Official Protocol Title:	An Open-Label Study to Investigate the Single-Dose Pharmacokinetics of MK-3866 when Administered to Subjects with Moderate and Severe Hepatic Impairment
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TITLE:

An Open-Label Study to Investigate the Single-Dose Pharmacokinetics of MK-3866 when Administered to Subjects with Moderate and Severe Hepatic Impairment

IND NUMBER: 133,048

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SUMMARY OF CHANGES

PRIMARY REASON FOR THIS AMENDMENT:

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
2.1	Trial Design	Change the trial treatment dose from 200 mg to 150 mg.	Upon review of pharmacokinetic and safety data from MK-3866 PN002, the multiple ascending dose study, it was determined that the starting dose for subjects with hepatic impairment should be 150 mg.
4.2.1	Rationale for the Trial and Selected Subject Population		
4.2.2	Rationale for Dose Selection		
5.2	Trial Treatment, Table 2		
9.1	Investigational Product		

ADDITIONAL CHANGES FOR THIS AMENDMENT:

Minor typographical and formatting errors were corrected throughout the protocol. Additional changes are listed below.

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
2.1	Trial Design	For the timing of the infusion, a variance of ±5 minutes was added.	To provide flexibility to the total MK-3866 infusion time of 30 minutes.
4.2.1	Rationale for the Trial and Selected Subject Population	Add that maximum exposure is unlikely to exceed 2.7-fold higher than 150 mg.	To provide further rationale for dose.
5.5	Concomitant Medication (Allowed and Prohibited)	Clarify the restrictions on use of enzyme/transporter inhibitors and inducers.	Inhibitors of OATP1B1/1B3 transporters are also prohibited.
		Clarify the window for withholding allowed prescription medications after study treatment adminitration.	Certain allowed prescription medications must be withheld for 4 hours after study treatment administration.

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
6.0	Trial Chart	Clarify time points for Concomitant Medication Review and Adverse Events Monitoring.	Assessments will be conducted throughout study.
		Update footnote "a" to state that subjects will return to the clinical research unit 14 days after the last dose for follow-up procedures, and to determine if any adverse events have occurred soince the last study visit.	To provide details regarding the post trial visit.
7.1.2.4	Vital Signs (Blood Pressure, Pulse Rate, Respiratory Rate, Body Temperature)	Remove the statement body temperature will be measured "with an oral or tympanic thermometer".	To not limit the clinical reseach unit's options and to allow the site to follow its typical process for measuring body temperature.
9.1	Investigational Product	Change "dosing concentration" to "dose".	To clarify that the dose to be administered will be 150 mg.

1.0 TRIAL SUMMARY

Abbreviated Title	MK-3866 Hepatic Impairment Study
Sponsor Product Identifiers	MK-3866
Trial Phase	1
Clinical Indication	Treatment of bacterial infection
Trial Type	Interventional
Type of control	Healthy matching subjects
Route of administration	Intravenous
Trial Blinding	None. This is an open-label study.
Treatment Groups	Panel A) 6 subjects with moderate hepatic impairment (HI) Panel B) 6 subjects with severe HI Panel C) At least 6 (up to 12) healthy subjects
Number of trial subjects	At least 18 (up to 24)
Estimated duration of trial	The Sponsor estimates that the trial will require approximately 56 days from the time the first subject signs the informed consent form (ICF) until the last subject's last study-related visit.
Duration of Participation	Each subject will participate in the trial for approximately 43 days from the time the subject signs the ICF through the final contact. After a screening phase of 28 days, each subject will receive a single dose of the assigned treatment. Each subject will be followed for 14 days after receiving the study treatment.

2.0 TRIAL DESIGN

2.1 Trial Design

This is an open-label, single-dose study to evaluate the pharmacokinetics (PK) of intravenous (IV) MK-3866 in subjects with moderate and severe hepatic impairment (HI) compared to that of matched healthy subjects. Subjects with moderate (Panel A) and severe (Panel B) HI (classified using the Child-Pugh scale) shall be enrolled in parallel, and each Panel shall enroll a minimum of 2 subjects of each gender.

Enrollment of healthy matching control subjects (Panel C) shall commence following the completion of enrollment of either Panel A or B, whichever is completed first. Each healthy control subject will be matched to the mean body mass index (BMI; ±10%) and age (±15 years) of the subjects in the first HI Panel to complete enrollment. A total of 6 healthy subjects shall be enrolled into Panel C at this stage, and there should be a minimum of 2 subjects of each gender.

Following the completion of enrollment of the second HI panel, the matching characteristics (age and BMI) of the already-enrolled healthy subjects in Panel C will be compared against the mean values of the HI panel that is completed second. If any of the subjects already enrolled in Panel C do not also meet the matching criteria for the second completed HI panel, additional healthy subjects will be enrolled into Panel C in order to provide 6 healthy control

subjects who match the mean BMI (±10%) and age (±15 years) of the subjects in the second HI panel. The gender of the additional healthy subject(s) will be selected to ensure that there is a minimum of 2 subjects of each gender in the group of subjects within Panel C who match with the second HI panel. On the basis of this study design Panel C may ultimately include more than 6 subjects, but no more than 12. Although enrollment efforts into Panels A and B will commence at the same time, it is expected to take longer to enroll subjects into Panel B.

The PK comparisons between each hepatically impaired Panel (A and B) and healthy controls (Panel C) will include only control subjects who meet the matching criteria for the respective HI panel.

Subjects in Panels A, B and C will receive a single IV dose of 150 mg MK-3866 (30 minute infusion, ± 5 minutes). Plasma PK assessments will be performed at pre-specified time points up to 72 hours post-dose for moderate and severe HI and up to 48 hours postdose for the healthy match control group.

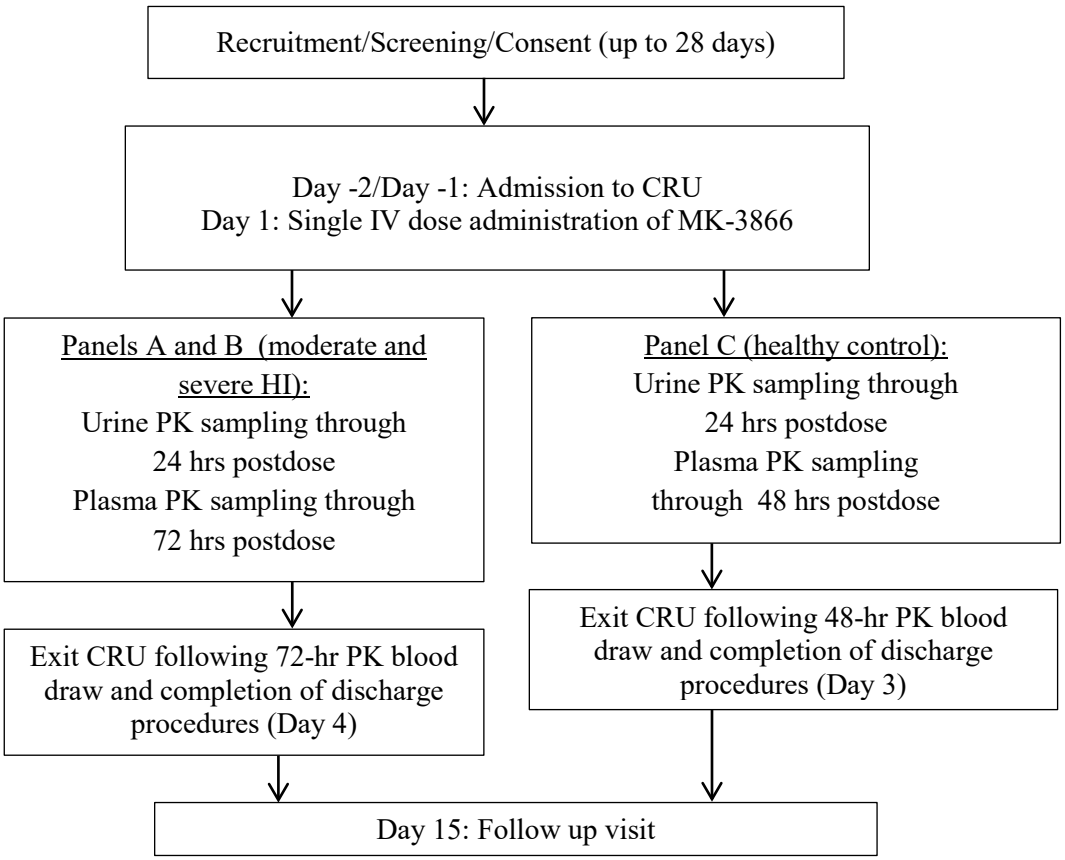
Safety will be monitored throughout by repeated clinical and laboratory evaluations and the post-trial visit will occur approximately 14 days after administration of study drug.

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart - Section 6.0. Details of each procedure are provided in Section 7.0 – Trial Procedures.

Because this is a Phase I assessment of MK-3866 in humans, the PK, pharmacodynamic (PD) and safety profiles of the compound are still being elucidated. This protocol is therefore written with some flexibility to accommodate the inherent dynamic nature of Phase I clinical trials. Please refer to Section 7.1.5 – Visit Requirements for examples of modifications permitted within the protocol parameters.

2.2 Trial Diagram

Figure 1 Trial Diagram



CRU = Clinical research unit; HI = hepatic impairment; hrs = hours; IV = intravenous; PK = pharmacokinetic

3.0 OBJECTIVES & ESTIMATIONS

3.1 Primary Objectives & Estimations

Objective (1): To compare the plasma PK of MK-3866 following a single intravenous (IV) dose in subjects with moderate hepatic insufficiency (HI) to that of healthy matched control subjects, including area under the concentration-time curve (AUC) from time 0 hours to infinity (AUC0-inf), AUC from time 0 hours to the last quantifiable concentration (AUC0-last), concentration at the end of infusion (Ceoi), time of maximum concentration (Tmax), terminal elimination half-life (t1/2), clearance (CL), and volume of distribution (Vz).

Estimation (1): The AUC0-inf following a single IV dose of MK-3866 administered to subjects with moderate HI will be estimated and compared to the AUC0-inf when administered to healthy matched control subjects.

Objective (2): To compare the plasma PK (e.g., AUC0-inf, AUC0-last, Ceoi, Tmax, t1/2, CL, Vz) of MK-3866 following a single IV dose in subjects with severe hepatic insufficiency (HI) to that of healthy matched control subjects.

Estimation (2): The AUC0-inf following a single IV dose of MK-3866 administered to subjects with severe HI will be estimated and compared to the AUC0-inf when administered to healthy matched control subjects.

3.2 Secondary Objectives & Estimations

Objective (1): To compare the urine PK (e.g., fraction of the dose excreted unchanged in urine [fe], renal clearance [CLR]) of MK-3866 following a single IV dose of MK-3866 in subjects with varying degrees of HI to those of healthy matched control subjects.

