Official Protocol Title:	A Two-Part, Open-Label Study to Investigate the Single-Dose Pharmacokinetics of MK-8931 when Administered to Subjects with Mild and Moderate Hepatic Insufficiency
NCT number:	NCT02910739
Document Date:	05-Jan-2017

Celerion Project No.: CA13011

Merck Protocol No.: MK-8931-016-01

US IND No.: 110,186

A Two-Part, Open-Label Study to Investigate the Single-Dose Pharmacokinetics of MK-8931 when Administered to Subjects with Mild and Moderate Hepatic Insufficiency

Compliance Statement

Merck clinical studies 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.

Confidentiality Statement

1 PROTOCOL REVISION HISTORY

Date/Name	Description
05 Jan 2017 by PPD	Final Protocol Amendment 1 This protocol amendment was generated to facilitate subjects' recruitment by adding a second Investigator and clinical site and by modifying the inclusion and exclusion criteria for subjects with hepatic insufficiency (HI). Changes to the protocol are presented with new text in **bold** font and deleted text in ~~strikethrough~~ font. 1. The PPD was added as a second clinical site, with PPD as the principal Investigator for the site. In Section 2 - Principal Investigator and Sponsor – Signatories, the titles were updated to indicate multiple investigators and clinical sites, and PPD was added as the second principal Investigator with contact information added as follows: PPD PPD PPD **USA** **Tel.:** PPD **E-mail:** PPD 2. Subject lower age limit was reduced from 55 to 45 years of age, inclusive. In Section 5 – Synopsis, under Number of Subjects, the sentence was modified as follows: "Up to 32, adult, male and female subjects between ~~55~~ **45** and 85 years of age (inclusive) will be enrolled. In Section 9.2.1.1 – Subjects with Hepatic Insufficiency, Criterion #1 was modified as follows: "Adult male or female subjects, ~~55~~ **45**-85 years of age, inclusive, at screening." In order to maintain the age match between subjects with HI and healthy subjects, the update in age limit was applied to healthy subjects as well. Thus, Section 9.2.1.2 – Healthy Control Subjects, the first sentence of Criterion #1 was modified as follows: "Healthy adult male or female subjects, ~~55~~ **45**-85 years of age, inclusive, at screening."

	3. Since many subjects with HI suffer from hepatitis C (HCV) infection, the criterion was updated to exclude only subjects with HCV and decompensated liver disease. Section 9.2.2.1 - Subjects with Hepatic Insufficiency, Criterion #8 was modified as follows: "Positive results at screening for human immunodeficiency virus (HIV) **or** ~~,~~ hepatitis B surface antigen (HBsAg)~~,~~ or hepatitis C virus (HCV) (i.e., HCV antibody positive, HCV RNA positive) **with decompensated liver disease**. 4. Fridericia's correction of the QT interval (QTcF) upper limit for male subjects was increased from 460 msec to 480 msec. Section 9.2.2.1 - Subjects with Hepatic Insufficiency, Criterion #11 and Section 9.2.2.2 – Healthy Control Subjects, Criterion #11 were modified as follows: "QTcF interval is > ~~460~~ **480** msec ~~(males) or > 480 msec (females)~~ or has ECG findings deemed abnormal with clinical significance by the Investigator or designee at screening." 5. The washout period from participation in a previous clinical trial was update to 28 days from the last dosing in the previous study only and not 28 days from the date of the last blood collection or dosing, whichever is later. Section 9.2.2.1 - Subjects with Hepatic Insufficiency, Criterion #18 and Section 9.2.2.2 - Healthy Control Subjects, Criterion #18 were modified as follows: "Participation in another clinical trial within 28 days prior to dosing. The 4-week window will be derived from the date of the last ~~blood collection or~~ dosing~~, whichever is later,~~ in the previous study to Day 1 of the current study."
02 Sep 2016 by PPD	Final Protocol

2 PRINCIPAL INVESTIGATORS AND SPONSOR – SIGNATORIES

A Two-Part, Open-Label Study to Investigate the Single-Dose Pharmacokinetics of MK-8931 when Administered to Subjects with Mild and Moderate Hepatic Insufficiency

SPONSOR:

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
(hereafter referred to as the Sponsor or Merck)
One Merck Drive
P.O. Box 100
Whitehouse Station, New Jersey, 08889-0100, USA

SPONSOR'S REPRESENTATIVE:

PPD

Merck & Co., Inc.
P.O. Box 2000
Rahway, New Jersey 07065, USA
Tel.: PPD
E-mail: PPD

Signature Date

PRINCIPAL INVESTIGATORS AND CLINICAL SITES:

PPD

USA
Tel.: PPD
E-mail: PPD

Signature Date

PPD

USA
Tel.: PPD
E-mail: PPD

Signature Date

3 ADDITIONAL KEY CONTACTS FOR THE STUDY

Protocol Author

PPD
PPD
Celerion
100 Alexis-Nihon Boulevard, Suite 360
Montreal, Quebec, H4M 2N8, Canada
Tel.: PPD
Fax: PPD
E-mail: PPD

Certified Clinical Laboratory

Reliable Research Laboratory
1525 NW 167th Street Suite 140
Miami Gardens, Florida 33169, USA
Contact: PPD
Tel.: PPD
E-mail: PPD

