory reporting	Reporting not required	Within 24 hours of learning of event
Event of Clinical Interest (ECI) (Do not require regulatory reporting)	Report if: – Due to medical intervention – Led to study withdrawal	Report if: – Non- DILI ECIs not requiring regulatory reporting	Reporting not required	Within 5 calendar days of learning of event

8.4.2 Detection of AEs, SAEs, and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AE, SAE and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.4.3 Follow-up of AEs, SAEs, and other Reportable Safety Events

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events (including ECIs, cancer, and overdose) will be followed until resolution or stabilization, until the event is otherwise explained, or the participant is lost to follow-up (see Section 7.3). In addition, the investigator will make every attempt to follow all non-serious AEs that occur in participants assigned treatment for outcome. Detailed follow-up procedures are given in Appendix 4.

8.4.4 Regulatory Reporting Requirements for SAEs

Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safe use of the study drug are met.

The Sponsor has a legal responsibility to notify local regulatory authorities about the safety information on the study drug. All AEs will be reported to regulatory authorities, IRB/IECs, and the principal investigator, etc. in accordance with all applicable global laws and regulations "the Ministerial Ordinance on Good Clinical Practice (GCP) for Drugs," "the Ministerial Ordinance on Good Post-marketing Study Practice (GPSP) for Drugs," and the "Ministerial Ordinance on Good Vigilance Practice for Drugs, Quasi-drugs, Cosmetics, and Medical Devices (GVP)."

Investigator safety reports will be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to the principal investigator, etc. as appropriate.

The principal investigator, etc. who receives an investigator safety report describing an SAE or other significant safety information (e.g., summary or listing of SAEs) from the Sponsor will file it along with the investigator's brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5 Pregnancy and Exposure During Breastfeeding

Information in this section is not applicable since information on the pregnancy of participants' female partners is not required for this study.

8.4.6 Disease-related Events/Disease-related Outcomes Not Qualifying as AEs or SAEs

This section is not applicable.

8.4.7 Events of Clinical Interest (ECIs)

Non-serious AEs and SAEs specified as ECIs will be reported to the Sponsor.

The following events are specified as ECIs for this study:

1) An overdose of Sponsor's product, as defined in Section 8.5, that is not associated with clinical symptoms or abnormal laboratory results.
2) An elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) lab value that is greater than or equal to 3× the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2× the upper limit of normal and, at the same time, an alkaline phosphatase (ALP) lab value that is less than 2× the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.†

   † Note: These criteria are based upon U.S. regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. Refer to the Investigator Study File Binder (or equivalent) for the guidance for the assessment and follow up of participants meeting these criteria.

It may also be appropriate to conduct additional evaluation for an underlying etiology even in the setting of laboratory tests that do not meet the criteria for the reference specified above (AST, ALT, bilirubin, and ALP). In these cases, the decision to proceed with additional evaluation will be made by the investigator through a consultation with the Sponsor. However, abnormalities of liver blood tests that do not meet the criteria noted above are not ECIs for this study.

8.5 Treatment of Overdose

If a participant has taken, whether accidentally or intentionally, any drug as part of the study that exceeds the protocol-specified dose, the investigator will decide whether a dose is to be considered an overdose in consultation with the Sponsor.

8.6 Pharmacokinetics

Samples for the measurement of drug concentrations will be collected at time points specified in "1.3 Study Schedule." Pharmacokinetic parameters will be calculated using the plasma MK-0518 concentrations measured.

8.6.1 Blood Collection for Plasma MK-0518 Concentrations

Refer to Appendix 1 for the procedures of plasma sample collection, processing, storage, and shipment.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Future Biomedical Research Sample Collection

Future biomedical research samples will not be collected in this study.

8.9 Planned Genetic Analysis Sample Collection

No genetic analysis is planned in this study.

8.10 Biomarkers

Biomarkers are not evaluated in this study.

8.11 Visit schedule

Visit schedule is specified in Section 1.3. Refer to Section 8 for specific procedures.

8.11.1 Screening

Within 3 weeks before study drug administration, the screening test will be performed, and potential participants will be evaluated to determine that they fulfill the inclusion criteria as set forth in Section 5. Screening procedures may be repeated as a result of consultation with the Sponsor.

Participants may be rescreened after consultation with the Sponsor. Rescreening will include all screening procedures specified in the study schedule, including a consent discussion.

8.11.2 Treatment Period

Participants will visit the study site on the day before the scheduled study drug administration and be admitted to the site until 48 hours after the administration.

8.11.3 Post-study examination

Participants will be required to return to the site 10 to 14 days after study drug administration for a post-study examination. If the post-study examination occurs less than 14 days after study drug administration, a subsequent follow-up telephone call will be made at 14 days after the administration or later to determine if any AEs have occurred since the post-study examination.

8.11.4 Critical Procedures Based on Study Objectives: Timing of Procedure

Secondary endpoints for this study will be evaluated using blood MK-0518 concentrations.

At any post-dose time point, blood samples for the measurement of MK-0518 concentrations need to be collected as the most exactly close to the specified time point as

possible. All other procedures will be completed as close to the specified time point as possible. Study procedures can be performed before or after the specified time points.

The order of priority for the procedures can be changed with joint agreement of the investigator and the Sponsor.

Any nonscheduled tests required for urgent evaluation of safety concerns take precedence over all prespecified procedures and items.

Variances from the specified times for the study procedures and sample collections will be permitted as follows:

- Table 3 shows the time windows for sample collections for drug concentration measurements.