Estimation (1): The CLR and fe of a single IV dose of MK-3866 in subjects with varying degrees of HI will be estimated and compared to those estimated in healthy matched control subjects.

Objective (2): To evaluate the safety and tolerability of MK-3866 in subjects with moderate and severe HI.

3.3 Exploratory Objectives

Objective (1): To explore the relationship between genetic variation and response to the treatment(s) administered, and mechanisms of disease. Variation across the human genome may be analyzed for association with clinical data collected in this study.

4.0 BACKGROUND & RATIONALE

4.1 Background

Refer to the Investigator's Brochure (IB) for detailed background information on MK-3866.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

MK-3866, [redacted] is being developed for use [redacted] ram-negative bacteria. MK-3866 has recently completed dosing the first-in-human (FIH) single ascending dose study (PN001).

The primary purpose of this study is to understand the effect of HI on the plasma PK of MK-3866 in order to guide dosing recommendations for patients with HI. As a proportion of patients with serious Gram-negative infections have baseline HI, it is important to evaluate the impact of HI on the plasma PK of MK-3866. This study will also evaluate the safety and tolerability of MK-3866 in subjects with moderate and severe HI.

Renal clearance is expected to be the major elimination pathway for MK-3866, as approximately 65% of MK-3866 is excreted in the urine following a single IV dose. Based on preclinical animal studies, hepatic elimination is anticipated to be a significant elimination pathway for MK-3866 as well and is expected to account for the remainder of the non-renal elimination of MK-3866, approximately 35%. MK-3866 is also a substrate for the liver specific transporters human organic anion transporting polypeptide (OATP) 1B1/SLCO1B1 (OATP1B1) and OATP1B3. Conducting a dedicated hepatic study for MK-3866 is in line with regulatory guidance which suggests a dedicated hepatic study be conducted for compounds in which hepatic elimination exceeds 20%.

In the FIH study of MK-3866 in healthy subjects, while single and divided doses of up to 2000 mg were generally well-tolerated, nausea was observed with an increased frequency at single doses above 800 mg. In each case, nausea was transient and its onset appeared to coincide temporally with the peak plasma concentration (although the relationship between PK and the development of nausea is currently under investigation).

It is predicted that the potential effect of HI on single-dose PK will be to reduce the clearance, thereby increasing the terminal half-life and AUC of MK-3866. It is assumed that there is generally a linear relationship between the effect on $t_{1/2}$ and AUC. Based on PN001, approximately 35% of MK-3866 may be hepatically eliminated; exposure increases with severe HI are anticipated to be approximately 1.5-fold. However, it is difficult to provide estimates for hepatic impairment; there is no single accepted measure to use in order to determine PK estimations for varying degrees of liver impairment. In consideration of both the PK and the tolerability of MK-3866 in subjects with HI, the dose of study drug in this trial was selected so that the exposure in all subjects should not exceed 800 mg in healthy subjects (AUC0-inf of 272 µM*hr and Ceoi of 97 µM), and is unlikely to exceed the exposure at 400 mg (2.7-fold higher than the 150 mg dose) in healthy subjects (AUC0-inf of 147 µM*hr and Ceoi of 52 µM). On the basis of these predicted exposures from a single 150 mg dose of MK-3866 in subjects with either moderate or severe HI, both panels can be recruited in parallel without posing a risk to subject safety.

4.2.1.1 Child-Pugh Classification of Hepatic Insufficiency

The Child classification, which should only be applied to patients with a diagnosis of hepatic cirrhosis, was initially used to assess the preoperative risk of patients with hepatic cirrhosis. The Child scale, as modified by Pugh, has been subsequently found useful in classifying a patient's level of HI for PK studies. The Child-Pugh scale (see Appendix 1) has been shown to correlate with hepatic (i.e., metabolic) clearance for several compounds.

In the current study, patients with chronic, stable HI with features of cirrhosis due to any etiology will be enrolled, and the Child-Pugh scale will be used to classify the severity of liver disease. The bilirubin score in the table is dependent upon the type of cirrhosis (primary biliary cirrhosis versus all other causes). Subjects' scores of 5 to 6, 7 to 9, and 10 to 15 on this scale are classified as having mild, moderate, and severe hepatic failure, respectively.

In addition, in order to ensure that the study subjects have laboratory abnormalities consistent with hepatic dysfunction (e.g., reduced serum albumin, increased serum bilirubin, and increased international normalized ratio [INR]), at least three subjects with moderate HI will

be required to have a score of at least 2 on one of the laboratory parameters on the Child-Pugh scale.

Table 1 Child-Pugh Classification of the Severity of Liver Disease

Scoring			
	Points Score for Increasing Abnormality		
Assessment	**1**	**2**	**3**
Encephalopathy†	None	1 or 2	3 or 4
Ascites	Absent	Slight	Moderate
Albumin (g/dL)	>3.5	2.8 to 3.5	<2.8
INR	<1.7	1.7 to 2.3	>2.3
Bilirubin (mg/dL)—not PBC‡§ Bilirubin (mg/dL)—only for PBC‡§	<2 <4	2 to 3 4 to 10	>3 >10
† Portal-system encephalopathy is Staged 0 to 4. ‡ PBC = Primary Biliary Cirrhosis. § Select only one dependent on type of cirrhosis.			
Interpretation			
Points	**Child-Pugh Class**		
5-6	A (mild hepatic impairment)		
7-9	B (moderate hepatic impairment)		
10-15	C (severe hepatic impairment)		

4.2.2 Rationale for Dose Selection

MK-3866 is currently undergoing evaluation in preclinical studies and in clinical trials with healthy subjects; therefore the planned clinical dose has not yet been established, but is presently projected to be approximately 300 mg. For safety, the well-tolerated dose of 150 mg will be administered to subjects with moderate and severe HI, and the control panel of healthy subjects matched to the moderate and severe HI panels.

4.2.3 Planned Exploratory Biomarker Research

4.2.3.1 Planned Genetic Analysis

Understanding genetic determinants of drug response and the molecular basis of disease is an important endeavor during medical research. This research will evaluate whether genetic variation within a clinical trial population correlates with response to the treatment(s) under evaluation and/or disease. If genetic variation is found to predict efficacy or adverse events, the data might inform optimal use of therapies in the patient population. Knowledge of the molecular basis of disease contributes to the development of novel biomarkers and the identification of new drug targets. This research contributes to understanding molecular basis

of disease and the genetic determinants of efficacy and safety associated with the treatments in this study.

4.2.4 Future Biomedical Research

The Sponsor will conduct Future Biomedical Research on DNA specimens consented for future biomedical research during this clinical trial.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented subjects. The objective of collecting/retaining specimens for Future Biomedical Research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that subjects receive the correct dose of the correct drug/vaccine at the correct time. The details of this Future Biomedical Research sub-trial are presented in Section 12.2 – Collection and Management of Specimens for Future Biomedical Research.

4.3 Benefit/Risk

Subjects in clinical trials generally cannot expect to receive direct benefit from treatment during participation, as clinical trials are designed to provide information about the safety and effectiveness of an investigational medicine.

Additional details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying Investigators Brochure (IB) and Informed Consent documents.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Panel A: Subjects with moderate HI.

Panel B: Subjects with severe HI.

Panel C: Healthy subjects.

5.1.2 Subject Inclusion Criteria

Subjects with HI

Subjects must fulfill all of the following inclusion criteria to be eligible for participation in the study, unless otherwise specified.

1. Is an adult male or female, 18-75 years of age, inclusive, at screening.
2. Has a BMI ≥19 and ≤40 kg/m^2, at screening.
3. Is a continuous non-smoker prior to screening and enrollment.

4. Baseline health is judged to be stable based on medical history (except for the HI condition), physical examination, vital signs, ECGs, and laboratory safety tests. Subjects who do not qualify based on a reversible condition or mild intercurrent illness may be rescreened after the underlying condition is resolved.
5. Has a diagnosis of chronic (>6 months), stable (no acute episodes of illness within the previous 2 months due to deterioration in hepatic function) HI with features of cirrhosis (confirmed by medical history).
6. Panel A only: Has a score on the Child-Pugh scale from 7 to 9 (moderate HI) at screening. At least 3 subjects must have a score of 2 or higher on at least one of the laboratory parameters (i.e., albumin, INR, and/or bilirubin) at screening on the Child-Pugh scale.
7. Panel B only: Has a score on the Child-Pugh scale from 10 to 15 (severe HI) at screening.
8. Is completely informed of the unknown risks of pregnancy and agrees not to become pregnant or father a child during the time they are participating in this study.
9. Has adequate peripheral venous access, as determined by the investigator, at the Screening visit.
10. For a female of childbearing potential: is either sexually inactive (abstinent) for 14 days prior to dosing and throughout the study or is using one of the following acceptable birth control methods:
    - Intrauterine device in place for at least 3 months prior to dosing and use a physical barrier method (e.g., condom, diaphragm) and spermicide throughout the study.
    - Double physical barrier methods (e.g., condom and diaphragm) with spermicide for at least 14 days prior to dosing and throughout the study.
    - Surgical sterilization of the partner (vasectomy for 4 months minimum) and use a physical barrier method (e.g., condom, diaphragm) and spermicide throughout the study.
    - Hormonal contraceptives for at least 3 months prior to dosing of the study and use a physical barrier method (e.g., condom, diaphragm) and spermicide throughout the study.
11. Female subjects who claim to be sexually inactive, but become sexually active during the course of the study must agree to use a double physical barrier method (e.g., condom and diaphragm) with spermicide from the time of the start of sexual activity through completion of the study or if having a surgically sterilized partner (vasectomy for 4 months minimum) must agree to use a physical barrier method (e.g., condom, diaphragm) and spermicide through completion of the study.
12. In addition, female subjects of childbearing potential will be advised to remain sexually inactive or to keep the same birth control method for at least 14 days following dosing.

13. Females of non-childbearing potential must have undergone one of the following sterilization procedures at least 6 months prior to the first dose:
    - hysteroscopic sterilization;
    - bilateral tubal ligation or bilateral salpingectomy;
    - hysterectomy;
    - bilateral oophorectomy;
    - or be postmenopausal with amenorrhea for at least 1 year prior to dosing and have follicle-stimulating hormone (FSH) serum levels consistent with postmenopausal status as per Investigator or designee's judgment.
14. Non-vasectomized male subjects must agree to use a condom with spermicide or abstain from sexual intercourse from dosing until 90 days after dosing. No restrictions are required for vasectomized males provided their vasectomy has been performed 4 months or more prior to dosing. Males who have been vasectomized less than 4 months prior to dosing must follow the same restrictions as non-vasectomized males.
15. Male subjects must agree not to donate sperm from dosing until 90 days after dosing.
16. Understands the study procedures in informed consent forms (ICFs), be willing and able to comply with the protocol, and provides written informed consent for the trial. The subject may also provide consent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.