Pharmacokinetic and Statistical Analyses

Celerion
100 Alexis-Nihon Boulevard, Suite 360
Montreal, Quebec, H4M 2N8, Canada
Tel.: PPD
Fax: PPD

and/or

Celerion
621 Rose Street
Lincoln, Nebraska 68502, USA
Tel.: PPD
Fax: PPD

4 TABLE OF CONTENTS

LIST OF APPENDICES

LIST OF TABLES

5 SYNOPSIS

Compound:	MK-8931
Clinical Indication:	Alzheimer's Disease
Study Phase and Type:	Phase I – Interventional
Study Objectives and Estimations:	**Part 1:** **Primary:** Objective: To compare the plasma pharmacokinetics (e.g., AUC0-∞, AUC0-last, AUC0-24hr, Cmax, C24hr, apparent terminal t½, and Tmax, as applicable) of MK-8931, following administration of a single oral dose of 40 mg MK-8931 to subjects with moderate hepatic insufficiency (HI) to that of healthy matched control subjects. Estimation: The plasma pharmacokinetics (AUC0-∞ and Cmax) of MK-8931 following a single oral dose of MK-8931 to subjects with moderate HI will be estimated and compared to those in healthy matched control subjects. **Secondary:** Objective: To evaluate the safety and tolerability of MK-8931 following administration of a single oral dose in subjects with moderate HI. **Part 2 (Optional):** **Primary:** Objective: To compare the plasma pharmacokinetics (e.g., AUC0-∞, AUC0-last, AUC0-24hr, Cmax, C24hr, apparent terminal t½, and Tmax, as applicable) of MK-8931, following administration of a single oral dose of 40 mg MK-8931 to subjects with mild HI to that of healthy matched control subjects. Estimation: The plasma pharmacokinetics (AUC0-∞ and Cmax) of MK-8931 following a single oral dose of MK-8931 to subjects with mild HI will be estimated and compared to those in healthy matched control subjects. **Secondary:** Objective: To evaluate the safety and tolerability of MK-8931 following administration of a single oral dose in subjects with mild HI.

	Parts 1 and 2: **Planned Exploratory Biomarker:** Objective: 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.
Summary of Study Design:	This is a 2-part, non-randomized, open-label, single-dose study to evaluate the pharmacokinetics of MK-8931, in subjects with moderate (Part 1) and mild (Part 2) HI compared to those in healthy matched control subjects. Part 1 will be initiated with subjects with moderate HI. Healthy control subjects will be enrolled following completion of enrollment of all subjects with moderate HI (Part 1). Each healthy control subject will be matched to the mean body mass index (BMI; ± 10%) and age (± 15 years) of the subjects with moderate HI. The number of healthy subjects of each gender will match that of the moderate HI subjects [±1]. Following completion of the clinical portion, a safety and pharmacokinetic analysis will be performed in order to support the decision to continue the study to Part 2. If a decision is made to continue with Part 2, subjects with mild HI will be enrolled. If any of the healthy control subjects from Part 1 do not also meet the matching criteria for the mild HI in Part 2, additional healthy control subjects will be enrolled in Part 2 to acquire data from a total of 8 healthy subjects that match the mean BMI (± 10%) and age (± 15 years) of mild HI (Part 2). The gender of the additional healthy subject(s) will be selected to ensure the number of healthy subjects of each gender will match that of the mild HI subjects (±1). The comparison between mild HI and healthy control subjects will include only the healthy controls who meet the matching criteria for mild HI. On Day 1 of either part, a single oral dose of MK-8931 will be administered followed by pharmacokinetic sampling for 120 hours. Blood samples for the potential assessment of protein binding of MK-8931 will be collected. Subjects (including subjects who terminate the study early) will return to the clinical research unit (CRU) approximately 14 days after study drug administration for follow-up procedures, and to determine if any adverse events have occurred since the last study visit.
Blinding:	This is an open-label study.

Number of Subjects:	Up to 32, adult, male and female subjects between 45 and 85 years of age (inclusive) will be enrolled. Eight (8) subjects with moderate HI (a score of 7 to 9, on the Child-Pugh scale) will be enrolled in Part 1. Eight (8) subjects with mild HI (a score of 5 to 6 on the Child-Pugh scale) will be enrolled in Part 2, if conducted. Eight (8) subjects with normal hepatic function will be enrolled once all subjects with moderate HI (Part 1) are enrolled. Each healthy control subject will be matched to the mean age (±15 years) and BMI (±10 %) of subjects with HI in Part 1. The number of healthy subjects of each gender will match that of the moderate HI subjects [±1]. If any of the healthy control subjects from Part 1 do not also meet the matching criteria for the mild HI in Part 2, additional healthy control subjects will be enrolled in Part 2 to acquire data from a total of 8 healthy subjects that match the mean BMI (± 10%) and age (± 15 years) of mild HI (Part 2). The gender of the additional healthy subject(s) will be selected to ensure the number of healthy subjects of each gender will match that of the mild HI subjects (±1).
Dosage, Dosage Form, Route, and Dose Regimen:	Each subject will receive a single oral dose of 40 mg MK-8931 (1 x 40 mg tablet) in a fasted state. All study drugs will be administered orally with approximately 240 mL of water.
Key Assessments:	**Pharmacokinetics:** The following pharmacokinetic parameters will be calculated for MK-8931 in plasma, as appropriate: AUC0-∞, AUC0-last, AUC0-24hr, Cmax, C24hr, Tmax, CL/F, Vz/F, and apparent terminal t½. An analysis of covariance (ANCOVA) model will be used for the analysis of the natural log (ln)-transformed AUC0-∞, AUC0-last, AUC0-24hr, Cmax, and C24hr. Protein binding for MK-8931 may also be analyzed. If protein binding is analyzed, the fraction of unbound drug (fu) in plasma will be reported. **Safety:** Safety will be monitored through physical examination, vital signs, 12-lead electrocardiograms (ECGs), adverse events and clinical laboratory tests. Summary statistics for the laboratory safety tests, 12-lead ECGs, and/or vital signs may also be computed and provided, as deemed clinically appropriate.