Table 3 Time Windows for Sample Collections for Drug Concentration Measurements

Sample Collection Time	Time Window
Before study drug administration	3 hours before to immediately before administration
0.5–12 hours after study drug administration	± 5 minutes
16–24 hours after study drug administration	± 15 minutes
48 hours after study drug administration	± 30 minutes

- Pre-dose safety evaluations: vital signs and ECG at 3 hours before study drug administration; laboratory tests and physical examination at 24 hours before study drug administration
- Post-dose safety evaluations (vital signs and laboratory tests)
  1. 5 hours after study drug administration: within 15 minutes of the specified time
  2. 4 hours after study drug administration: within 1 hours of the specified time (urine sample will be collected within 3 hours of the specified time)

8.11.5 Study Design/Dose/Procedures Modifications Permitted Within the Protocol Parameters

This study may employ some or none of the modifications described above. Any modifications meeting the study objectives will be described in a document by the Sponsor and agreed by the principal investigator. This document will be forwarded to the IRB/IEC at the discretion of the investigator.

9 Statistical Analysis Plan

9.1 Statistical Analysis Plan Summary

This section includes a statistical analysis plan summary for the study. The specific plan is provided in Section 9.2 of this study protocol.

9.1.1 Statistical Methods

Safety

Summary statistics of the measured values and their changes from baseline will be provided for laboratory test results, 12-lead ECGs, and vital signs together with a graph as appropriate. The changes from baseline will be shown, calculated with the scales of measurements (actual changes from baseline), or calculated on the natural log scale and back transformed (percent changes from baseline), depending on safety variables.

Pharmacokinetics

Summary of Pharmacokinetic Parameters

Individual values will be listed for each pharmacokinetic parameter, for which the number of participants (the number of participants with no missing measurements), arithmetic mean, standard deviation, percent coefficient variation (CV) (100 × standard deviation/arithmetic mean), median, minimum, maximum, geometric mean, and geometric percent CV (100 × sqrt (exp (s2) – 1) will be calculated. The s2 here denotes an estimate of variance on the natural log scale. $AUC_{0-\infty}$, C_{max}, and C_{24hr} will be natural log transformed, and mean 95% confidence intervals will be calculated based on the t distribution. The confidence interval of geometric means will be provided with the scale of measurement by taking the lower and upper 95% confidence limits.

9.1.2 Statistical Power

The precision of the estimates of $AUC_{0-\infty}$ and C_{24hr} will be assessed by calculating the half-width of the 95% confidence intervals expected for the given sample size and assumed variability. Assuming a true standard deviation of 0.367 log-[μM•hr] and 0.590 log-[nM] for natural log-$AUC_{0-\infty}$ and C_{24hr} between subjects as obtained from Study 812, then the half-width of the 95% confidence interval for the true mean $AUC_{0-\infty}$ and C_{24hr} on the natural log scale will be 0.233 log-[μM•hr] and 0.375 log-[nM]. The lower and upper 95% confidence limits for the true geometric mean $AUC_{0-\infty}$ and C_{24hr} will be given by OBS/1.263 and OBS × 1.263, OBS/1.455 and OBS × 1.455, where OBS is the observed geometric mean. Thus, for example, if the observed geometric mean $AUC_{0-\infty}$ was 50.1 [μM•hr] and C_{24hr} was 41.6 [nM], the 95% confidence interval would be 39.7 to 63.3 [μM•hr] and 28.6 to 60.5 [nM], respectively.

9.2 Statistical Analysis Plan

Statistical analysis of data obtained in this study will be performed or supervised by the biostatistics department under cooperation of the translational pharmacology department. Once the study is initiated, any changes to the statistical analysis plan described below will be documented in the clinical study report along with the reasons for the changes.

9.2.1 Hypotheses/Estimation

See "3. Hypotheses, Objectives, and Endpoints."

9.2.2 Endpoints

Primary endpoints are all AEs, laboratory test results, 12-lead ECGs, and vital signs.

Secondary endpoints are plasma MK-0518 concentrations and pharmacokinetic parameters ($AUC_{0-\infty}$, C_{max}, C_{24hr}, T_{max}, apparent $t_{1/2}$, CL/F, and Vz/F).

9.2.3 Analysis Populations

This section defines analysis populations. Data for all participants will be analyzed based on the treatment group in which individual participants have received administration.

All Subjects as Treated (AST): The set of all participants who have received at least 1 dose of the study drug, to be used for safety and tolerability evaluations.

Per-Protocol (PP): A subset of participants meeting the protocol criteria likely to provide data that sufficiently reflect efficacy under the scientific model. Protocol adherence will be determined by measures such as the exposure to study drug, the availability of measurements, and the absence of significant protocol deviations. Significant protocol deviations will be identified by the personnel involved in the collection, analysis, and interpretation of data. The data of all participants excluded from analysis will be identified and documented in the clinical study report along with the reasons for exclusion. This set of participants will be included in the pharmacokinetic analysis.

9.2.4 Statistical Methods

Safety

Summary statistics of the measured values and their changes from baseline will be provided for laboratory test results, 12-lead ECGs, and vital signs together with a graph as appropriate. The changes from baseline will be shown, calculated with the scales of measurements (actual changes from baseline), or calculated on the natural log scale and back transformed (percent changes from baseline), depending on safety variables.

Summary Statistics

Pharmacokinetic parameters for each participant will be listed, for which the number of participants (the number of participants with no missing measurements), arithmetic mean, standard deviation, percent CV (100 × standard deviation/arithmetic mean), median, minimum, maximum, geometric mean, and geometric percent CV (100 × sqrt (exp (s2) – 1) will be calculated. The s2 here denotes an estimate of variance on the natural log scale. $AUC_{0-\infty}$, C_{max}, and C_{24hr} will be natural log transformed, and mean 95% confidence intervals will be calculated based on the t distribution. The confidence interval of geometric means will be provided with the scale of measurement by taking the lower and upper 95% confidence limits.

Analysis of the pharmacokinetic similarity between Japanese and non-Japanese populations

For the analysis of pharmacokinetic similarity between Japanese and non-Japanese populations, pharmacokinetic parameters for a single dose of MK-0518 in Japanese and non-Japanese participants (Studies 812 and 824) will be compared in an exploratory manner. Pharmacokinetic parameters including $AUC_{0-\infty}$, C_{max} and T_{max} will be provided in graphs by race. $AUC_{0-\infty}$, C_{24hr} and C_{max} will be natural log transformed, for which geometric mean ratios and 90% confidence intervals will also be calculated based on the t distribution with a linear model having ethnicity (Japanese/non-Japanese) as a term.