Healthy control subjects

Subjects must fulfill all of the following inclusion criteria to be eligible for participation in the study, unless otherwise specified.

1. Is a healthy adult male or female, 18-75 years of age, inclusive, at screening. Age must be within ±15 years of the mean age of subjects in the first HI panel to complete enrollment (either Panel A or B). For any additional healthy subjects, age must be within ±15 years of the mean age of subjects in the second HI panel to complete enrollment. A similar number of males and females (±1) will be enrolled in the HI and healthy groups. The gender of the additional healthy subject(s) enrolled will be selected to ensure the number of healthy subjects of each gender will match that of the subjects enrolled in each HI panel (±1).
2. Has a BMI ≥19 and ≤40 kg/m^2 at screening. BMI must be within ±10% of the mean BMI of the subjects in the first HI panel to complete enrollment (either Panel A or B). For any additional healthy subject enrolled, BMI must be within ±10% of the mean BMI of subjects in the second HI panel to complete enrollment.
3. Is a continuous non-smoker.
4. Is medically healthy with no clinically significant medical history, physical examination, laboratory profiles, vital signs, or ECGs, as deemed by the Investigator.

5. Is completely informed of the unknown risks of pregnancy and agrees not to become pregnant or father a child during the time they are participating in this study.
6. For a female of childbearing potential: is either sexually inactive (abstinent) for 14 days prior to dosing and throughout the study or is using one of the following acceptable birth control methods:
    - Intrauterine device in place for at least 3 months prior to dosing and use a physical barrier method (e.g., condom, diaphragm) and spermicide throughout the study.
    - Double physical barrier methods (e.g., condom and diaphragm) with spermicide for at least 14 days prior to dosing and throughout the study.
    - Surgical sterilization of the partner (vasectomy for 4 months minimum) and use a physical barrier method (e.g., condom, diaphragm) and spermicide throughout the study.
    - Hormonal contraceptives for at least 3 months prior to dosing of the study and use a physical barrier method (e.g., condom, diaphragm) and spermicide throughout the study.
7. Female subjects who claim to be sexually inactive, but become sexually active during the course of the study must agree to use a double physical barrier method (e.g., condom and diaphragm) with spermicide from the time of the start of sexual activity through completion of the study or if having a surgically sterilized partner (vasectomy for 4 months minimum) must agree to use a physical barrier method (e.g., condom, diaphragm) and spermicide through completion of the study.
8. In addition, female subjects of childbearing potential will be advised to remain sexually inactive or to keep the same birth control method for at least 14 days following dosing.
9. Females of non-childbearing potential must have undergone one of the following sterilization procedures at least 6 months prior to the first dose:
    - hysteroscopic sterilization;
    - bilateral tubal ligation or bilateral salpingectomy;
    - hysterectomy;
    - bilateral oophorectomy;
    - or be postmenopausal with amenorrhea for at least 1 year prior to dosing and have FSH serum levels consistent with postmenopausal status as per Investigator or designee's judgment.
10. Non-vasectomized male subjects must agree to use a condom with spermicide or abstain from sexual intercourse from dosing until 90 days after dosing. No restrictions are required for vasectomized males provided their vasectomy has been performed 4 months or more prior to dosing. Males who have been vasectomized less than 4 months prior to dosing must follow the same restrictions as non-vasectomized males.

11. Male subjects must agree not to donate sperm from dosing until 90 days after dosing.
12. Understands the study procedures in ICFs, be willing and able to comply with the protocol, and provides written informed consent for the trial, including for Future Biomedical Research. Future Biomedical Research participation is voluntary and is not required in order to participate in the trial.

5.1.3 Subject Exclusion Criteria

Subjects with HI

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

1. Subject is mentally or legally incapacitated or has significant emotional problems at the time of the screening visit or expected during the conduct of the study.
2. Has a history or presence of clinically significant medical or psychiatric condition or disease other than hepatic impairment in the opinion of the Investigator might confound the results of the study or poses an additional risk to the patient by their participation in the study. Remote history of cholecystectomy that is not an active issue may be included at the discretion of the investigator.
3. Has a clinically significant history of cancer. Remote history with full cure or limited disease with complete resection (cure) may be included at the discretion of the investigator.
4. Has a history of drug or alcohol abuse within the past 6 months prior to dosing.
5. Consumes more than 3 glasses of alcoholic beverages (1 glass is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce]) per day, within 6 months of screening. Subjects that consume 4 glasses of alcoholic beverages per day may be enrolled at the discretion of the investigator.
6. Consumes excessive amounts, defined as more than 6 servings (1 serving is approximately equivalent to 120 mg of caffeine) of coffee, tea, cola, energy-drinks, or other caffeinated beverages per day.
7. Has a history of a liver transplant.
8. Has a history or presence of hypersensitivity or idiosyncratic reaction to the study drugs or related compounds.
9. Has moderate or severe renal insufficiency (estimated glomerular filtration rate [eGFR] of $\leq$60 mL/min/1.73 m^2 for moderate HI subjects or $\leq$50 mL/min/1.73 m^2 for severe HI subjects, calculated according to the Modification of Diet in Renal Disease [MDRD] study equation).
10. Is a female patient who is pregnant or lactating.
11. Has positive results for the urine or breath alcohol screen and/or urine drug screen at screening or check-in, unless the positive drug screen is due to prescription drug use and is approved by the Investigator and the Sponsor Medical Monitor.
12. Has positive results at screening for human immunodeficiency virus (HIV).

13. Subjects with active hepatitis C virus (HCV) infection (defined as detectable HCV RNA) or hepatitis B virus (HBV) infection (defined as HBsAg positive). Patients with prior/inactive HCV infection (defined as undetectable HCV RNA) or past HBV infection (defined as HBsAg negative and HBsAb positive) may be enrolled. Subjects with detectable HCV RNA but with stable alanine transaminase (ALT) and aspartate transaminase (AST) values, no elevation in either ALT or AST greater than 2-fold the upper limit of normal (ULN) for at least 3 months, may be enrolled with the joint agreement of the sponsor and principal investigator after review of their historical ALT and AST values.
14. Is unable to refrain from or anticipates the use of any medication or substance (including prescription or over-the-counter, vitamin supplements, natural or herbal supplements) listed in Section 5.5 for the prohibited time period.
15. Has taken amiodarone at any time in their life.
16. Has seated heart rate is equal to or lower than 44 bpm or higher than 100 bpm at screening.
17. Has seated blood pressure is less than 90/40 mmHg or greater than 180/105 mmHg at screening.
18. Has PR interval >240 msec or QRS >140 msec at screening.
19. Has QTcF interval >490 msec or deemed clinically abnormal by the Investigator at screening.
20. Has been on a diet incompatible with the on-study diet, in the opinion of the Investigator, within the 28 days prior to the dose of study drugs, and throughout the study.
21. Has donated blood >500 mL or had significant blood loss within 56 days prior to the dose of study drugs.
22. Has donated plasma within 7 days prior to the dose of study drugs.
23. Is working at or has an immediate family member (spouse or children) who works at the investigational site or is a Sponsor staff directly involved with this trial.
24. Dosed in another clinical trial within 28 days prior to dosing of study drugs. The 28-day window will be derived from the date of the last dosing in the previous study to Day 1 of the current study.
25. Subject who dosed in one part (e.g., Panel 1) will not be enrolled in the other part (e.g., Panel 2).

Healthy control subjects

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

1. Is mentally or legally incapacitated or has significant emotional problems at the time of the screening visit or expected during the conduct of the study.
2. Has a history or presence of clinically significant medical or psychiatric condition or disease in the opinion of the Investigator might confound the results of the study or

poses an additional risk to the patient by their participation in the study. Remote history of cholecystectomy that is not an active issue may be included at the discretion of the investigator.

3. Has a history of any illness that, in the opinion of the Investigator, might confound the results of the study or poses an additional risk to the subject by their participation in the study.
4. Has a history or presence of alcoholism or drug abuse within the past 2 years prior to dosing.
5. Has a history or presence of hypersensitivity or idiosyncratic reaction to the study drugs or related compounds.
6. Has moderate or severe renal insufficiency (eGFR ≤60 mL/min/1.73 m^2 calculated according to the Modification of Diet in Renal Disease study equation).
7. Has positive macroscopic urine protein at screening and check-in (trace protein by dipstick will be allowed).
8. Is a female subject who is pregnant or lactating.
9. Has positive results for the urine or breath alcohol screen and/or urine drug screen at screening or check-in, unless the positive drug screen is due to prescription drug use and is approved by the Investigator and the Sponsor Medical Monitor.
10. Has positive results at screening for HIV, HBsAg, or HCV.
11. Is unable to refrain from or anticipates the use of any medication or substance (including prescription or over-the-counter, vitamin supplements, natural or herbal supplements) listed in Section 5.5 for the prohibited time period.
12. Has taken amiodarone at any time in their life.
13. Has seated heart rate is equal to or lower than 44 bpm or higher than 100 bpm at screening.
14. Has seated blood pressure is less than 90/40 mmHg or greater than 150/90 mmHg at screening.
15. Has PR interval >200 msec, QRS >110 msec at screening.
16. Has QTcF interval >450 msec or deemed clinically abnormal by the Investigator at screening.
17. Has been on a diet incompatible with the on-study diet, in the opinion of the Investigator, within the 28 days prior to the dose of study drugs, and throughout the study.
18. Has donated blood >500 mL or had significant blood loss within 56 days prior to the dose of study drugs.
19. Has donated plasma within 7 days prior to the dose of study drugs.
20. Is working at or has an immediate family member (spouse or children) who works at the investigational site or is a Sponsor staff directly involved with this trial.

21. Dosing in another clinical trial within 28 days prior to dosing of study drugs. The 28-day window will be derived from the date of the last dosing in the previous study to Day 1 of the current study.

5.2 Trial Treatment

The treatment to be used in this trial is outlined below in Table 2.

Table 2 Trial Treatment

Drug	Dose	Dose Frequency	Route of Administration	Panel	Use
MK-3866	150 mg	Single dose	Intravenous	A	Experimental
MK-3866	150 mg	Single dose	Intravenous	B	Experimental
MK-3866	150 mg	Single dose	Intravenous	C	Experimental

Trial treatment should begin on the day of treatment allocation or as close as possible to the date on which the subject is allocated.

All supplies indicated in Table 2 above will be provided centrally by the Sponsor.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of trial treatments in accordance with the protocol and any applicable laws and regulations.

5.2.1 Dose Selection

5.2.1.1 Dose Selection (Preparation)

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background & Rationale. There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each subject.

5.2.2 Timing of Dose Administration

MK-3866 for IV administraton will be prepared and dosed per the instructions outlined in the Study Operation Manual.