6 STUDY EVENTS FLOW CHART

Study Procedures [a]	S [b]	Study Days																FU [c]
Days →		-1	1										2	3	4	5	6	
Hours →		(C-I) [d]	P	0	0.5	1	2	3	4	6	8	12	24	48	72	96	120	
Administrative Procedures																		
Informed Consent	X																	
Informed Consent for Future Biomedical Research	X																	
Inclusion/Exclusion Criteria	X	X																
Medical History	X																	
Safety Evaluations																		
Physical Examination [e]	X																	
Height	X																	
Weight	X	X																
12-Lead Electrocardiogram	X		X [f]				X											X [g]
Vital Signs (heart rate & blood pressure)	X		X [f]				X										X	X [g]
Vital Signs (respiratory rate & temperature)	X																	
Assessment of Liver Function using Child-Pugh Classification [h]	X																	
Hematology, Serum Chemistry [i], and Urinalysis	X	X																X [g]
Serum Pregnancy Test (female subjects only)	X	X																
Serum FSH (postmenopausal females only)	X																	
Urine Drug Screen	X	X																
Urine or Breathalyzer Alcohol Screen	X																	
HIV/Hepatitis Screen	X																	
Adverse Events Monitoring	X								X									X
Concomitant Medication Monitoring	X								X									
Study Drug Administration / Pharmacokinetics																		
MK-8931 Administration				X														
Blood for MK-8931 Pharmacokinetics			X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Blood for MK-8931 Protein Binding			X				X						X					
Other Procedures																		
Blood for Genetic Analysis [j]				X														
Confinement in the CRU [k]									X									
Visit and Return Visit	X																	X

a. For details on Procedures, refer to Section 10 and/or corresponding appendices.

b. Within 28 days prior to the study drug administration.

c. Subjects (including subjects who terminate the study early) will return to the CRU approximately 14 days after study drug administration for follow-up procedures, and to determine if any adverse events have occurred since the last study visit.

d. Subjects will be admitted to the CRU on Day -1, at the time indicated by the CRU.

e. A symptom-driven physical examination may be performed at other times at the Investigator's discretion.

f. To be performed within 24 hours prior to dosing.

g. To be performed on the follow-up visit and prior to early termination from the study if occurs.

h. To be performed in subjects with HI only.

i. Samples for serum chemistry will be obtained following a fast of at least 8 hours; however, in case of dropouts or rechecks, subjects may not have fasted for 8 hours before the serum chemistry sample is taken.

j. 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.

k. At the Investigator's discretion, subjects may be released from the CRU prior to Day 6; if so, subjects will then be asked to return to the CRU for subsequent study procedures.

Abbreviations: AE = Adverse events, C-I = Check-in, CRU = Clinical research unit, DNA = deoxyribonucleic acid, FBR = Future Biomedical Research, FSH = Follicle-stimulating hormone, FU = Follow-Up, HI = Hepatic insufficiency, HIV = Human immunodeficiency virus, IEC = Independent ethics committee, IRB = Institutional review board, P = Predose, S = Screening.

7 BACKGROUND AND RATIONALE

7.1 Background

Alzheimer's disease is a slowly developing neurodegenerative disease that is the leading cause of dementia and a leading cause of death in the elderly. Alzheimer's disease is characterized by histopathological features in the brain including neurovascular and parenchymal amyloid deposits (plaques) composed of the Aβ peptides, intraneuronal neurofibrillary tangles composed of hyperphosphorylated microtubule-associated protein tau, neuronal and synaptic loss, and neuroinflammation. The Aβ peptides are hypothesized to be intimately involved in the etiology of AD via their aggregation to form toxic complexes.

MK-8931 is a potent inhibitor of human β–site amyloid precursor protein (APP) cleaving enzyme (BACE1, also known as β-secretase), one of the enzymes responsible for production of the Aβ peptides, that is being developed for the treatment of Alzheimer's disease. Inhibition of BACE1 by MK-8931 has been shown to reduce Aβ peptide levels in the plasma, cerebrospinal fluid, and brain/cortex of multiple animal species as well as in the plasma and cerebrospinal fluid in humans. Preclinical toxicology data with MK-8931 at the systemic exposures achieved, provide no contraindications to clinical trials with this compound via the oral route.

Refer to the Confidential Clinical Investigator's Brochure (IB) for detailed background information on MK-8931 in the following areas:

- Physical, Chemical, and Pharmaceutical Properties and Formulation
- Nonclinical Pharmacology
- Safety Pharmacology and Supplemental Safety Pharmacology Studies
- Pharmacokinetics and Product Metabolism in Animals
- Toxicology (Preclinical Safety Assessment)
- Effects in Humans and Clinical Experience

7.2 Rationale

7.2.1 Rationale for this Study and Study Design

In most AD patients, symptoms begin to appear in their mid-60s and progress slowly with age [1]. Since advancing age is associated with reduction in renal and hepatic clearance [2], HI is an expected comorbidity in the target patient population for MK-8931. This study will evaluate the effect of hepatic insufficiency on the plasma pharmacokinetics of MK-8931 in order to guide dosing recommendations. This study will also evaluate the safety and tolerability of MK-8931 following administration of a single oral dose in subjects with moderate and mild HI.

Results from an absorption, distribution, metabolism and elimination study (MK-8931-005) suggest that MK-8931 is [redacted]

[redacted] Based on these data, it is anticipated that exposures of MK-8931 will be increased in subjects with moderate HI compared with healthy matched controls.

A reduced study design enrolling subjects with moderate (Part 1) and mild (Part 2) HI is proposed. The decision to initiate Part 2 of the study will be made upon an analysis using preliminary pharmacokinetic data from Part 1. Once all subjects with moderate HI (Part 1) are enrolled, a healthy control group will be enrolled with demographics which are matched to the mean demographic parameters to control for the influence of covariates.

In the target patient population, 60 mg MK-8931 QD was well-tolerated for up to 3 months, and provided an exposure ~1.5-fold above the exposure observed with a 40 mg dose, the highest dose being investigated in the Phase III studies. Accordingly, the pharmacokinetic condition to initiate Part 2 of the study will be met if the point estimate for the AUC0-∞ ratio of geometric means (subjects with moderate HI / healthy matched control subjects) exceeds 1.5. Healthy control subjects from Part 1 who match the gender (±1) and mean BMI (± 10%) and age (± 15 years) of subjects with mild HI in Part 2 will be used as part of the control group for Part 2. Additional healthy adult subjects matching the subjects with mild HI may be enrolled in Part 2 to acquire data from a total of 8 healthy matching subjects.

The Child-Pugh classification will be used to categorize HI due to its widespread use and acceptance by regulatory agencies (including the U.S. Food and Drug Administration (FDA) [3]. This study design is supported by FDA guidelines for drugs which undergo substantial hepatic metabolism and for which an indication is sought for patients with HI [3].