9.2.5 Multiplicity

No multiplicity adjustments will be performed, since this study defines no hypotheses for testing.

9.2.6 Sample Size and Power Calculations

Precision of Pharmacokinetic Parameters

The precision of the estimates of $AUC_{0-\infty}$ and C_{24hr} will be assessed by calculating the half-width of the 95% confidence intervals expected for the given sample size and assumed variability. Assuming a true standard deviation of 0.367 log-[μM•hr] and 0.590 log-[nM] for natural log- $AUC_{0-\infty}$ and C_{24hr} between subjects as obtained from Study 812 in 12 subjects receiving raltegravir, then the half-width of the 95% confidence interval for the true mean $AUC_{0-\infty}$ and C_{24hr} on the natural log scale will be 0.233 log-[μM•hr] and 0.375 log-[nM]. The lower and upper 95% confidence limits for the true geometric mean values will be given by OBS/1.263 and OBS × 1.263, OBS/1.455 and OBS × 1.455, where OBS is the observed geometric mean. Thus, for example, if the observed geometric mean $AUC_{0-\infty}$ was 50.1 [μM•hr] and C_{24hr} was 41.6 [nM], the 95% confidence interval would be 39.7 to 63.3 [μM•hr] and 28.6 to 60.5 [nM], respectively.

10 Appendices (Supporting Documentation and Operational Considerations)

10.1 Appendix 1: Procedures for the Handling of Samples for Drug Concentration Measurements

Tools to be prepared

1) Plastic vacuum blood collection tubes with EDTA-2K that can contain 4 mL of whole blood each (BD Vacutainer blood collection tube, brochure No. 367862; or Fischer blood collection tube, brochure No. 02-683-99C)
2) 3.6 mL cryotubes manufactured by NUNC (NUNC brochure No. 366524)
   Note: No other tube than the one specified above (3.6 mL cryotubes by NUNC) should be used.
3) Pipettes
   Eppendorf Reference® pipettes 1,000 µL (single channel) (International Eppendorf brochure No. 4900 000.524, North America article brochure No. 022471651) or equivalents
4) Pipette Tips
   epTIPS Reloads 50–1250 µL containing 10 × 96 tips (brochure No. 0030073487) or equivalents (made of polypropylene)
5) Centrifuge
   A centrifuge that can ensure a relative centrifugal force (RCF) of 1000 to 1500 (× g) for 10 minutes at 4°C to 10°C. The RCF depends on the radius of centrifuge rotor. The formula for calculating RCF from spin speed and the radius of centrifuge rotor is: $RCF = 11.2 \times r \times (rpm/1000)^2$. The r here denotes the radius (cm) of rotor, and rpm the number of spins per minute set on the centrifuge. For example, a Beckman refrigerated centrifuge with a GH-3.8 rotor has a speed of 2500 rpm and a force of 1150 RCF.
6) Freezer capable of ≤−20°C to −30°C operation

Blood collections

Blood collections will be performed at specified time points in accordance with the protocol study schedule.

Labeling on Samples

1) Whole blood samples
   Vacuum blood collection tubes will be properly labeled.
2) Plasma samples
   NUNC tubes will have a Sponsor-supplied barcode label attached. The label displays a treatment/randomization number, the date of sample collection, and blood collection point (time since administration). The label on the NUNC tube will be attached to the point 30% below the top to display the volume of split plasma. Only 1 sheet of label will be attached to each tube to ensure the appropriate functioning of autosampler.

Procedure

1) Collect approximately 4 mL of whole blood using a plastic vacuum blood collection tube with EDTA-2K, and mix it by inverting 8 to 10 times. Attach an appropriate label to the vacuum blood collection tube as described above.
2) Cool the tube in ice immediately after blood collection. Centrifuge it for 10 minutes at 4°C to 10°C at a force of 1000 to 1300 RCF (× g). When an immediate centrifuge is not possible, cool it in ice and centrifuge it within 30 minutes after blood collection.
3) Immediately after centrifuging whole blood, take whole volume of plasma using a plastic pipette and carefully aliquote it into 3.6 mL cryotubes by NUNC (with a barcode label attached). Plasma samples will be kept with dry ice at −20°C to −30°C until they are shipped to the measurement site.

   Note: A previously unused plastic pipette will be used for each sample. When the immediately processing of whole blood samples is not possible, cool them in ice. Plasma samples will be freezed within 60 minutes after blood collection.

Shipment of samples

The personnel involved in the processing, packing, and shipment of samples will be instructed by the principal investigator to perform operations in accordance with the dangerous goods regulations established by International Air Transport Association (IATA).

1) Sample storage boxes will contain at least 10 kg of dry ice and have a label stating "HUMAN SAMPLES: NONINFECTIOUS" attached.
2) Each batch of sample shipment will have sample inventory attached.
3) Samples will be shipped at intervals previously confirmed between the Sponsor and the principal investigator. Samples will be shipped on Monday or Tuesday (Japan time) to reach the drug concentration measurement site (Syneos Health) by Friday (local time).
   Note: On the day of shipment, Syneous Health PPD will be informed of the shipment (Sponsor name, protocol number, shipping company, airbill number, shipper name, telephone number, shipment date, the number of packing boxes shipped, the type of samples, the number of samples, and precautions for the handling of samples) via FAX PPD or E-mail PPD cc, PPD).
4) Samples will be shipped to the following address:
   Syneos Health
   2500 Einstein
   Quebec (Québec), G1P A2, Canada
   TEL: PPD

   Note: Samples will be kept at −20°C to −30°C.