5.2.3 Trial Blinding

This is an open-label trial; therefore, the Sponsor, investigator and subject will know the treatment administered.

5.3 Treatment Allocation

Subjects participating in this trial will be allocated by non-random assignment.

5.4 Stratification

Treatment allocation will be stratified according to the following factors:

1. Panel A: At least 3 subjects will have a score of 2 or higher on at least one of the laboratory parameters (i.e., albumin, INR, and/or bilirubin) at screening on the Child-Pugh scale. At least 2 subjects of each gender will be enrolled.
2. Panel B: At least 2 subjects of each gender will be enrolled.
3. Panel C: Healthy control subjects in Panel C will be matched to the mean BMI (±10%) and age (±15 years) of the HI subjects in Panels A and B. Refer to Section 2.1 for further details.

5.5 Concomitant Medications (Allowed and Prohibited)

Concomitant therapies will be prohibited as indicated in the exclusion criteria (Section 5.1.3).

If a subject does not discontinue all prior medications within 14 days or 5 half-lives of starting the trial, he/she may be included in the study if the investigator can rationalize that the specific use of a prior medication is not clinically relevant within the context of the trial.

Concurrent therapy with any medication during the course of the protocol including both prescription and non-prescription drugs must first be discussed with the Investigator and Sponsor Clinical Monitor prior to dosing, unless appropriate medical care necessitates that therapy should begin before the Investigator and Sponsor Clinical Monitor can be consulted.

Hormonal contraceptives and hormone replacement therapy are not prohibited. Ibuprofen (up to 1.2 g per 24 hour period) may be permitted during the study.

Appropriate sources will be consulted by the Investigator or designee to confirm lack of PK/PD interaction with drug.

If deviations occur, the Investigator in consultation with the Sponsor Clinical Monitor will decide on a case-by-case basis.

All medications taken by subjects during the course of the study will be recorded.

Subjects who are taking medications for stable diseases for approximately 2 weeks for subjects with HI and approximately 1 month for healthy subjects prior to dosing will be allowed to participate in the study at the discretion of the Investigator and following consultation with the Sponsor Clinical Monitor. If a subject is prescribed prohibited medication, upon discussion between the Sponsor and the Investigator, the Investigator may substitute the previously prescribed medication to an allowed one for the purpose of this study.

All prescription or non-prescription medications (including St. John's Wort) that are strong inhibitors or strong inducers of CYP3A enzymes or P-gp transporters will be prohibited. Inhibitors of OATP1B1/1B3 transporters are also prohibited. CYP3A and P-gp enzyme/transporter inhibitors and inducers will not be allowed for at least 14 days and OATP1B1/1B3 inhibitors will not be allowed for at least 28 days prior to first dosing and throughout the study. Medications of particular concerns are HIV protease inhibitors, statins, antiarrhythmic agents, medications associated with QT prolongation, hepatotoxic drugs, investigational agents, and systemic corticosteroids. Weak CYP3A, and/or P-gp inhibitors or CYP3A and/or P-gp inducers may be deemed acceptable following consultation with the Sponsor Clinical Monitor and the Investigator.

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Diuretics will be prohibited within 4 hours prior to dosing and within 4 hours post dosing. Subjects on diuretics must be on a stable dose for at least 2 weeks prior to study drug administration, to participate in this study.

Certain prescription medications used to treat manifestations of hepatic disease or medications needed to treat stable diseases (e.g., ACE inhibitors, angiotensin II receptor antagonists, beta-blockers) will be allowed during the study provided the subjects are on a stable regimen for approximately 2 weeks (or 5 half-lives of the compound, whichever is longer) prior to study drug administration and is able to withhold the use within 4 hours prior to and 4 hours post administration of the study drug.

5.6 Rescue Medications & Supportive Care

No rescue or supportive medications are specified to be used in this trial.

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

Subjects will refrain from consumption Seville oranges and grapefruits, or any juice or other product that contains Seville oranges or grapefruits, beginning approximately 2 weeks (14 days) prior to administration of the initial dose of trial drug, throughout the trial and until the posttrial visit.

Subject also will refrain from consumption of all juices 24 hours prior to and after administration of each dose of trial drug on PK days. All fruits except for Seville oranges and grapefruits are allowed on all days of the trial.

Water will be restricted 1 hour prior to and 1 hour after study drug administration, but will be allowed ad libitum at all other times. Other fluids may be given as part of the standard meals and/or snacks, but will be restricted at all other times throughout the confinement period.

Subjects will fast for at least 1 hour prior to dosing and will continue the fast for at least 1 hour after the end of the infusion.

On all days that subjects are confined in the CRU, standard meals and snacks will be provided at appropriate times. When confined in the CRU, subjects will fast from all food and drink except water between meals and snacks.

Each meal and/or snack served at the CRU will be standardized, and will be similar in caloric content and composition.

5.7.1 Alcohol, Caffeine, Tobacco, Activity

5.7.1.1 Alcohol

Subjects are prohibited from consumption of alcohol from 48 hours prior to Day 1 dosing until the completion of the end-of-study postdose procedures.

5.7.1.2 Caffeine Restrictions

Subject must not consume coffee, tea, cola, energy-drinks, or other caffeinated beverages or foods containing caffeine or xanthine from 24 hours prior to the first dose of study medication until after the post-trial visit.

5.7.1.3 Smoking Restrictions

Smoking is not permitted during the trial.

5.7.1.4 Activity Restrictions

Subjects will avoid unaccustomed strenuous physical activity (i.e., weight lifting, running, bicycling, etc.) from the pre-trial (screening) visit until administration of the initial dose of trial drug, throughout the trial and until the post-trial visit.

5.8 Subject Withdrawal/Discontinuation Criteria

5.8.1 Discontinuation of Treatment

Discontinuation of treatment does not represent withdrawal from the trial.

As certain data on clinical events beyond treatment discontinuation may be important to the study, they must be collected through the subject's last scheduled follow-up, even if the subject has discontinued treatment. Therefore, all subjects who discontinue trial treatment prior to completion of the treatment period will still continue to participate in the trial as specified in Section 6.0 - Trial Flow Chart and Section 7.1.4.1 – Withdrawal/Discontinuation, or if available, Protocol Clarification Letter.

Subjects may discontinue treatment at any time for any reason or be dropped from treatment at the discretion of the investigator should any untoward effect occur. In addition, a subject may be discontinued from treatment by the investigator or the Sponsor if treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at treatment discontinuation are provided in Section 7.1.4 – Other Procedures.

A subject must be discontinued from treatment but continue to be monitored in the trial for any of the following reasons:

- The subject or subject's legally acceptable representative requests to discontinue treatment.
- The subject has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the subject at unnecessary risk from continued administration of study drug.

- The subject has a confirmed positive serum pregnancy test.
- The subject has a positive urine drug screen at any time during the course of the trial.

For subjects who are discontinued from treatment but continue to be monitored in the trial, all visits and procedures, as outlined in the trial flowchart, should be completed.

Discontinuation from treatment is "permanent." Once a subject is discontinued, he/she shall not be allowed to restart treatment.

5.8.2 Withdrawal from the Trial

A subject must be withdrawn from the trial if the subject or subject's legally acceptable representative withdraws consent from the trial.

If a subject withdraws from the study, they will no longer receive treatment or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the trial including the procedures to be performed should a subject repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the subject, as well as specific details regarding withdrawal from Future Biomedical Research are outlined in Section 7.1.4 – Other Procedures.

5.9 Subject Replacement Strategy

A subject who discontinues from the trial may be replaced at the discretion of the Sponsor.

5.10 Beginning and End of the Trial

The overall trial begins when the first subject signs the informed consent form. The overall trial ends when the last subject completes the last study-related phone-call or visit, discontinues from the trial or is lost to follow-up (i.e. the subject is unable to be contacted by the investigator).

A trial may be paused during review of newly available preclinical/clinical safety, PK, PD, efficacy or biologic data or other items of interest, prior to a final decision on continuation or termination of the trial. It may be necessary to keep the trial open for gathering/reviewing of additional supportive data to optimally complete the objective(s) of the trial. If necessary, the appropriate amendment(s) to the protocol and/or appropriate communication(s) will be generated. The overall trial end will then not be identified until the Sponsor has made the decision to end the trial following this review period. The Competent Authority(ies) and Institutional Review Board(s)/Independent Ethics Committee(s) [IRB(s)/IEC(s)] will be appraised of the maximum duration of the trial beyond the last subject out and the justification for keeping the trial open.

5.11 Clinical Criteria for Early Trial Termination

There are no pre-specified criteria for terminating the trial early.

6.0 TRIAL FLOW CHART

Table 3 Trial Flow Chart – Panels A and B

Panels A and B (Subjects with HI)																						
	Screening Up to 28 days	Check-in Day -2/Day -1	Day 1																Day 2	Day 3	Day 4	Post-trial[a]
				Hours																		
			Predose	0	0.5	0.75	1	1.5	2	3	4	4.5	6	8	9	10	12	24	48	72	
Administrative Procedures																						
Informed Consent	X																					
Informed Consent for Future Biomedical Research	X																					
Inclusion/Exclusion Criteria	X	X																				
Subject Identification Card	X																					
Medical History	X	X																				
Concomitant Medication Review	X----------																					----------X
Clinic Procedures/Assessments																						
Full Physical Examination	X	X																	X		X	X
Child-Pugh Scale classification	X																					
Height	X																					
Weight	X																					X
12-Lead Electrocardiogram[b]	X		X		X				X										X		X	
Vital Signs (heart rate, blood pressure)	X		X		X				X										X		X	X
Vital Signs (respiratory rate, body temperature)	X		X																			X
IV MK-3866 Administration[c]				X-------X																		

Panels A and B (Subjects with HI)																						
	Screening Up to 28 days	Check-in Day -2/Day -1	Day 1																Day 2	Day 3	Day 4	Post-trial[a]
				Hours																		
			Predose	0	0.5	0.75	1	1.5	2	3	4	4.5	6	8	9	10	12	24	48	72	
Adverse Events Monitoring	X----------X																					
Laboratory Procedures/Assessments																						
Laboratory Safety Tests (Hematology, Urinalysis, Chemistry)	X	X																X		X	X
Serum β-Human Chorionic Gonadotropin (β-hCG) (females only)	X	X[d]																			
Serum Follicle Stimulating Hormone (FSH) - if applicable	X																				
Urine Drug/Alcohol/Cotinine Screen	X	X																			
HIV/Hepatitis Screen (per site SOP)	X																				
Blood for Genetic Analysis[e]			X																		
Pharmacokinetic Evaluations																						
Blood for Plasma MK-3866 Assay[f]			X		X	X	X	X	X	X		X	X	X		X	X	X	X	X	
Urine for Urinary MK-3866 Assay[g]			X	X----------X																		