7.2.2 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, et al.[4], has been subsequently found useful in classifying a patient's level of HI for pharmacokinetic studies. The Child-Pugh scale has been shown to correlate with hepatic (i.e., metabolic) clearance for several compounds [3].

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. Only 5 of the 6 parameters listed in Table 1 are scored. 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 4 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

	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.

7.2.3 Rationale for Dose Selection

Based on human pharmacokinetic and pharmacodynamic data and pharmacokinetic/pharmacodynamic modeling for the 2 dose levels currently in clinical outcomes evaluation (i.e., 12 and 40 mg), doses of 40 mg have a high probability of achieving ≥ 75% reduction in CSF Aβ40 and doses of 12 mg have a high probability of achieving ≥ 50% reduction in CSF Aβ40 in elderly subjects. As 40 mg is the highest dose being evaluated in Phase III studies and likely the highest possible marketed dose, a single dose of 40 mg has been chosen for this study.

A potential enhancement in exposure of up to 13-fold due to the effects of hepatic insufficiency would fall within previously studied safety and tolerability margins established with a 550 mg dose in a single dose study. This safety margin is deemed sufficient to account for a possible increase in exposure due to the moderate and mild HI of the study subjects.

7.2.4 Rationale for Endpoints

The primary endpoints for this study will include the pharmacokinetic parameters AUC0-∞ and Cmax which best describe the systemic exposure of MK-8931 following a single dose, in subjects with hepatic impairment or healthy control subjects.

7.2.5 Rationale for Planned Exploratory Biomarker Research

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.

7.2.6 Rationale for 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 Appendix 2 – Collection and Management of Specimens for Future Biomedical Research.

8 STUDY OBJECTIVES, ESTIMATIONS AND ENDPOINTS

8.1 Objectives and Estimations

8.1.1 Primary

Part 1:

Objective: To compare the plasma pharmacokinetics (e.g., AUC0-∞, AUC0-last, AUC0-24hr, Cmax, C24hr, apparent terminal t½, and Tmax, as applicable) of MK-8931, following administration of a single oral dose of 40 mg MK-8931 to subjects with moderate HI to that of healthy matched control subjects.

Estimation: The plasma pharmacokinetics (AUC0-∞ and Cmax) of MK-8931 following a single oral dose of MK-8931 to subjects with moderate HI will be estimated and compared to those in healthy matched control subjects.

Part 2 (Optional):

Objective: To compare the plasma pharmacokinetics (e.g., AUC0-∞, AUC0-last, AUC0-24hr, Cmax, C24hr, apparent terminal t½, and Tmax, as applicable) of MK-8931, following administration of a single oral dose of 40 mg MK-8931 to subjects with mild HI to that of healthy matched control subjects.

Estimation: The plasma pharmacokinetics (AUC0-∞ and Cmax) of MK-8931 following a single oral dose of MK-8931 to subjects with mild HI will be estimated and compared to those in healthy matched control subjects.

8.1.2 Secondary

Part 1:

Objective: To evaluate the safety and tolerability of MK-8931 following administration of a single oral dose in subjects with moderate HI.

Part 2 (Optional):

Objective: To evaluate the safety and tolerability of MK-8931 following administration of a single oral dose in subjects with mild HI.

8.1.3 Planned Exploratory Biomarker (Parts 1 and 2)

Objective: 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.

8.2 Analysis Endpoints

Pharmacokinetics:

The primary pharmacokinetic endpoints are AUC0-∞ and Cmax for MK-8931 in subjects with HI versus healthy matched subjects.

The pharmacokinetic parameters AUC0-last, AUC0-24hr, C24hr, Tmax, CL/F, Vz/F, and apparent terminal t½, as appropriate, for MK-8931 will also be computed.

Safety:

Safety endpoints will include all types of adverse events, physical examinations, vital signs (heart rate and blood pressure), 12-lead ECGs, and clinical laboratory tests (hematology, serum chemistry, and urinalysis).

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is a 2-part, non-randomized, open-label, single-dose study to evaluate the pharmacokinetics of MK-8931, in subjects with moderate (Part 1) and mild (Part 2) HI compared to those in healthy matched control subjects.

Up to 32, adult, male and female subjects will be enrolled.

Screening of subjects will occur within 28 days prior to dosing.

Part 1 will be initiated with subjects with moderate HI. Healthy control subjects will be enrolled following completion of enrollment of all subjects with moderate HI (Part 1). Each healthy control subject will be matched to the mean body mass index (BMI; ± 10%) and age (± 15 years) of the subjects with moderate HI. The number of healthy subjects of each gender will match that of the moderate HI subjects (±1). Following completion of the clinical portion, a safety and pharmacokinetic analysis will be performed in order to support the decision to continue the study to Part 2.

If a decision is made to continue with Part 2, subjects with mild HI will be enrolled. If any of the healthy control subjects from Part 1 do not also meet the matching criteria for the mild HI in Part 2, additional healthy control subjects will be enrolled in Part 2 to acquire data from a total of 8 healthy subjects that match the mean BMI (± 10%) and age (± 15 years) of mild HI (Part 2). The gender of the additional healthy subject(s) will be selected to ensure the number of healthy subjects of each gender will match that of the mild HI subjects (±1). The comparison between mild HI and healthy control subjects will include only the healthy controls who meet the matching criteria for mild HI.

On Day 1 of either part, a single oral dose of MK-8931 will be administered followed by pharmacokinetic sampling for 120 hours. Blood samples for the potential assessment of protein binding of MK-8931 will be collected.

Safety will be monitored throughout the study by repeated clinical and laboratory evaluations.

Subjects may be replaced at the discretion of the Sponsor.

9.1.1 Confinement, Return Visits and Follow-up

Subjects will be housed from Day -1 at the time indicated by the CRU until after the 120-hour blood draw and/or study procedures. At the Investigator's discretion, subjects may be released from the CRU prior to Day 6; if so, subjects will then be asked to return to the CRU for subsequent study procedures. At all times, a subject may be required to remain at the CRU for longer at the discretion of the Investigator.