10.2 Appendix 2: Regulatory, Ethical, and Study Oversight Considerations

10.2.1 Guidelines for Clinical Study Operations

I. Introduction

A. Purpose

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., N.J., U.S.A. (MSD) (including its subsidiaries) conducts clinical studies worldwide to evaluate the safety and effectiveness of its own products. MSD is committed to designing, implementing, conducting, analyzing and reporting these studies in compliance with the highest ethical and scientific standards. Protection of participants in clinical studies is the overriding concern in the design of clinical studies. In all cases, MSD clinical studies will be conducted in compliance with local laws and regulations (e.g., International Council for Harmonisation Good Clinical Practice [ICH-GCP]) and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Highest ethical and scientific standards must be endorsed for all clinical studies sponsored by MSD irrespective of the external party (parties) employed for their execution (e.g., contract research organizations, collaborative research institutes). This Guideline is not intended to apply to studies that are observational or retrospective. Further, this Guideline does not apply to investigator-initiated clinical studies, which are not under the full control of MSD.

II. Scientific Issues

A. Study Conduct

1. Study Design

Except for pilot or estimation trials, study protocols will be hypothesis-driven to assess safety, efficacy, and/or pharmacokinetic or pharmacodynamic indices of MSD or comparator products. MSD may conduct outcome studies, studies to assess or validate various endpoints (outcome measures), or studies to determine participant preferences, etc. The design (e.g., participant population, duration, statistical power) must be adequate to address the specific purpose of the study. Participants must meet protocol-specified inclusion criteria to be enrolled in the study.

2. Site Selection

MSD selects study sites based on medical expertise, access to appropriate participants, adequacy of facilities and relevant staff, previous performance in clinical studies, as well as financial considerations. Prior to study initiation, study sites are evaluated by MSD personnel to assess the ability to appropriately conduct the study.

3. Site Monitoring/Scientific Integrity

Study sites are examined to assess compliance with the study protocol and general principles of Good Clinical Practice (GCP). MSD reviews clinical data for accuracy,

completeness, and consistency by verifying them versus source documentation according to standard operating procedures. Per MSD policies and procedures, if fraud, scientific/research misconduct, or serious GCP-noncompliance is suspected, the issues are investigated. When necessary, the study at the relevant site will be discontinued, and the responsible regulatory authorities and ethics review committees will be notified.

B. Publication and Authorship

Regardless of study outcome, MSD commits to publish (e.g., submit a paper or give a presentation at a scientific meeting) primary and secondary results of the studies registered to clinical trial registries for marketed products, according to the prespecified analysis plans. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses that are important to patients, physicians, and payers. Some early phase or pilot studies are intended to be hypothesis-generating rather than hypothesis testing. In such cases, publication of results may not be appropriate since the study may be underpowered and/or due to the analyses complicated by statistical issues such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors. In summary, authorship should reflect significant contribution to the design and conduct of the study, performance or interpretation of the analysis, and writing of the manuscript. All named authors must be able to defend the study results and conclusions. MSD funding for the study will be acknowledged in publications.

III. Participant Protection

A. Institutional Review Board (IRB)/Independent Ethics Committee (IEC) Review

All clinical studies will be reviewed and approved by an IRB/IEC before being initiated at each study site. Significant changes or revisions to the protocol will be approved by the ethics committee prior to implementation, except changes required urgently to protect participant safety that may be enacted in anticipation of ethics committee approval. For each site, the ethics committee and the Sponsor (personnel specified in the procedures) will approve the ICF for participants.

B. Safety

The guiding principle in decision-making in clinical studies is that participant protection is of primary importance. Potential participants will be informed of the risks and benefits of study participation as well as alternative courses of treatment, when enrolled in the study. At a minimum, study designs will take into account the local standard of care.

All participation in MSD clinical studies is voluntary. Participants enter the study only after informed consent is obtained. Participants may withdraw from an MSD study at any time, without any influence on medical care that may otherwise be available to them.

C. Confidentiality

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible. Unless required by law, only investigators, study collaborators, Sponsor (or representative), ethics committee, and/or regulatory authorities will have access to medical records that might identify the participant by name.

D. Genetic Research

Genetic research will only be conducted in accordance with a protocol and informed consent form approved by an ethics committee.

IV. Financial Considerations

A. Payments to Study Sites

Clinical studies are time- and labor-intensive. It is MSD's policy to compensate study sites by fair procedures for the work performed in support of MSD trials. MSD does not pay any incentives to enroll participants in its studies. However, when enrollment is particularly challenging, additional payments will be discussed to compensate for recruiting efforts for that extra time was spent.

MSD does not pay for participant referrals. However, MSD may compensate physicians for time spent on chart review to identify potentially eligible participants.

B. Clinical Research Funding

Informed consent forms will disclose that the study is sponsored by MSD and that the study site is being funded for performing the study. However, the ethics committee may wish to alter the wording of the disclosure statement to be consistent with financial practices at the relevant institution. As noted above, all publications resulting from MSD studies will indicate MSD as the Sponsor.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings) will be consistent with local guidelines and practices.

V. Principal Investigator Commitment

Principal investigators will be expected to review and understand MSD's Guidelines for Clinical Study Operations attached to the study protocol, and in signing the protocol, agree to support ethical and scientific standards provided in the guidelines.

10.2.2 Compliance with Financial Disclosure Requirements

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is investigators' responsibility to comply with any such request.

Investigators agree, if requested for disclosure of financial details by the Sponsor in accordance with the above regulations, to provide the Sponsor with accurate and complete information. Investigators further agree to provide this information on a Certification/Disclosure Form (commonly known as a financial disclosure form) provided by the Sponsor. Investigators also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries and regions that do not have laws protecting personal data.

10.2.3 Protection of Data

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.

Participants must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to participants.

Participants must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by IRB/IEC members, and by inspectors from regulatory authorities.

10.2.3.1 Confidentiality of Data

By signing this protocol, the principal investigator affirms to the Sponsor that information furnished to the principal investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the IRB, IEC, or expert committee, affiliated institutions including the study site and employees, only under an appropriate agreement/understanding on confidentiality with such board or committee, affiliated institutions and employees. Data generated by this study will be considered confidential, except to the extent that it is included in a publication as provided in the Publication section of this protocol.