Panels A and B (Subjects with HI)																					
	Screening Up to 28 days	Check-in Day -2/Day -1	Day 1															Day 2	Day 3	Day 4	Post-trial[a]
				Hours																	
			Predose	0	0.5	0.75	1	1.5	2	3	4	4.5	6	8	9	10	12	24	48	72	

PK = pharmacokinetic

a. All subjects who receive at least one dose of MK-3866 will return to the Clinical Research Unit (CRU) approximately 14 days after the last dose for follow-up procedures, and to determine if any adverse events have occurred since the last study visit.

b. Screening and predose ECGs will be performed in triplicate. At other times, single ECGs will be performed.

c. MK-3866 will be administered via a 30-minute IV infusion.

d. Women who are of non-childbearing potential (confirmed with FSH test) will not have pregnancy testing at check-in.

e. This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at the site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for future biomedical research if the subject signs the FBR consent. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.

f. PK sampling scheme in plasma:

Predose, 0.5 (end of infusion), 0.75, 1, 1.5, 2, 3, 4.5, 6, 8, 10, 12, 24, 48, 72 hours postdose

g. PK sampling scheme in urine:

Predose, then pooled in the following increments: 0-4, 4-8, 8-12, 12-24 hours postdose

Table 4 Trial Flow Chart – Panel C

Panel C (Healthy Control Subjects)																				
	Screening Up to 28 days	Check-in Day -2/Day -1	Day 1															Day 2	Day 3	Post-trial[a]
				Hours																
			Predose	0	0.5	0.75	1	1.5	2	3	4	4.5	6	8	9	10	12	24	48	
Administrative Procedures																				
Informed Consent	X																			
Informed Consent for Future Biomedical Research	X																			
Inclusion/Exclusion Criteria	X	X																		
Subject Identification Card	X																			
Medical History	X	X																		
Concomitant Medication Review	X----------																			----------X
Clinic Procedures/Assessments																				
Full Physical Examination	X	X																	X	X
Height	X																			
Weight	X																			X
12-Lead Electrocardiogram[b]	X		X		X				X										X	
Vital Signs (heart rate, blood pressure)	X		X		X				X				X						X	X
Vital Signs (respiratory rate, body temperature)	X		X																	X
IV MK-3866 Administration[c]				X--------X																
Adverse Events Monitoring	X----------																			----------X

Panel C (Healthy Control Subjects)																					
	Screening Up to 28 days	Check-in Day -2/Day -1	Day 1																Day 2	Day 3	Post-trial[a]
				Hours																	
			Predose	0	0.5	0.75	1	1.5	2	3	4	4.5	6	8	9	10	12	24	48	
Laboratory Procedures/Assessments																					
Laboratory Safety Tests (Hematology, Urinalysis, Chemistry)	X	X																	X	X	
Serum β-Human Chorionic Gonadotropin (β-hCG) (females only)	X	X[d]																			
Serum Follicle Stimulating Hormone (FSH) - if applicable	X																				
Urine Drug/Alcohol/Cotinine Screen	X	X																			
HIV/Hepatitis Screen (per site SOP)	X																				
Blood for Genetic Analysis[e]			X																		
Pharmacokinetics Evaluations																					
Blood for Plasma MK-3866 assay[f]			X		X	X	X	X	X	X		X	X	X		X	X	X	X		
Urine for Urinary MK-3866 Assay[g]			X	X----------X																	

Panel C (Healthy Control Subjects)																			
	Screening Up to 28 days	Check-in Day -2/Day -1	Day 1														Day 2	Day 3	Post-trial[a]
				Hours															
			Predose	0	0.5	0.75	1	1.5	2	3	4	4.5	6	8	9	10	12	24	48	

PK = pharmacokinetic

a. All subjects who receive at least one dose of MK-3866 will return to the Clinical Research Unit (CRU) approximately 14 days after the last dose for follow-up procedures, and to determine if any adverse events have occurred since the last study visit.

b. Screening and predose ECGs will be performed in triplicate. At other times, single ECGs will be performed.

c. MK-3866 will be administered via a 30-minute IV infusion.

d. Women who are of non-childbearing potential (confirmed with FSH test) will not have pregnancy testing at check-in.

e. This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at the site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for future biomedical research if the subject signs the FBR consent. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.

f. PK sampling scheme in plasma:

Predose, 0.5 (end of infusion), 0.75, 1, 1.5, 2, 3, 4.5, 6, 8, 10, 12, 24, 48 hours postdose

g. PK sampling scheme in urine:

Predose, then pooled in the following increments: 0-4, 4-8, 8-12, 12-24 hours postdose

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The investigator or qualified designee must obtain documented consent from each potential subject or each subject's legally acceptable representative prior to participating in a clinical trial or Future Biomedical Research. If there are changes to the subject's status during the trial (e.g., health or age of majority requirements), the investigator or qualified designee must ensure the appropriate consent is in place.

7.1.1.1.1 General Informed Consent

Consent must be documented by the subject's dated signature or by the subject's 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 should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or qualified designee will explain the Future Biomedical Research consent to the subject, answer all of his/her questions, and obtain written informed consent before performing any procedure related to the Future Biomedical Research sub-trial. A copy of the informed consent will be given to the subject.

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

7.1.1.3 Subject Identification Card

All subjects will be given a Subject Identification Card identifying them as participants in a research trial. The card will contain trial site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will provide the subject with a Subject Identification Card immediately after the subject provides written informed consent. At the time of treatment allocation/randomization, site personnel will add the treatment/randomization number to the Subject Identification Card.

7.1.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee.

7.1.1.5 Prior and Concomitant Medications Review

7.1.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 14 days before the first dose of trial medication.

7.1.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial.

7.1.1.6 Assignment of Screening Number

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur prior to randomization or treatment allocation. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects.

Any subject who is screened multiple times will retain the original screening number assigned at the initial screening visit.

Specific details on the screening visit requirements (screening/rescreening) are provided in Section 7.1.5.1.

7.1.1.7 Assignment of Treatment Number

All eligible subjects will be allocated, by non-random assignment, and will receive a treatment number. The treatment number identifies the subject for all procedures occurring after treatment allocation. Once a treatment number is assigned to a subject, it can never be re-assigned to another subject.

A single subject cannot be assigned more than 1 treatment number.

7.1.1.8 Trial Compliance

Administration of trial medication will be witnessed by the investigator and/or trial staff.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Body Weight and Height

Body weight and height will be obtained with the subjects' shoes off, jacket or coat removed, as follows:

- Document the subject's weight in kilograms (kg), to the nearest 0.1 kg.
- Measure the subject's height on a calibrated stadiometer. Document this height in meters, to the nearest 0.01 meter (0.01 meter = 1 centimeter, cm).

7.1.2.2 Body Mass Index

Body Mass Index (BMI) equals a subject's weight in kilograms divided by height in meters squared ($BMI=kg/m^2$). Subject's BMI will be documented to the nearest 0.1 $kilogram/(meter)^2$. Subject's BMI will not be rounded to the nearest whole number.

7.1.2.3 12-Lead Electrocardiogram

Special care must be taken for proper lead placement by qualified personnel. Skin should be clean and dry prior to lead placement. Subjects may need to be shaved to ensure proper lead placement. Female subjects may need to remove their bra. The ECG instrument calibration will be current and the machine will be assessed for correct date and time prior to each use.

Subjects should be resting in the semi-recumbent position for at least 10 minutes prior to each ECG measurement. Subject position during ECG collection should be consistent throughout the study.

Fridericia's formula will be used to correct QT.

7.1.2.4 Vital Signs (Blood Pressure, Pulse Rate, Respiratory Rate, Body Temperature*)*

Subjects should be seated (or semi-recumbent if indicated for other procedures or adverse events) for at least 10 minutes prior to having vital sign measurements obtained. The correct size of the blood pressure cuff and the correct positioning on the subjects' arm is essential to increase the accuracy of blood pressure measurements. The same method (e.g., manual or automated) must be used for all measurements for each individual subject and should be same for all subjects.

Body temperature will be measured. The same method must be used for all measurements for each individual subject and should be the same for all subjects.

Additional vital signs measurements may be performed as deemed medically necessary by research personnel. Additional vital sign measurements will be taken after the subject has been in a semi-recumbent position for a minimum of 3 minutes. All unscheduled vital sign measurements will be reported and transferred to the eCRF.

Subjects will remain seated, except as otherwise required for study procedures or personal needs, for the first 4 hours after dosing. Should the need to move about occur during the first 4 hours after each dose, subjects may be escorted to such procedures or activities by research personnel as deemed medically necessary.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. The total amount of blood to be drawn/collected over the course of the trial (from pre-trial to post-trial visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per subject can be found in Section 12.3.

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry and urinalysis are specified in Table 5.

Table 5 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Follicle stimulating hormone (FSH), if applicable
Hemoglobin	Alkaline phosphatase (ALP)	Bilirubin	Serum β-human chorionic gonadotropin (β-hCG)
Platelet count	Alanine aminotransferase (ALT)	Glucose	Hepatitis B surface antigen
Red blood cell count	Amylase	Ketones	Hepatitis C antibody
WBC: total and differentials including: Absolute lymphocytes Absolute monocytes Absolute eosinophils Absolute basophils Absolute neutrophils	Aspartate aminotransferase (AST)	Leukocyte esterase	Human immunodeficiency virus (HIV)
	Blood urea nitrogen (BUN)	Nitrite	Urine drug, cotinine, and alcohol screen (amphetamines, benzodiazepines, barbiturates, cannabinoids, cocaine, opiates, cotinine, alcohol)
	Bicarbonate	pH	
	Bilirubin, direct	Protein	
	Bilirubin, total	Specific gravity	International normalized ratio (INR)
	Calcium (Ca)	Urobilinogen	
	Chloride (Cl^+)	Microscopic exam, if abnormal results are noted	
	Creatinine		

Hematology	Chemistry	Urinalysis	Other
	Creatinine phosphokinase (CPK)		
	Gamma glutamyl transpeptidase (gGT)		
	Glucose		
	Lactate dehydrogenase (LDH)		
	Lipase		
	Phosphorus		
	Potassium (K^+)		
	Protein, total		
	Sodium (Na^+)		

Laboratory safety tests will be performed after at least an 8-hour fast.

7.1.3.2 Pharmacokinetic/Pharmacodynamic Evaluations

The decision as to which plasma and/or urine samples collected will be assayed for evaluation of PK/PD will be collaboratively determined by the Department of Quantitative Pharmacology and Pharmacometrics (QP2) and the appropriate department within Early-Stage Development, (e.g., samples at lower doses may not be assayed if samples at higher doses reveal undetectable drug concentrations). If indicated, these samples may also be assayed and/or pooled for assay in an exploratory manner for metabolites and/or additional PD markers.