Subjects (including subjects who terminate the study early) will return to the CRU approximately 14 days after study drug administration for follow-up procedures, and to determine if any adverse events have occurred since the last study visit.

9.1.2 Study Duration

The duration of the study from screening to follow-up is approximately 6 weeks.

9.2 Selection of Study Population

9.2.1 Inclusion Criteria

9.2.1.1 Subjects with Hepatic Insufficiency

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

1. Adult male or female subjects, 45-85 years of age, inclusive, at screening.

2. BMI ≥ 19 and ≤ 40 kg/m^2, at screening.

3. Continuous non-smokers or light smokers (< 10 cigarettes/day or the equivalent). Subjects must agree to consume no more than 10 cigarettes or equivalent/day from the time of screening and throughout the period of sample collection.

4. Baseline health is judged to be stable based on medical history (except for the hepatic insufficiency 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 re-screened after the underlying condition is resolved.

5. Subject 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 due to any etiology.

6. Part 1 only: Subject's score on the Child-Pugh scale must range from 7 to 9 (moderate HI) at screening. At least 4 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. Part 2 only: Subject's score on the Child-Pugh scale must range from 5 to 6 (mild HI) at screening.

8. Subjects must be completely informed of the unknown risks of pregnancy and agree not to become pregnant or father a child during the time they are participating in this study.

9. For a female of childbearing potential: either be sexually inactive (abstinent) for 14 days prior to dosing and throughout the study or be using one of the following acceptable birth control methods:

    a. 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.

    b. double physical barrier methods (e.g., condom and diaphragm) with spermicide for at least 14 days prior to dosing and throughout the study.

c. 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.

d. 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.

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.

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.

10. 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.

11. 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.

12. Male subjects must agree not to donate sperm from dosing until 90 days after dosing.

13. 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, including for Future Biomedical Research. Future Biomedical Research participation is voluntary and is not required in order to participate in the trial.

9.2.1.2 Healthy Control Subjects

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

1. Healthy adult male or female subjects, 45-85 years of age, inclusive, at screening. For healthy subjects enrolled in Part 1, age must be within ± 15 years of the mean age of subjects with moderate HI (Part 1). For any additional healthy subject enrolled in Part 2, age must be within ± 15 years of the mean age of subjects with mild HI (Part 2). 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 in Part 2 will be selected to ensure the number of healthy subjects of each gender will match that of the mild HI subjects (±1).

2. BMI ≥ 19 and ≤ 40 kg/m^2 at screening. For healthy subjects enrolled in Part 1, BMI must be within ± 10% of the mean BMI of the subjects with moderate HI (Part 1). For any additional healthy subject enrolled in Part 2, BMI must be within ± 10% of the mean BMI of subjects with mild HI (Part 2).

3. Continuous non-smokers or light smokers (< 10 cigarettes/day or the equivalent). Subjects must agree to consume no more than 10 cigarettes or equivalent/day from the time of screening and throughout the period of sample collection.

4. Medically healthy with no clinically significant medical history, physical examination, laboratory profiles, vital signs, or ECGs, as deemed by the Investigator.

5. Subjects must be completely informed of the unknown risks of pregnancy and agree not to become pregnant or father a child during the time they are participating in this study

6. For a female of childbearing potential: either be sexually inactive (abstinent) for 14 days prior to dosing and throughout the study or be using one of the following acceptable birth control methods:

    a. 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.

    b. double physical barrier methods (e.g., condom and diaphragm) with spermicide for at least 14 days prior to dosing and throughout the study.

    c. 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.

    d. 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.

    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.

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.

7. 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.

8. 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.

9. Male subjects must agree not to donate sperm from dosing until 90 days after dosing.

10. 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.

9.2.2 Exclusion Criteria

9.2.2.1 Subjects with Hepatic Insufficiency

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. History or presence of clinically significant medical or psychiatric condition or disease in the opinion of the Investigator.

3. 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. History or presence of alcoholism or drug abuse within the past 2 years prior to dosing.

5. History or presence of hypersensitivity or idiosyncratic reaction to the study drug or related compounds.

6. Female subjects who are pregnant or lactating.

7. Positive results for the urine drug and/or alcohol 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.

8. Positive results at screening for human immunodeficiency virus (HIV) or hepatitis B surface antigen (HBsAg) or hepatitis C virus (HCV) (i.e., HCV antibody positive, HCV RNA positive) with decompensated liver disease.

9. Seated blood pressure is less than 90/40 mmHg or greater than 180/105 mmHg at screening.

10. Seated heart rate is lower than 40 bpm or higher than 99 bpm at screening.

11. QTcF interval is > 480 msec or has ECG findings deemed abnormal with clinical significance by the Investigator or designee at screening.

12. Abnormal hemoglobin level deemed clinically significant by the Investigator at screening.

13. 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) as indicated in Section 9.3.1 for the prohibited time period.

14. Has been on a diet incompatible with the CRU-provided standard meals/snacks, in the opinion of the Investigator, within the 28 days prior to dosing of study drug, and throughout the study.

15. Donation of blood or had significant blood loss within 56 days prior to dosing of study drug.

16. Plasma donation within 28 days prior to dosing of study drug.

17. Is or has an immediate family member (e.g., spouse, parent/legal guardian, sibling or child) who is investigational site or Sponsor staff directly involved with this study.

18. Participation in another clinical trial within 28 days prior to dosing. The 4-week window will be derived from the date of the last dosing in the previous study to Day 1 of the current study.

19. Subject who dosed in one part (e.g., Part 1) will not be enrolled in the other part (e.g., Part 2).

9.2.2.2 Healthy Control Subjects

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. History or presence of clinically significant medical or psychiatric condition or disease in the opinion of the Investigator.

3. 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. History or presence of alcoholism or drug abuse within the past 2 years prior to dosing.