10.2.3.2 Confidentiality of Participant Records

By signing this protocol, the principal investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult study documents (hereinafter, direct access) and/or copy them to verify worksheet/CRF report form data. By signing the consent form, participants agree to these direct access and copy. If study documents will be photocopied during the process of verifying worksheet/CRF information, participants will be identified by individual unique codes only; full names will be masked prior to transmission to the Sponsor.

By signing this protocol, the principal investigator agrees to treat participant data used and disclosed in connection with this study in accordance with all applicable privacy protection laws, regulations and rules.

10.2.3.3 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and affiliation of each IRB/IEC that reviews and approves this study. The Sponsor is also required to document that each IRB/IEC meets regulatory and GCP requirements by obtaining and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.2.4 Publication Policy

The results of this study may be published or presented at scientific meetings. The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practices, the Sponsor will support publication of multicenter studies only in their entirety and not as individual site data. In a multicenter study, coordinating investigators will be designated by mutual agreement.

If publication activity is not directed by the Sponsor, investigators agree to provide all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

Authorship eligibility will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2.5 Study Registration and Results Posting

Under the terms of the Food and Drug Administration Amendments Act (FDAAA) of 2007 and the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. MSD will review the protocol, and register and update necessary information in accordance with applicable requirements. Registration and updates are not limited to FDAAA or the EMA clinical trial directive mandated studies. The information registered will allow participants to identify potentially appropriate studies for their disease conditions and obtain information on appropriate study site locations and contact information by calling study contact center, etc.

By signing this protocol, the principal investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials directive or other locally mandated registries are the obligations of the Sponsor and agrees not to submit any information about this study to those registries.

10.2.6 Compliance with Law, Audit, and Debarments

By signing this protocol, the principal investigator agrees to conduct the study in conformance with this protocol, GCP, and other applicable laws and regulations relating to the conduct of the study.

The Guidelines for Clinical Study Operations, a collection of guides and considerations that govern the ethical and scientific conduct of clinical studies sponsored by MSD, is provided in this appendix.

The principal investigator agrees not to seek reimbursement from participants, their insurance providers, or from government programs related to medical benefit for procedures included as part of the study reimbursed by the Sponsor.

The principal investigator will promptly inform the Sponsor of any regulatory authority investigation and inspection conducted for this study.

The principal investigator agrees to provide the Sponsor with relevant information from investigation/inspection observations and findings to allow the Sponsor to assist in responding to any citations resulting from regulatory authority investigation/inspection, and will provide the Sponsor with a copy of the proposed response for consultation before submission to the regulatory authority.

Persons debarred from conducting or working on clinical studies legally or by a regulatory authority will not be allowed to conduct this study or participating in the study operations in any circumstances. The principal investigator will immediately notify the Sponsor in writing if any person who is involved in conducting the study is "debarred" or if any proceeding for debarment is pending or, to the best of the principal investigator's knowledge, threatened.

10.2.7 Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The principal investigator will verify that data records are accurate by physically or electronically signing the CRF.

Detailed information regarding Data Management procedures for this study will be provided separately.

The principal investigator must maintain accurate documentation (source data) that supports the information recorded in the CRF.

The principal investigator will permit study-related monitoring, audits, IRB/IEC review, and regulatory agency investigations and provide direct access to source data documents.

Study documentation will be promptly and fully disclosed to the Sponsor by the principal investigator upon request and also shall be made available at the study site upon request for inspection, copying, review, and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. For deficiencies detected in the study documentation and worksheets/CRFs, the principal investigator agrees to promptly take any appropriate measures that are requested by the Sponsor or any regulatory authorities as a result of an audit or investigation.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data review and verification to confirm that data recorded in the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulations.

Records and documents, including signed ICF, pertaining to the conduct of this study will be retained by the principal investigator for 15 years after study completion unless local regulatory requirements or institutional provisions require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.2.8 Source Documents

Source documents provide evidence for the existence of participants and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or eCRF that are transcribed from source documents must be consistent with the source documents, and reasons for any discrepancies must be explained. The principal investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.2.9 Discontinuation of the Study, and Discontinuation of Study Site Participation

The Sponsor or its delegate may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons according to applicable regulations, rules and GCP. In the event the Sponsor prematurely terminates a particular study site, the Sponsor will promptly notify the study site's IRB/IEC of that.

10.3 Appendix 3: Clinical Laboratory Tests

The laboratory tests shown in Table 4 will be performed at the study site at each assessment point. However, blood sampling for laboratory tests (screening test, 24 hours before and after study drug administration) will be performed after confirming the elapse of at least 8 hours after a meal.

Table 4 Protocol-specified Safety Laboratory Tests

Laboratory Test Category	Parameters			
Hematology	Platelet count	WBC count and differential: Neutrophils, lymphocytes, monocytes, eosinophils, basophils		
	RBC count			
	Hemoglobin			
	Hematocrit			
Clinical Chemistry	Blood urea nitrogen	Potassium	AST	Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the upper limit of normal)
	Albumin	Chloride	Fasting blood glucose	Creatinine
	Sodium	ALT	Total protein	Creatine kinase
Urinalysis	• Specific gravity • Urinalysis for pH, glucose, protein and occult blood • Microscopy (if urine occult blood or protein is abnormal)			
Other Tests	• Serology: hepatitis B surface antigen, hepatitis C virus antibody, syphilis and HIV antigen and antibody (CRF completion not required) • Drug screen: benzodiazepines, barbiturates, tricyclic antidepressants, phencyclidines, stimulants, cannabis, cocaine, morphine (CRF completion not required)			

The investigator must review each clinical laboratory result and document the results of review.