7.1.3.2.1 Blood Collection for Plasma MK-3866

For all subjects, blood samples for the determination of MK-3866 plasma concentration will be collected and processed at scheduled time points as delineated in the Study Events Flow Chart (Section 6.0).

Instructions for blood sampling, collection, processing, and sample shipment for MK-3866 will be provided in the Study Operations Manual.

7.1.3.2.2 Urine Collection for Urinary MK-3866

Prior to the predose sample, each subject will be instructed as to urine collection methods.

Urine samples for determination of MK-3866 concentrations will be collected at over selected intervals as outlined in the Study Events Flow Chart (Section 6.0). On Day 1, a spot collection will be obtained prior to dosing for the pre-dose sample. Subjects will be asked again to empty their bladder within approximately 15 minutes prior to dosing, and no urine will be collected at this time unless it is needed for the pre-dose sample. Only one predose urine sample will be collected on Day 1.

After administration of MK-3866, during the entire postdose in-house observation period, all urine will be collected completely. Urine portions will be pooled per subject within any planned collection interval. Just prior to the end of each sampling interval, subjects will be

encouraged to void their bladder again to complete the collection. If they do void at any time during the collection interval, the time should be documented. Should this be the case, subjects need to attempt to void again at the end of the collection period, as scheduled. However, should subjects be unable to void, this will be documented as well.

Urine will be refrigerated during the collection intervals. The weight of an empty urine collection container and total weight of urine collected during each timed interval will be recorded.

Instructions for urine sampling, collection, processing, and sample shipment for MK-3866 will be provided in the Study Operations Manual.

7.1.3.3 Planned Genetic Analysis Sample Collection

Instructions for Planned Genetic Analysis sampling, collection, processing, and sample shipment will be provided in the Study Operations Manual.

7.1.3.4 Future Biomedical Research Samples

The following specimens are to be obtained as part of Future Biomedical Research:

- DNA for future research

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

The investigator or trial coordinator must notify the Sponsor when a subject has been discontinued/withdrawn from the trial. If a subject discontinues for any reason at any time during the course of the trial, the subject may be asked to return to the clinic (or be contacted) for a post-trial visit (approximately 14 days after the last dose of trial drug is given to have the applicable procedures conducted. However, the investigator may decide to perform the post-trial procedures at the time of discontinuation or as soon as possible after discontinuation. If the post-trial visit occurs prior to 14 days after the last dose of trial drug is given, the investigator should perform a follow-up phone call 14 days after the last dose of trial drug to determine if any adverse events have occurred since the post-trial clinic visit. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events.

7.1.4.1.1 Withdrawal from Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the subject's consent for Future Biomedical Research will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the subject of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed prior to the request being received

by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject's personal information and their specimens. In this situation, the request for specimen withdrawal cannot be processed.

7.1.4.1.2 Lost to Follow-up

If a subject fails to return to the clinic for a required study visit and/or if the site is unable to contact the subject, the following procedures are to be performed:

- The site must attempt to contact the subject and reschedule the missed visit.. If the subject is contacted, the subject should be counseled on the importance of maintaining the protocol-specified visit schedule.

- The investigator or designee must make every effort to regain contact with the subject at each missed visit (e.g. phone calls and/or a certified letter to the subject's last known mailing address or locally equivalent methods). These contact attempts should be documented in the subject's medical record.

- Note: A subject is not considered lost to follow up until the last scheduled visit for the individual subject. The amount of missing data for the subject will be managed via the pre-specified data handling and analysis guidelines.

7.1.4.2 Subject Blinding/Unblinding

This is an open label trial; there is no blinding for this trial.

7.1.4.3 Domiciling

Subjects will report to the clinical research unit (CRU) the evening two days prior to the scheduled day of trial drug administration. Subjects who are enrolled in Panels A and B (subjects with HI) will remain in the unit until at least 72 hours post-dose. Subjects who are enrolled in Panel C (healthy control subjects) will remain in the unit until at least 24 hours post-dose. At the discretion of the investigator, subjects may be requested to remain in the CRU longer.

7.1.4.4 Calibration of Critical Equipment

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

Critical equipment for this trial includes: IV pumps, vital sign machines, ECG machines, scales, centrifuges, refrigerators, and freezers.

7.1.5 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.5.1 Screening

Approximately 28 days prior to treatment allocation/randomization, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1.

Subjects with HI who do not qualify based on a reversible condition or mild intercurrent illness may be rescreened after the underlying condition is resolved. Rescreening should include all screening procedures listed in the protocol flow chart, including consent review. Rescreen procedures cannot be conducted the day prior to treatment allocation if there are Day -2/Day -1 procedures planned per protocol.

7.1.5.2 Treatment Period

A single IV dose of MK-3866 will be administered on Day 1.

7.1.5.3 Discontinued Subjects Continuing to be Monitored in the Trial

If the subject discontinues, the subject will be asked to return to the clinic for the end-of-trial assessment. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2.

7.1.5.4 Post-Trial

Subjects will be required to return to clinic approximately 14 days after the last dose of trial drug for the post-trial visit. If the post-trial visit occurs less than 14 days after the last dose of trial drug, a subsequent follow-up phone call should be made at 14 days post the last dose of trial drug to determine if any adverse events have occurred since the post-trial clinic visit.

7.1.5.5 Critical Procedures Based on Trial Objectives: Timing of Procedure

For this trial, the PK blood sample for MK-3866 is the critical procedure.

At any post-dose timepoint, the PK blood sample MK-3866 needs to be collected as close to the exact timepoint as possible. All other procedures should be completed as close to the prescribed/scheduled time as possible. Trial procedures can be performed prior or after the prescribed/scheduled time.

The order of priority can be changed during the trial with joint agreement of the investigator and the Sponsor Clinical Director.

Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

The following variance in procedure collection times will be permitted.

- PK collection as outlined in Table 6 below

Table 6 Pharmacokinetic Collection Windows

Collection Time	Collection Window
0-1 hour	±5 minutes
>1 hour	±15 minutes
>24 hours	±30 minutes

- Predose standard safety evaluations:
    - Vital signs and ECG: ±3 hours
    - Laboratory safety tests and physical examinations: ±24 hours
- Postdose standard safety evaluations (vital signs, ECG, laboratory safety tests, physical exam): ±30 minutes

7.1.5.6 Trial Procedures Modifications Permitted within Protocol Parameters

Up to additional 50 mL of blood may be drawn for safety, PK and/or PD analyses. The total blood volume withdrawn from any single subject will not exceed the maximum allowable volume during his/her participation in the entire trial (Section 12.3).

This is a Phase I assessment of MK-3866 in humans, and the PK, PD and safety profiles of the compound is still being elucidated. This protocol is written with some flexibility to accommodate the inherent dynamic nature of Phase I clinical trials.

The timing of procedures for assessment of safety procedures (e.g., vital signs, ECG, safety laboratory tests, etc.) currently outlined in the protocol may be modified during the trial based on newly available safety, tolerability, PK or PD data (e.g., to obtain data closer to the time of peak plasma concentrations). Additional laboratory safety tests may be added to blood samples previously drawn to obtain additional safety information (e.g., adding creatinine kinase to serum chemistry panel that was already drawn). These changes will not increase the number of trial procedures for a given subject during his/her participation in the entire trial.

It is understood that the current trial may employ some or none of the alterations described above. Any alteration made to this protocol to meet the trial objectives must be detailed by the Sponsor in a letter to the Trial File and forwarded to the investigator for retention. The letter may be forwarded to the IRB/ERC at the discretion of the investigator.

7.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example),

symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Sponsor's product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

Sponsor's product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by the Sponsor for human use.

Adverse events may occur during clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

For randomized subjects only, all adverse events that occur after the consent form is signed but before treatment allocation/randomization must be reported by investigator if they are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. From the time of treatment allocation/randomization through 14 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in Section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Electronic reporting procedures can be found in the Electronic Data Capture (EDC) data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor

The subject has taken (accidentally or intentionally) any drug administered as part of the protocol and exceeding the dose as prescribed by the protocol. It is up to the investigator or the reporting physician to decide whether a dose is to be considered an overdose, in consultation with the Sponsor.

If an adverse event(s) is associated with ("results from") the overdose of Sponsor's product or vaccine, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of Sponsor's product or vaccine meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported by the investigator within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial.

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. Pregnancies and lactations that occur from the time of treatment allocation/randomization through 14 days following cessation of Sponsor's product must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is an other important medical event.

Note: In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by the Sponsor for collection purposes.

- Is a cancer;
- Is associated with an overdose.

Refer to Table 7 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 14 days following cessation of treatment, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to the Sponsor's product that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor.

All subjects with serious adverse events must be followed up for outcome.

7.2.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported to the Sponsor.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 14 days following cessation of treatment, any ECI, or follow up to an ECI, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor, either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent). Events of clinical interest for this trial include:

1. an overdose of Sponsor's product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.
2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

   *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that must trigger an additional evaluation for an underlying etiology. The trial site guidance for assessment

and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

It may also be appropriate to conduct additional evaluation for an underlying etiology in the setting of abnormalities of liver blood tests including AST, ALT, bilirubin, and alkaline phosphatase that do not meet the criteria noted above. In these cases, the decision to proceed with additional evaluation will be made through consultation between the study investigators and the Sponsor Clinical Director. However, abnormalities of liver blood tests that do not meet the criteria noted above are not ECIs for this trial.

7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events with respect to the elements outlined in Table 7. The investigator's assessment of causality is required for each adverse event. Refer to Table 7 for instructions in evaluating adverse events.

Table 7 Evaluating Adverse Events

Maximum Intensity	**Mild**	awareness of sign or symptom, but easily tolerated (for pediatric trials, awareness of symptom, but easily tolerated)
	Moderate	discomfort enough to cause interference with usual activity (for pediatric trials, definitely acting like something is wrong)
	Severe	incapacitating with inability to work or do usual activity (for pediatric trials, extremely distressed or unable to do usual activities)
Seriousness	A serious adverse event (AE) is any adverse event occurring at any dose or during any use of Sponsor's product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred [Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.]; or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect (**in offspring of subject taking the product regardless of time to diagnosis); or	
	Is a cancer (although not serious per ICH definition, is reportable to the Sponsor within 24 hours to meet certain local requirements); **or**	
	Is associated with an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Sponsor's product to be discontinued?	
Relationship to Sponsor's Product	Did the Sponsor's product cause the adverse event? The determination of the likelihood that the Sponsor's product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information **The following components are to be used to assess the relationship between the Sponsor's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the adverse event:	
	Exposure	Is there evidence that the subject was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	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 a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Sponsor's Product (continued)	**The following components are to be used to assess the relationship between the Sponsor's product and the AE: (continued)**	
	Dechallenge	Was the Sponsor's product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the Sponsor's product in this trial? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time.) NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AND THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following:	**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).**	
Yes, there is a reasonable possibility of Sponsor's product relationship.	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 AE is more likely explained by the Sponsor's product than by another cause.	
No, there is not a reasonable possibility of Sponsor's product relationship	Subject did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a subject with overdose without an associated AE.)	