5. History or presence of hypersensitivity or idiosyncratic reaction to the study drug or related compounds.

6. Female subjects who are pregnant or lactating.

7. Positive results for the urine drug and/or urine or breath alcohol screen at screening or check-in.

8. Positive results at screening for HIV, HBsAg, or HCV (i.e., HCV antibody positive, HCV RNA positive).

9. Seated blood pressure is less than 90/40 mmHg or greater than 140/90 mmHg at screening.

10. Seated heart rate is lower than 40 bpm or higher than 99 bpm at screening.

11. QTcF interval is > 480 msec or has ECG findings deemed abnormal with clinical significance by the Investigator or designee at screening.

12. Abnormal hemoglobin level deemed clinically significant by the Investigator at screening.

13. 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) as indicated in Section 9.3.1 for the prohibited time period.

14. Has been on a diet incompatible with the CRU-provided standard meals/snacks, in the opinion of the Investigator, within the 28 days prior to dosing of study drug, and throughout the study.

15. Donation of blood or had significant blood loss within 56 days prior to dosing of study drug.

16. Plasma donation within 28 days prior to dosing of study drug.

17. Is or has an immediate family member (e.g., spouse, parent/legal guardian, sibling or child) who is investigational site or Sponsor staff directly involved with this study.

18. Participation in another clinical trial within 28 days prior to dosing. The 4-week window will be derived from the date of the last dosing in the previous study to Day 1 of the current study.

9.2.3 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the Investigator should any untoward effect occur. In addition, a subject may be withdrawn by the Investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal procedures, including specific details regarding withdrawal from Future Biomedical Research, are provided in Section 9.2.3.1.

Discontinuation is “permanent”. Once a subject is discontinued, he/she shall not be allowed to enroll again.

Subjects may be replaced at the discretion of the Sponsor.

A subject must be discontinued from the study for any of the following reasons:

- The subject withdraws consent.
- The subject has a confirmed positive serum pregnancy test.
- The subject has a medical condition or personal circumstance which, in the opinion of the Investigator and/or Sponsor, places the subject at unnecessary risk through continued participation in the trial or does not allow the subject to adhere to the requirements of the protocol.

A subject may be discontinued from the study for any of the following reasons:

- Adverse events.
- Difficulties in blood collection.
- Protocol violation.

9.2.3.1 Withdrawal/Discontinuation

The Investigator or designee must notify the Sponsor when a subject has been discontinued/withdrawn from the study. If a subject discontinues for any reason at any time during the course of the study, the procedures scheduled at early termination (as outlined in Section 6) will be performed. Furthermore, the subject will be asked to return to the clinic for a follow-up (approximately 14 days after dosing of study drug), to determine if any adverse events have occurred since the last 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 10.1.6.

9.2.3.1.1 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 (PPD 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.

9.3 Study Restrictions

9.3.1 Prohibitions and Concomitant Therapy

Consumption of foods and beverages containing the following substances will be prohibited as indicated:

- Xanthines/Caffeine: 24 hours before dosing until the last pharmacokinetic sample collection;
- Alcohol: 48 hours before dosing until the last pharmacokinetic sample collection;
- Grapefruit/Seville orange: 14 days before dosing until the last pharmacokinetic sample collection.

Concurrent therapy with any medication during the course of the study 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. During the study, acetaminophen (up to 2 g per 24 hours) may be administered at the discretion of the Investigator or designee.

Appropriate sources will be consulted by the Investigator or designee to confirm lack of pharmacokinetic/pharmacodynamic interaction with the 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 with HI:

[redacted]

Subjects who are taking medications for stable diseases for approximately 2 weeks (or 5 half-lives of the compound, whichever is longer) 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.

In addition, 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 following consultation with the Sponsor Clinical Monitor and the Investigator, 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 administration of the study drug.

Diuretics will be restricted for 4 hours prior to dosing until 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.

Iron supplements or other metal cations; or multivitamins containing iron or zinc will be restricted for the 6 hours prior to and after dosing as they may potentially affect absorption of the study drugs.

Lactulose will be restricted for the 6 hours prior to and after dosing as it may potentially affect absorption of the study drugs.

Healthy Control Subjects:

Any medication or substance (including prescription or over-the-counter (e.g., acetaminophen), vitamin supplements, natural or herbal supplements) which cannot be discontinued at least 14 days prior to dosing and throughout the study are prohibited. [redacted]

[redacted] be deemed acceptable following consultation with the Sponsor Clinical Monitor and the Investigator.

Subjects who are taking medications for stable diseases for approximately 1 month (or 5 half-lives of the compound, whichever is longer) 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.

9.3.2 Meals

Water (except water provided with dosing) 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 overnight for at least 10 hours prior to study drug administration. Subjects will continue the fast for at least 4 hours postdose. Standard meals will be provided at approximately 4 and 9 hours postdose, and at appropriate time thereafter. A snack will also be provided at approximately 12 hours postdose, and at appropriate time thereafter. When confined in the CRU, subjects will fast from all food and drink except water between meals and snacks.

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

9.3.3 Activity

Following dosing, subjects will remain seated or semi-reclined for the first 4 hours. Subjects will then resume normal activity. During the first 4 hours postdose, subjects may be allowed to rise for brief periods under supervision (e.g., in order to use the toilet facilities).

However, should adverse events occur at any time, subjects may be placed in an appropriate position or will be permitted to lie down on their right side.

Subjects will be instructed to refrain from strenuous physical activity which could cause muscle aches or injury, including contact sports at any time from screening until completion of the study.

Depending on the CRU rules and regulations, subjects may be prohibited from smoking during their confinement or during portions of their confinement.

9.4 Treatments

9.4.1 Treatments Administered

MK-8931 will be supplied as 40 mg tablets.

Each subject will receive a single oral dose of 40 mg MK-8931 (1 x 40 mg tablet), at Hour 0, on Day 1 in a fasted state.

All study drugs will be administered with approximately 240 mL of water, according to the allocation schedule.

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

Subjects will be instructed not to crush, split, or chew the study drug.

The exact clock time of dosing will be recorded.

9.4.2 Method of Assigning Subjects to Treatment Groups

Each subject will be assigned a unique identification number upon screening. Subjects who complete the study screening assessments and meet all the eligibility criteria will be assigned a unique allocation identification number prior to dosing, different from the screening number, and will receive the corresponding product, according to the allocation scheme generated at Celerion.