10.4 Appendix 4: AE Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.4.1 Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of a study drug, whether or not considered related to the study drug.
- Note: In other words, an AE denotes any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study drug.
- Note: For purposes of AE definition, the use of a study drug (also referred to as Sponsor's product in this Appendix) includes the use of any pharmaceutical product, biological product, vaccine, medical device, diagnostic agent, or protocol-specified procedure whether investigational (including placebo or active comparator product) or marketed, manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test (hematology, clinical chemistry, or urinalysis) results or other abnormal safety assessments (e.g., ECG, imaging assessments, vital sign measurements), including those that worsen from baseline, or those considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including an increase in frequency and/or intensity of the condition.
- A new condition detected or diagnosed after the initiation of study drug administration whether or not it may have been present before the start of the study.
- Signs, symptoms, or sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or sequelae of a suspected overdose of either study drug or a concomitant medication.
- For any reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the relevant clinical symptom or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect" or "intentional overdose without adverse effect."
- Any new cancer or progression of pre-existing cancer.

Events NOT meeting the AE definition

- Medical or surgical procedure (e.g., endoscopy, appendectomy): a condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study, or such a present or detected disease(s) or condition(s) that does not worsen.
- Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened.
- Refer to Section 8.4.6 for protocol-specific exceptions.

10.4.2 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions defined below are met.

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

a. Results in death
b. Is life-threatening
   - A "life-threatening" occurrence in the definition of "serious" refers to an event in which a participant was at risk of death at the time of its onset. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization
   - Hospitalization is defined as an inpatient admission, regardless of the length of stay, including admission as a precautionary measure for observation. (Note: Hospitalization for an elective procedure to treat a pre-existing illness that has not worsened during the study is not an SAE. A clinical condition that is detected prior to the use of an MSD product is documented in the participant's medical history.)
d. Results in permanent or significant disability/incapacity
   - The term "disability" means a substantial disruption of a person's ability to conduct normal life functions.
   - This definition is not intended to include events of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
   - In the offspring of a participant taking the study drug regardless of the time of diagnosis.
f. Other medically important events
   - Medical or scientific judgment will be exercised in deciding whether SAE reporting is appropriate in the situations described below. Important medical events that, even if they are not immediately life-threatening or they do not result in hospitalization or death, may jeopardize the participant or may require medical or surgical intervention to prevent serious conditions listed in the above definition are usually considered serious.

     Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood

dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.4.3 Additional Events to be Reported in the Same Manner as SAE

Additional events that should be reported in the same manner as SAE

- Events listed below, although not included in SAEs specified in ICH, are reportable to the Sponsor in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are regarded as serious.
- A new cancer (that is not a condition of the study)
- An AE associated with an overdose

10.4.4 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital clinical records, laboratory reports, diagnostic reports) related to the event.
- The investigator will enter all relevant AE/SAE information on the AE form on the CRF and worksheets.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of recording on the AE form of the CRF.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers (with the exception of the participant number assigned for this study), will be blinded on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

- "Severe" intensity of an AE is not a definition of an SAE. An event is classed as "serious" when it meets at least 1 of the conditions prespecified in the definition of an SAE.
- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) reported during the study and assign it to 1 of the following categories:
- Mild: An event that is easily tolerated by the participant, causing minimal discomfort, but not interfering with everyday activities (for pediatric studies, awareness of symptoms, but easily tolerated).
- Moderate: An event causing severe discomfort that interferes with normal everyday activities (for pediatric studies, definitely acting like something is wrong).
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category

used for rating the intensity of an event; and both AE and SAE can be assessed as severe (for pediatric studies, extremely distressed or unable to do usual activities).

Assessment of causality

- Did the Sponsor's product cause the AE?
- The determination of the likelihood that the Sponsor's product caused the AE will be provided by the investigator. A signature (autograph, seal, and initials are also acceptable)/date will be provided by the investigator on the source document or worksheet that supports the causality noted on the AE form, ensuring that a medically qualified assessment of causality was done. The document with a signature (autograph, seal, and initials are also acceptable) must be retained for the time frame specified in regulatory requirements. The assessment criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between an AE and the Sponsor's product based upon the available information.
- The following conditions are to be used for causality assessment; the greater the correlation with these conditions and their respective criteria (the number of applicable items or intensity), the more likely the Sponsor's product caused the AE:
- Exposure to the Sponsor's product: The presence or absence of evidence that the participant was actually exposed to the Sponsor's product such as; a reliable dosing record, a reliable record of compliance assessment (pill count, participant diary, etc.), a record of the presence or absence of expected drug effect, or a record related to the measurement of drug/metabolite in the body
- Temporal relationship: Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with an effect induced by the Sponsor's product?
- Likely cause: Is it unable to explain the AE reasonably by other cause than the Sponsor's product (underlying disease, other drug(s)/vaccine(s), medical history or other participant or environmental factors)?
- Dechallenge: Was the Sponsor's product discontinued or its dose reduced?
- Did the AE resolve or improve by discontinuation or dose reduction?
- If "yes," this is a positive dechallenge.
- If "no," this is a negative dechallenge.

  Note: The dechallenge criterion is not applicable if:

  (1) the outcome of the AE resulted in death or permanent disability
  (2) the AE resolved/improved despite continuation of the study product
  (3) the study is a single-dose study
  (4) Sponsor's product(s) is/are used only 1 time
- Rechallenge: Was the participant re-exposed to the Sponsor's product?
- Did the AE recur or worsen by re-exposure?
- If "yes," this is a positive rechallenge.
- If "no," this is a negative rechallenge.

  Note: The rechallenge criterion is not applicable if:

(1) the outcome of the AE resulted in death or permanent disability
(2) the study is a single-dose study
(3) Sponsor's product(s) is/are used only 1 time

Note: If a rechallenge is planned for an AE that was serious and suspected to be relate to the Sponsor's product, or if re-exposure to the Sponsor's product poses additional potential significant risk to the participant, then the rechallenge must be approved in advance by the Sponsor development director/medical expertise, and if required, the IRB/IEC.