7.2.5 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, i.e., per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan Summary

8.1.1 Source of Variance Estimates: Precision and Sample Size

The sample size selected for each population to evaluate the effect of HI on the PK of MK-3866 was not chosen to satisfy any a priori statistical requirement. This sample size (N=6 per group) has historically been shown to be sufficient for studies of this type and should provide adequate data to support the planned analyses. Nevertheless, estimates of the expected precision of the estimates based on these sample sizes are presented below.

The precision of the estimates of ratios of geometric means obtained from this study can be assessed by calculating the half-width of the 90% confidence intervals expected for the given sample size and assumed variability. The estimated between-subject variance for log AUC0-∞ is 0.0196 log ngƎhr/mL from a previous study (PN001). Since the between subject variability in severe hepatic insufficient subjects is usually higher in many studies, the between subject variability obtained from healthy were inflated by a factor of 2 for severe hepatic insufficient subjects and was used for the following calculations. With 6 hepatic insufficient subjects and 6 healthy matched subjects, the half-width of the 90% confidence interval for the arithmetic mean AUC0-∞ on the log scale will be 0.179 log ng•hr/mL. The lower and upper 90% confidence limits for the true ratio of geometric meansr will be given by OBS/1.163 and OBS x 1.197, where OBS is the observed ratio of geometric means. Thus, for example, if the observed ratio of geometric means was 1.5, the 90% confidence interval would be (1.25, 1.79).

8.1.2 Statistical Core Methods:

8.1.2.1 Primary PK Analysis

Separately for each pharmacokinetic parameter, individual values of AUC0-∞, AUC0-last, AUC0-24, Ceoi, and CL will be natural log-transformed and evaluated with a linear fixed effects model containing a categorical effect for populations. The REPEATED statement with the GROUP=Population option will be used in SAS PROC MIXED to estimate separate variances for each population. The Kenward and Roger adjustment will be used to calculate the denominator degrees of freedom for the fixed-effect (DDFM=KR). Ninety-five percent (95%) confidence intervals for the least squares means for each population will be constructed on the natural log scale and will reference the t-distribution. Exponentiating the least-squares means and their corresponding 95% confidence intervals will yield estimates for the population geometric means and confidence intervals about the geometric means on the original scale.

To compare subjects with HI in each of the hepatic insufficient categories (moderate HI and severe HI) to matching subjects with normal hepatic function, a two sided 90% confidence interval for the true difference in means (HI – normal hepatic function) will be calculated for each PK parameters (AUC0-∞, AUC0-last, AUC0-24, Ceoi, and CL) using the mean square error from the model and referencing a t-distribution. For each of the HI populations, these confidence limits will be exponentiated to obtain the 90% confidence interval for the true ratio of geometric means (HI/normal hepatic function) for each pharmacokinetic parameter.

Figures showing individual pharmacokinetic values with GMs (95% confidence intervals) by population, plotted on the natural log scale, will be provided for AUC0-∞, AUC0-last, AUC0-24, Ceoi, and CL.

Individual values will be listed for each PK parameter (AUC0-∞, AUC0-last, AUC0-24, Ceoi, Tmax, CL, Vz, and apparent terminal t½) by population, and the following (non model-based) descriptive statistics will be provided: N (number of subjects with non-missing data), arithmetic mean, standard deviation, arithmetic percent CV (calculated as 100 x standard deviation/arithmetic mean), median, minimum, maximum, geometric mean, and geometric percent CV (calculated as 100 x sqrt(exp(s2) - 1), where s2 is the observed variance on the natural log-scale).

8.1.2.2 Secondary PK Analysis

8.1.2.2.1 Objective 1

Separately for each urine pharmacokinetic parameter, individual values of fe and CLr will be natural log-transformed and evaluated with a linear fixed effects model, which is described in the primary analysis. Ninety-five percent (95%) confidence intervals for the least squares means for each population will be constructed. To compare subjects with HI in each of the hepatic insufficient categories (moderate HI and severe HI) to matching subjects with normal hepatic function, a two sided 90% confidence interval for the true difference in means (HI – normal hepatic function) will be calculated for each urine PK parameters (fe and CLr).

Individual values will be listed for each urine PK parameter (fe and CLr) by population, and non model-based descriptive statistics will be provided

8.1.2.2.2 Objective 2

The safety and tolerability of MK-3866 will be evaluated by clinical assessment of adverse experiences and other safety measurements. Summary statistics for the laboratory safety tests, ECGs, and/or vital signs may also be provided, as deemed clinically appropriate.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of

investigational product in accordance with the protocol and any applicable laws and regulations.

Clinical Supplies will be provided by the Sponsor as summarized in Table 8.

Table 8 Product Descriptions

Product Name & Potency	Dosage Form
MK-3866 180 mg	Lyophilized Powder for Injection

MK-3866 clinical supplies will be supplied as a sterile lyophilized powder to be reconstituted and diluted in saline for IV infusion. The lyophilized powder will be reconstituted at the CRU with 12 mL of 0.9% sodium chloride for injection (normal saline) in the original vial to make a stock solution that is further diluted with saline to accommodate the study protocol dose of 150 mg.

9.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

9.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor and/or designee are not blinded. MK-3866 IV infusion is included in the label text; random code/disclosure envelopes or lists are not provided.

9.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

9.5 Discard/Destruction/Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial. For all trial sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the institutional review board, ethics review committee (IRB/ERC) or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this trial will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.2 Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/ERC, or regulatory authority representatives may consult and/or copy trial documents in order to verify worksheet/case report form data. By signing the consent form, the subject agrees to this process. If trial documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

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

10.1.3 Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and trial site personnel, may be used and disclosed for trial management purposes, as part of a regulatory submissions, and as required by law. This information may include:

1. name, address, telephone number and e-mail address;
2. hospital or clinic address and telephone number;
3. curriculum vitae or other summary of qualifications and credentials; and
4. other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, in your country and other countries, including countries that do not have laws protecting such information. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory authorities or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

If this is a multicenter trial, in order to facilitate contact between investigators, the Sponsor may share an investigator's name and contact information with other participating investigators upon request.

10.1.4 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this trial. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting 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 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 the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) 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 that do not have laws protecting personal data.

10.3 Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (e.g., International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by Merck, is provided in Section 12.1 - Merck Code of Conduct for Clinical Trials.

The investigator also agrees to allow monitoring, audits, IRB/ERC review and regulatory authority inspection of trial-related documents and procedures and provide for direct access to all trial-related source data and documents.

The investigator agrees not to seek reimbursement from subjects, their insurance providers or from government programs for procedures included as part of the trial reimbursed to the investigator by the Sponsor.

The investigator shall prepare and maintain complete and accurate trial documentation in compliance with Good Clinical Practice standards and applicable federal, state and local laws, rules and regulations; and, for each subject participating in the trial, provide all data, and, upon completion or termination of the clinical trial, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Trial documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the trial site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the trial documentation and worksheets/case report forms.

The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. By signing this protocol, the investigator agrees that documentation shall be retained until at least 2 years after the last approval of a marketing application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Because the clinical development and marketing application process is variable, it is anticipated that the retention period can be up to 15 years or longer after protocol database lock. The Sponsor will determine the minimum retention period and notify the investigator when documents may be destroyed. The Sponsor will determine the minimum retention period and upon request, will provide guidance to the investigator when documents no longer need to be retained. The sponsor also recognizes that documents may need to be retained for a longer period if required by local regulatory requirements. All trial documents shall be made available if required by relevant regulatory authorities. The investigator must consult with and obtain written approval by the Sponsor prior to destroying trial and/or subject files.

ICH Good Clinical Practice guidelines recommend that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this trial.

Persons debarred from conducting or working on clinical trials by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's trials. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the trial is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

In the event the Sponsor prematurely terminates a particular trial site, the Sponsor will promptly notify that trial site's IRB/IEC.

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center trial (including multinational). When more than one trial site is open in an EU country, Merck, as the Sponsor, will designate, per country, a national principal coordinator (Protocol CI), responsible for coordinating the work of the principal investigators at the different trial sites in that Member State, according to national regulations. For a single-center trial, the Protocol CI is the principal investigator. In addition, the Sponsor must designate a principal or coordinating investigator to review the trial report that summarizes the trial results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the trial [Clinical Study Report (CSR) CI]. The Sponsor may consider one or more factors in the selection of the individual to serve as the Protocol CI and or CSR CI (e.g., availability of the Protocol/CSR CI during the anticipated review process, thorough understanding of clinical trial methods, appropriate enrollment of subject cohort, timely achievement of trial milestones). The Protocol CI must be a participating trial investigator.

10.4 Compliance with Trial Registration and Results Posting Requirements

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 trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. Merck, as Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. Merck entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

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

10.5 Quality Management System

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (SOPs) to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical trial.

10.6 Data Management

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate.

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

10.7 Publications

This trial is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. The Sponsor will work with the authors to submit a manuscript describing trial results within 12 months after the last data become available, which may take up to several months after the last subject visit in some cases such as vaccine trials. However, manuscript submission timelines may be extended on OTC trials. For trials intended for pediatric-related regulatory filings, the investigator agrees to delay publication of the trial results until the Sponsor notifies the investigator that all relevant regulatory authority decisions on the trial drug have been made with regard to pediatric-related regulatory filings. Merck will post a synopsis of trial results for approved products on www.clinicaltrials.gov by 12 months after the last subject's last visit for the primary outcome, 12 months after the decision to discontinue development, or product marketing (dispensed, administered, delivered or promoted), whichever is later.

These timelines may be extended for products that are not yet marketed, if additional time is needed for analysis, to protect intellectual property, or to comply with confidentiality agreements with other parties. Authors of the primary results manuscript will be provided the complete results from the Clinical Study Report, subject to the confidentiality agreement. When a manuscript is submitted to a biomedical journal, the Sponsor's policy is to also include the protocol and statistical analysis plan to facilitate the peer and editorial review of the manuscript. If the manuscript is subsequently accepted for publication, the Sponsor will allow the journal, if it so desires, to post on its website the key sections of the protocol that are relevant to evaluating the trial, specifically those sections describing the trial objectives and hypotheses, the subject inclusion and exclusion criteria, the trial design and procedures, the efficacy and safety measures, the statistical analysis plan, and any amendments relating to those sections. The Sponsor reserves the right to redact proprietary information.

For multicenter trials, subsequent to the multicenter publication (or after public disclosure of the results online at www.clinicaltrials.gov if a multicenter manuscript is not planned), an investigator and his/her colleagues may publish their data independently. In most cases, publication of individual trial site data does not add value to complete multicenter results, due to statistical concerns. In rare cases, publication of single trial site data prior to the main paper may be of value. Limitations of single trial site observations in a multicenter trial should always be described in such a manuscript.

Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors must meet conditions 1, 2 and 3. Significant contributions to trial execution may also be taken into account to determine authorship, provided that contributions have also been made to all three of the preceding authorship criteria. Although publication planning may begin before conducting the trial, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to

the trial and writing, as discussed above. The first author is responsible for defending the integrity of the data, method(s) of data analysis and the scientific content of the manuscript.

The Sponsor must have the opportunity to review all proposed abstracts, manuscripts or presentations regarding this trial 45 days prior to submission for publication/presentation. Any information identified by the Sponsor as confidential must be deleted prior to submission; this confidentiality does not include efficacy and safety results. Sponsor review can be expedited to meet publication timelines.

11.0 LIST OF REFERENCES

None

12.0 APPENDICES

12.1 Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

Merck, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing and reporting these trials in compliance with the highest ethical and scientific standards. Protection of subject safety is the overriding concern in the design of clinical trials. In all cases, Merck clinical trials will be conducted in compliance with local and/or national regulations and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Such standards shall be endorsed for all clinical interventional investigations sponsored by Merck irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials which are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials which are not under the control of Merck.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of Merck or comparator products. Alternatively, Merck may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine subject preferences, etc.

The design (i.e., subject population, duration, statistical power) must be adequate to address the specific purpose of the trial. Research subjects must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

Merck selects investigative sites based on medical expertise, access to appropriate subjects, adequacy of facilities and staff, previous performance in Merck trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by Merck personnel to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice. Merck reviews clinical data for accuracy, completeness and consistency. Data are verified versus source documentation according to standard operating procedures. Per Merck policies and procedures, if fraud, misconduct or serious GCP-non-Compliance are suspected, the issues are promptly investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified and data disclosed accordingly.

B. Publication and Authorship

To the extent scientifically appropriate, Merck seeks to publish the results of trials it conducts. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing. In such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues of multiplicity.

Merck's policy on authorship is consistent with the requirements outlined in the ICH-Good Clinical Practice guidelines. In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. Merck funding of a trial will be acknowledged in publications.

III. Subject Protection

A. IRB/ERC review

All clinical trials will be reviewed and approved by an independent IRB/ERC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the IRB/ERC prior to implementation, except that changes required urgently to protect subject safety and well-being may be enacted in anticipation of IRB/ERC approval. For each site, the IRB/ERC and Merck will approve the subject informed consent form.

B. Safety

The guiding principle in decision-making in clinical trials is that subject welfare is of primary importance. Potential subjects will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care. Subjects are never denied access to appropriate medical care based on participation in a Merck clinical trial.

All participation in Merck clinical trials is voluntary. Subjects are enrolled only after providing informed consent for participation. Subjects may withdraw from a Merck trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

Merck is committed to safeguarding subject confidentiality, to the greatest extent possible. Unless required by law, only the investigator, sponsor (or representative) and/or regulatory authorities will have access to confidential medical records that might identify the research subject by name.

D. Genomic Research

Genomic Research will only be conducted in accordance with informed consent and/or as specifically authorized by an Ethics Committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is Merck's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of Merck trials. Merck does not pay incentives to enroll subjects in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

Merck does not pay for subject referrals. However, Merck may compensate referring physicians for time spent on chart review to identify potentially eligible subjects.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by Merck, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local IRB/ERC may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, publications resulting from Merck trials will indicate Merck as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices including, in the U.S., those established by the American Medical Association (AMA).

V. Investigator Commitment

Investigators will be expected to review Merck's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

* In this document, "Merck" refers to Merck Sharp & Dohme Corp. and Schering Corporation, each of which is a subsidiary of Merck & Co., Inc. Merck is known as MSD outside of the United States and Canada. As warranted by context, Merck also includes affiliates and subsidiaries of Merck & Co., Inc."

12.2 Collection and Management of Specimens for Future Biomedical Research

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens consented and/or collected in this trial as outlined in Section 7.1.3.4 – Future Biomedical Research Samples will be used in various experiments to understand:

- The biology of how drugs/vaccines work
- Biomarkers responsible for how a drug/vaccine enters and is removed by the body
- Other pathways drugs/vaccines may interact with
- The biology of disease

The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor or those working for or with the Sponsor.

3. Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

All subjects enrolled in the clinical trial will be considered for enrollment in the Future Biomedical Research sub-trial.

b. Informed Consent

Informed consent for specimens (i.e., DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all subjects or legal guardians, at a trial visit by the investigator or his or her designate. Informed consent for Future Biomedical Research should be presented to the subjects on the visit designated in the trial flow chart. If delayed, present consent at next possible Subject Visit. Consent

forms signed by the subject will be kept at the clinical trial site under secure storage for regulatory reasons.

A template of each trial site's approved informed consent will be stored in the Sponsor's clinical document repository.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of subject consent for Future Biomedical Research will be captured in the electronic Case Report Forms (eCRFs). Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen(s)

Collection of specimens for Future Biomedical Research will be performed as outlined in the trial flow chart. In general, if additional blood specimens are being collected for Future Biomedical Research, these will usually be obtained at a time when the subject is having blood drawn for other trial purposes.

4. Confidential Subject Information for Future Biomedical Research

In order to optimize the research that can be conducted with Future Biomedical Research specimens, it is critical to link subject' clinical information with future test results. In fact little or no research can be conducted without connecting the clinical trial data to the specimen. The clinical data allow specific analyses to be conducted. Knowing subject characteristics like gender, age, medical history and treatment outcomes are critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for Future Biomedical Research, the Sponsor has developed secure policies and procedures. All specimens will be single-coded per ICH E15 guidelines as described below.

At the clinical trial site, unique codes will be placed on the Future Biomedical Research specimens. This code is a random number which does not contain any personally identifying information embedded within it. The link (or key) between subject identifiers and this unique code will be held at the trial site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses utilizing the Future Biomedical Research specimens may be performed by the Sponsor, or an additional third party (e.g., a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third party analyses will conform to the specific scope of analysis outlined in this sub-trial. Future Biomedical Research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and ask that their biospecimens not be used for Future Biomedical Research. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical

records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the subject's specimens will be flagged in the biorepository and restricted to main study use only. If specimens were collected from study participants specifically for Future Biomedical Research, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the subject of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject's personal information and their specimens. In this situation, the request for withdrawal of consent and/or destruction cannot be processed.

7. Retention of Specimens

Future Biomedical Research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the main study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the trial site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not utilized in a particular trial, the trial site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated trial administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards to protect against unauthorized access.

9. Reporting of Future Biomedical Research Data to Subjects

No information obtained from exploratory laboratory studies will be reported to the subject, family, or physicians. Principle reasons not to inform or return results to the subject include: Lack of relevance to subject health, limitations of predictive capability, and concerns regarding misinterpretation.

If important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to rapidly report this information to doctors and subjects. Subjects will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population

Every effort will be made to recruit all subjects diagnosed and treated on Sponsor clinical trials for Future Biomedical Research.

11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the subject have been minimized. No additional risks to the subject have been identified as no additional specimens are being collected for Future Biomedical Research (i.e., only leftover samples are being retained).

The Sponsor has developed strict security, policies and procedures to address subject data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation there is risk that the information, like all medical information, may be misused.

12. Questions

Any questions related to the future biomedical research should be e-mailed directly to clinical.specimen.management@merck.com.

13. References

1. National Cancer Institute: http://www.cancer.gov/dictionary/?searchTxt=biomarker
2. International Conference on Harmonization: DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES - E15; http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/definitions-for-genomic-biomarkers-pharmacogenomics-pharmacogenetics-genomic-data-and-sample-cod.html
3. Industry Pharmacogenomics Working Group. Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/
4. Industry Pharmacogenomics Working Group. Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

12.3 Approximate Blood Volumes Drawn by Trial Visit and by Sample Types

Panels A and B	Pre-trial	Treatment Period	Post-trial	Total Collections	mL Per Collection	Total mL/ Test
Laboratory safety tests	1	3	1	5	12.5	62.5
HIV/Hepatitis Screen (at the discretion of the investigator)	1	-	-	1	5.0	5.0
Blood for Planned Genetic Analysis	-	1	-	1	8.5	8.5
Blood (plasma) for MK-3866	-	15	-	15	6.0	90.0
					Total Blood Volume Per Subject for Panels A and B†	166.0 mL

* Pre-trial laboratory safety tests will include serum β-hGC testing for all females and follicle-stimulating hormone (FSH) testing for post-menopausal females

† If additional pharmacokinetic and/or safety analysis is necessary, additional blood (up to 50 mL) may be obtained.

Panel C	Pre-trial	Treatment Period	Post-trial	Total Collections	mL Per Collection	Total mL/ Test
Laboratory safety tests*	1	2	1	4	12.5	50.0
HIV/Hepatitis Screen (at the discretion of the investigator)	1	-	-	1	5.0	5.0
Blood for Planned Genetic Analysis	-	1	-	1	8.5	8.5
Blood (plasma) for MK-3866	-	14	-	14	6.0	84.0
					Total Blood Volume Per Subject for Panel C†	147.5 mL

* Pre-trial laboratory safety tests will include serum β-hGC testing for all females and follicle-stimulating hormone (FSH) testing for post-menopausal females

† If additional pharmacokinetic and/or safety analysis is necessary, additional blood (up to 50 mL) may be obtained.

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

13.2 Investigator

I agree to conduct this clinical trial in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol). I agree to conduct the trial in accordance with generally accepted standards of Good Clinical Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse events as defined in Section 7.0 – TRIAL PROCEDURES (Assessing and Recording Adverse Events). I also agree to handle all clinical supplies provided by the Sponsor and collect and handle all clinical specimens in accordance with the protocol. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol and the referenced Investigator's Brochure is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the trial is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure or access by third parties.

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

14.0 APPENDIX 1

14.1 Child-Pugh Scale for the Assessment of Hepatic Impairment

Parameter	Score for Observed Findings		
	1	**2**	**3**
Encephalopathy Grade	None	1 or 2	3 or 4
Ascites	Absent	Slight	Moderate to Severe
Serum Bilirubin (mg/dL)	<2	2–3	>3
Serum Albumin (g/dL)	>3.5	2.8–3.5	<2.8
International Normalized Ratio (INR)	<1.7	1.7–2.3	>2.3
Grade 0: normal consciousness, personality, neurological examination, electroencephalogram Grade 1: restless, sleep disturbed, irritable/angered, tremor, impaired handwriting, 5 cps waves Grade 2: lethargic, time-disoriented, inappropriate behavior, asterixis, ataxia, slow triphasic waves Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves Grade 4: unarousable coma, no personality/behavior, decerebrate, slow 2 to 3 cps delta activity			