Subjects will receive the treatment on one occasion.

If replacement subjects are used, the replacement subject number will be 100 more than the original (e.g., allocation number 0101 will replace allocation number 0001).

9.4.3 Blinding

This is an open-label study.

9.4.4 Treatment Compliance

A qualified designee will be responsible for monitoring the administration of timed oral doses. A mouth check will be performed by the qualified designee to ensure that the subjects have swallowed the study drug. Once a subject has finished the water, the qualified designee will use a flashlight and a tongue depressor to check the subject's mouth. Subjects' hands will also be verified to ensure that the study drug was ingested.

9.4.5 Study Design or Procedure Modifications Permitted within Protocol Parameters

This is a Phase I assessment of MK-8931 in humans, and the pharmacokinetic, pharmacodynamic and safety profiles of the compound are still being elucidated. This protocol is written with some flexibility to accommodate the inherent dynamic nature of

Phase I clinical trials. Modifications to the clinical or laboratory procedures may be required to achieve the scientific goals of the trial objectives and/or to ensure appropriate safety monitoring of the trial subjects.

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 study based on newly available safety, tolerability, pharmacokinetic or pharmacodynamic 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 chemistry panel that was already drawn). These changes will not increase the number of study procedures for a given patient/subject during his/her participation in the entire trial.

It is understood that the current study 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 in a Protocol Clarification Letter and forwarded to the Investigator for retention. The Protocol Clarification Letter may be forwarded to the Institutional Review Board (IRB) at the discretion of the Investigator.

10 STUDY PROCEDURES

The Study Events Flow Chart (Section 6) summarizes the clinical procedures to be performed at each visit. Individual clinical procedures are described in detail below. Additional evaluations/testing may be deemed necessary by the Investigator and/or the Sponsor for reasons related to subject safety.

For this study, the blood collection for MK-8931 is the critical parameter and needs to be collected as close to the exact time point as possible. All other procedures should be completed as close to the prescribed/scheduled time as possible, but can be performed prior or after the prescribed/scheduled time.

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

10.1 Safety Assessment

10.1.1 Screening

Within 28 days prior to dosing, medical history and demographic data, including name, sex, age, race, ethnicity, body weight (kg), height (cm), and BMI (kg/m^2) will be recorded. Each subject will have a physical examination, vital sign measurements (heart rate, blood pressure, temperature, and respiratory rate), 12-lead ECG and the laboratory tests of hematological, hepatic and renal function, and additional tests as noted in Section 10.1.5.

10.1.2 Physical Examination

A physical examination will be performed as per Study Events Flow Chart (Section 6). Symptom-driven physical examinations may be performed at other times, if deemed necessary by the Investigator or designee.

10.1.3 Vital Signs

Single measurements of body temperature, respiratory rate, blood pressure, and heart rate, will be measured as outlined in the Study Events Flow Chart (Section 6).

Vital signs may be taken at any other times, if deemed necessary. Blood pressure and heart rate measurements will be performed with subjects in a seated position for at least 1 minute, except when they are supine or semi-reclined because of study procedures and/or adverse events (e.g., nausea, dizziness) or if deemed necessary by the Investigator.

Blood pressure and heart rate will be measured within 24 hours prior to Day 1 dosing for the predose time point. When scheduled postdose, vital signs will be performed within approximately 10 minutes of the scheduled time point.

10.1.4 ECG Monitoring

Single 12-lead ECGs will be performed as outlined in the Study Events Flow Chart (Section 6).

ECGs will be performed with subjects in a supine position for at least 5 minutes. All ECG tracings will be reviewed by the Study Physician or his/her designee.

ECGs will be measured within 24 hours prior to Day 1 dosing for the predose time point. When scheduled postdose, ECGs will be performed within approximately 20 minutes of the scheduled time point.

A subject will be withdrawn from the study by the Study Physician or his/her designee if, in their medical judgment, ECG findings are present which make continued study participation not in the subject's best interest.

10.1.5 Laboratory Tests

All tests listed below will be performed as per Study Events Flow Chart (Section 6). In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the Investigator.

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

Serum Chemistry*
- Blood urea nitrogen
- Bilirubin (total and direct)
- Alkaline phosphatase
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Albumin
- Sodium
- Potassium
- Chloride
- Glucose (fasting)
- Creatinine**

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

Additional Tests
- HIV test
- HBsAg
- HCV (antibodies & RNA)
- Urine drug screen
  - Opiates
  - Amphetamines
  - Barbiturates
  - Benzodiazepines
  - Cocaine
  - Cannabinoids
- Urine or breathalyzer alcohol screen
- Serum pregnancy test (for females only)
- FSH (for postmenopausal females only)
- Prothrombin INR (HI patients only)

* Serum chemistry tests will be performed after at least an 8-hour fast; however, in case of dropout or rechecks, subjects may not have fasted for 8 hours before the serum chemistry sample is taken.
** At screening, creatinine clearance will be calculated using Cockcroft-Gault formula.
*** If urinalysis is positive for protein, blood, nitrite and/or leukocyte esterase, a microscopic examination (red blood cell, white blood cell, bacteria, casts, and, epithelial cells) will be performed.

10.1.6 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 unfavorable 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 allocated subjects only, all adverse events that occur after the consent form is signed but before enrollment 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 enrollment 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 10.1.6.3.1. The Investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

10.1.6.1 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. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

10.1.6.2 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 enrollment 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 enrollment 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. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Pregnant partners of male subjects will not be followed.

10.1.6.3 Immediate Reporting of Adverse Events

10.1.6.3.1 Serious Adverse Events

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

- Death
- Immediately life threatening
- Persistent or significant disability/incapacity
- Inpatient hospitalization or prolongation of hospitalization
- Congenital anomaly/birth defect
- 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 serious adverse events to meet certain local requirements. Therefore, these events are considered serious by the Sponsor for collection purposes.

- Cancer
- Overdose

Refer to Table 2 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until enrollment, 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 enrollment 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. 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.