- Consistency with study drug profile: Is the onset of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?
- The assessment of relationship will be documented on the CRFs/worksheets by an investigator according to his/her best clinical judgment, including consideration of the above elements.
- Use the following criteria as guidance (not all criteria need to be met to be indicative of a relationship with the Sponsor's product).
- Related: There is a reasonable possibility of a relationship with the Sponsor's product.
  There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The cause of the AE is more likely explained by the Sponsor's product than by other factors (other drugs, underlying disease, medical history, or other participant or environmental factors).
- Not related: There is not a reasonable possibility of a relationship with the Sponsor's product.
  The participant did not receive the Sponsor's product, the temporal sequence of the AE onset relative to the administration of the Sponsor's product is not reasonable, or the cause of the AE is more likely explained by another cause than the Sponsor's product. (An overdose without an associated AE is also considered as "not related.")
- For each AE/SAE, the investigator must document in the medical records that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, even in such cases, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The investigator may change his/her opinion on causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to arrange for the conduct of supplemental measurements and/or evaluations or perform them as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or assessments, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the CRF.
- The investigator will submit any additional information on SAE to the Sponsor within 24 hours of receipt of the information.

10.4.5 Reporting of AE, SAE, and Other Reportable Safety Events to the Sponsor

SAE Reporting to the Sponsor via Paper CRF

- If an electronic data collection tool is not operational at the study site, facsimile or secure e-mail transmission of a paper CRF (SAE report form) is the preferred method to report an SAE to the Sponsor.
- In exceptional circumstances (e.g., in the absence of facsimile equipment), notification by telephone is acceptable with a copy of the paper CRF (SAE report form) sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the paper CRF (SAE report form) within the specified reporting time frames.
- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

10.5 Appendix 5: Criteria for 12-lead ECG Abnormalities

Criteria for 12-lead ECG Abnormalities		
	Drop-out of screening	Clinically meaningful finding after randomization (criteria for the need of a measure)
Rhythm		
Sinus tachycardia	> 110 bpm	Heart rate > 110 bpm and increased by ≥ 25 bpm from baseline
Sinus bradycardia	< 40 bpm	Heart rate < 40 bpm and decreased by ≥ 5 bpm from baseline
Sinus arrest/cardiac arrest	> 2.0 seconds	> 2.0 seconds
Atrial extrasystole	> 1 beat	≥ 3 beats
Ventricular extrasystole	All	≥ 3 beats
Ectopic atrial rhythm	Make an assessment along with other findings	Make an assessment along with other findings
Junctional rhythm	Junctional rhythm present and heart rate < 40 bpm	Junctional rhythm present and heart rate < 40 bpm
Idioventricular rhythm	All	All
Atrial fibrillation	All	All
Atrial flutter	All	All
Supraventricular tachycardia	All	All
Ventricular tachycardia	All	All
Axis		
Left axis deviation	Right bundle branch block and left anterior fascicular hemiblock	New left anterior fascicular hemiblock
Right axis deviation	Right bundle branch block and left posterior fascicular hemiblock	New left posterior fascicular hemiblock
Conducting system		
First degree AV block	PR interval ≥ 230 msec	PR interval ≥ 230 msec and prolonged by > 15 msec, or PR interval prolonged by > 25%
Second degree AV block	Mobitz II	Mobitz II
Third degree AV block	All	All
Left bundle branch block	All	All
Right bundle branch block	Right bundle branch block and left anterior fascicular hemiblock, or right bundle branch block and left posterior fascicular hemiblock	New right bundle branch block (not including intermittent, associated with heart rate)
Incomplete right bundle branch block (ORS interval < 120 msec)	Not excluded	Not regarded as a clinically meaningful finding
Short PR interval/preexcitation syndrome	Delta wave present and PR interval < 120 msec	Delta wave present and PR interval < 120 msec
Other intraventricular delay	QRS ≥ 130 msec	QRS ≥ 130 msec and prolonged by ≥ 10 msec
QTcB or QTcF interval		
Male	QTc interval ≥ 470 msec	QTc interval ≥ 500 msec or prolonged by ≥ 60 msec from baseline
Hypertrophy		
Atrial abnormality	Definitive evidence of mitral P wave or P wave pulmonale	Definitive evidence of mitral P wave or P wave pulmonale
Ventricular abnormality	Strain pattern present in addition to the voltage criteria for left ventricular hypertrophy	Strain pattern present in addition to the voltage criteria for left ventricular hypertrophy

Criteria for 12-lead ECG Abnormalities		
	Drop-out of screening	Clinically meaningful finding after randomization (criteria for the need of a measure)
Myocardial infarction		
Acute or recent	All	All
Old	All	All
ST-T wave		
ST-segment elevation suggestive of myocardiopathy	≥ 2 contiguous leads	≥ 2 contiguous leads
ST-segment reduction suggestive of myocardial ischemia	≥ 2 contiguous leads	≥ 2 contiguous leads
T-wave inversion suggestive of myocardial ischemia	≥ 2 contiguous leads	≥ 2 contiguous leads
Nonspecific ST-T change (≥ 2 leads)	Not excluded	≥ 2 contiguous leads
Pacemaker	All	All
Baseline is defined as a measurement prior to study drug administration during the treatment period.		

10.6 Appendix 6: Algorithm for Assessing Abnormal Laboratory Values

Laboratory values obtained at the screening test and predose will be evaluated as follows.

a) If all protocol-specified laboratory values are normal, the participant may enter the study.
b) If a protocol-specified laboratory value does not meet the inclusion criteria or meets the exclusion criteria (including a repeat value if obtained), the participant will be excluded from the study.
c) If a laboratory value not specified in the inclusion/exclusion criteria is outside the normal range, the following choices are available:
    1. The participant may be excluded from the study.
    2. The participant may be included in the study if the abnormal value(s) is not clinically significant (NCS) (the investigator must annotate the laboratory value "NCS" on the laboratory test source document).
    3. The participant may enter the study if the abnormality is due to a co-existing medical condition which is not excluded per protocol (e.g., elevated eosinophil count due to asthma or seasonal allergies) (the co-existing medical condition will be annotated as a cause on the laboratory test source document).
    4. The abnormal test may be repeated (with the following choices).
        (a) If the repeat test value is within the normal range, the participant may enter the study.
        (b) If the repeat test value is still abnormal, the investigator will evaluate the participant eligibility for enrollment with a complete history and physical examination, etc., looking especially for diseases that could result in the abnormal laboratory value in question. If such diseases can be ruled out, and if the abnormal laboratory value is not clinically relevant, then the participant may enter the study.
d) If there is any clinical uncertainty regarding the reason for the abnormal value, the participant will be excluded from the study.

10.7 Appendix 7: Study Administrative Structure

10.7.1 Sponsor

10.7.1.1 Sponsor Name and Address

MSD K.K.
Kitanomaru Square, 1-13-12, Kudan-kita, Chiyoda-ku, Tokyo 102-8667

10.7.1.2 Sponsor Development Director

Post-marketing Survey Manager
PPD Clinical Pharmacology Development, Global Research and Development Division, MSD K.K.
Kitanomaru Square, 1-13-12, Kudan-kita, Chiyoda-ku, Tokyo 102-8667
Phone: PPD FAX: PPD
Role of the Sponsor Development Director
To lead clinical operations as the Sponsor development director.

10.7.1.3 Medical Expertise

Akinori Urae (physician), Chairman and Chief Executive Officer, Mediscience Plannning Inc.
1-11-44 Akasaka, Minato-ku, Tokyo 107-0052
Phone: PPD FAX: PPD

10.7.1.4 Monitor (Representative)

PPD
Primary Care Area, Study Operation Department, Clinical Operation Area, Global Research and Development Division, MSD K.K.
Phone: PPD FAX: PPD

PPD
Colinical Pharmacology Development Department, Mediscience Plannning Inc.
Phone: PPD FAX: PPD

10.7.2 Contract Research Organization

10.7.2.1 Contract Organization for Monitoring, etc.

PPD
Clinical Pharmacology Development Department, Mediscience Plannning Inc.
1-11-44 Akasaka, Minato-ku, Tokyo 107-0052
Phone: PPD FAX: PPD

Role of the Contract Organization for Monitoring, etc.
To prepare a protocol (draft) for post-marketing clinical trials; prepare an ICF (draft); prepare a sample CRF (draft); perform monitoring, perform data management; perform statistical analyses; prepare a clinical study report (draft); and perform monitoring in accordance with GCP and GPSP as well as the Sponsor's standard operating procedures.

10.7.2.2 MSD K.K. Clinical Study Emergency Center

BI Medical, Inc.
Bunkyo Green Court Center Office 10th Floor, 2-28-8 Honkomagome, Bunkyo-ku, Tokyo 113-0021
Phone: PPD

Role of MSD K.K. Clinical Study Emergency Center

1) Contact during out of office hours (Monday to Friday: 18:00 to 9:00 next day. Holidays and MSD non-business days: 24 hours.)

10.7.3 Central Laboratory (Regarding Potential Drug-induced Liver Injury)

PPD Global Central Labs
2 Tesseneer Drive, Highland Heights, KY 41076, USA
Phone: PPD

Role of Central Laboratory (Regarding Potential Drug-induced Liver Injury)

1) To measure part or all of the Stage 1 and Stage 2 test parameters in participants meeting the criteria for potential drug-induced liver injury
2) To report test data to the investigator and the Sponsor

10.7.4 Drug Concentration Laboratory

Syneos Health
2500 rue Einstein, Québec (Québec), Canada G1P 0A2
Phone: PPD FAX: PPD

10.7.5 Principal Investigator

PPD
Internal Medicine, Sekino Clinical Pharmacology Clinic
3-28-3 Ikebukuro, Toshima-ku, Tokyo
Phone: PPD

10.8 Appendix 8: Abbreviations

Abbreviation	Definition
AIDS	Acquired immune Deficiency Syndrome
AUC	Area Under the Plasma Concentration-Time Curve
BMI	Body Mass Index
C_{24hr}	Plasma Concentration at 24 hours after Administration
CL/F	Apparent Total Clearance of the Drug from Plasma after Oral Administration
C_{max}	Maximum Plasma Drug Concentration
CV	Coefficient of Variation
CYP	Cytochrome P450
DILI	Drug-Induced Liver Injury
DNA	Deoxyribonucleic Acid
ECI	Event of Clinical Interest
EMA	European Medicines Agency
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FTC	Emtricitabine
GCP	Good Clinical Practice
GPSP	Good Post-Marketing Study Practice
HIV	Human Immunodeficiency Virus
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
NCS	Not Clinically Significant
OBS	Observed Geometric Mean
ONCEMRK	Evaluation of the Safety and Efficacy of Reformulated Raltegravir (MK-0518) 1200 mg Once Daily in Combination With TRUVADA™ in Human Immunodeficiency Virus (HIV)-1 Infected, Treatment-Naive Participants (MK-0518-292) (onceMRK)
P-gp	P-glycoprotein
RCF	Relative Centrifugal Force
RNA	Ribonucleic Acid
$t_{1/2}$	Elimination half-life
TDF	Tenofovir Disoproxil Fumarate
T_{max}	Time to Reach Maximum (peak) Plasma Concentration following Drug Administration
UDP	Uridine Diphosphate
Vz/F	Apparent Volume of Distribution during Terminal Phase after Non-Intravenous Administration

11 References

Not Applicable

[Contact Information]
Clinical Pharmacology Development, Clinical Research Area,
Global Research and Development Division, MSD K.K.
Kitanomaru Square
1-13-12, Kudan-kita, Chiyoda-ku, Tokyo 102-8667
Phone: PPD FAX: PPD

Clinical Pharmacology Development Department,
Mediscience Plannning Inc.
Phone: PPD FAX: PPD

[Out of Office Hours Emergency Contact Information]
Monday to Friday: 18:00 to 9:00 next day.
Holidays and MSD non-business days: 24 hours.
MSD Clinical Study Emergency Center (BI Medical, Inc.)
Phone: PPD