10.1.6.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as ECI and must be reported to the Sponsor.

For the time period beginning when the consent form is signed until enrollment, 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 enrollment 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. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Events of clinical interest for this trial include:

- an overdose of Sponsor's product, as defined in Section 10.1.6.1 that is not associated with clinical symptoms or abnormal laboratory results.

- For healthy control subjects:, an elevated AST or ALT laboratory value that is greater than or equal to three times (3X) the upper limit of normal (ULN) and an elevated total bilirubin laboratory value that is greater than or equal to 2X the ULN and, at the same time, an alkaline phosphatase laboratory value that is less than 2X the ULN, 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 may require 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.

  For healthy control subjects, 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.

- For subjects with HI:

  AST and ALT:

  - In subjects with baseline AST or ALT <2 x ULN – AST or ALT ≥5 x ULN;
  - In subjects with baseline AST or ALT ≥2 x ULN but <5 x ULN – AST or ALT >3 x the baseline level;
  - In subjects with baseline AST or ALT ≥5 x ULN – AST or ALT >2 x the baseline level or any AST or ALT value >20 x ULN.

  Total bilirubin:

  - In subjects with baseline total bilirubin <1.5 mg/dL – total bilirubin >2.0 mg/dL;
  - In subjects with baseline total bilirubin ≥1.5 mg/dL but ≤3.0 mg/dL – total bilirubin ≥2 x the baseline level;
  - In subjects with baseline total bilirubin >3.0 mg/dL – total bilirubin ≥2 x baseline level or any total bilirubin value >10 mg/dL.

  *Note: The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

10.1.6.4 Evaluating Adverse Events

An Investigator who is a qualified physician will evaluate all adverse events with respect to the elements outlined in Table 2. The Investigator's assessment of causality is required for each adverse event. Refer to Table 2 or instructions in evaluating adverse events.

Table 2: Evaluating Adverse Events

Maximum Intensity (Severity)	**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 is any adverse event occurring at any dose or during any use of Sponsor's product that:	
	None	
	†**Death**; or	
	†**Immediately 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	
	†**Persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Inpatient hospitalization or prolongation of 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 [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse event.); or	
	†**Congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis); or	
	Cancer; or	
	Overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. 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 event 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	The action taken is in reference to the either the Sponsor's Product or the Interacting Drug. Did the adverse event cause the Sponsor's product or the Interacting Drug to be:	
	None	
	Reduced	
	Interrupted	
	Discontinued	
	Increased	
	Not Applicable	
	Unknown	

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 adverse event form, ensures that a medically qualified assessment of causality was done. This initialled 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.	
Relationship to Sponsor's Product (continued)	**The following components are to be used to assess the relationship between the Sponsor's product and the adverse event**; 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 adverse event follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the adverse event compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the adverse event not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors
	Dechallenge	Was the Sponsor's product discontinued or dose/exposure/frequency reduced? If yes, did the adverse event 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 adverse event resulted in death or permanent disability; (2) the adverse event 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 adverse event 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 adverse event 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 U.S. CLINICAL MONITOR AND THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the adverse event 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).
Related (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 adverse event onset relative to the administration of the Sponsor's product is reasonable. The adverse event is more likely explained by the Sponsor's product than by another cause.
Not Related (there is not a reasonable possibility of Sponsor's product relationship)	Subject did not receive the Sponsor's product OR temporal sequence of the adverse event onset relative to administration of the Sponsor's product is not reasonable OR there is another obvious cause of the adverse event. (Also entered for a subject with overdose without an associated adverse event.)

10.1.6.5 Sponsor Responsibility for Reporting Adverse Events

All adverse events will be reported to regulatory authorities, IRB or independent ethics committees (IECs), and Investigators in accordance with all applicable global laws and regulations.

10.2 Pharmacokinetic Assessment

10.2.1 Blood Sampling and Processing

For all subjects, blood samples for the determination of MK-8931 plasma concentration and protein binding (optional) will be collected and processed according to Appendix 4 and Appendix 5, respectively, at scheduled time points as delineated in the Study Events Flow Chart (Section 6).

The allowable deviation window is as follows:

Table 3: Time Deviation Window Allowed for Blood Sampling

Sample collection time	Allowed deviation
0.0 – 8.0 hour	≤± 2 minutes
>8.0 – 24.0 hour	≤± 5 minutes
>24.0 – 72.0 hour	≤± 10 minutes
>72.0 – 120.0 hour	≤± 15 minutes

10.3 Planned Genetic Analysis Sample Collection

Sample collection, storage and shipment instructions for Planned Genetic Analysis samples are provided in Appendix 3.

10.4 Future Biomedical Research Samples

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

- DNA for future research.

10.5 Blood Volume Drawn for Study Assessments

Table 4: Blood Volume During the Study

Sample Type	Number of Time Points	Approximate Volume per Time Point * (mL)	Approximate Sample Volume Over Course of Study (mL)
Screening laboratory safety tests (including hematology, serum chemistry, and serology), FSH (for postmenopausal female subjects only) and serum pregnancy (for female subjects only).	1	12.5	12.5
Screening PT/INR (for HI patients only)	1	4.5	4.5
Blood for Planned Genetic Analysis	1	8.5	8.5
On-study hematology and serum chemistry (includes serum pregnancy when scheduled at the same time)	2	12.5	25 **
Blood for MK-8931 concentrations	14	4	56
Blood for MK-8931 protein binding	3	10	30
Total Blood Volume for Subjects with Hepatic Insufficiency (mL)→			136.5 **, §
Total Blood Volume for Healthy Subjects (mL)→			132 **, §

* Represents the largest collection tube that may be used for this (a smaller tube may be used).

** An additional hematology and serum chemistry test will be performed in the event of early termination; therefore an additional 12.5 mL may be collected.

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

11 DATA ANALYSIS

11.1 Pharmacokinetic Parameters

Pharmacokinetic parameters for plasma MK-8931 will be calculated as follows:

AUC0-last:	Area under the concentration versus time curve, from 0 to the time of the last quantifiable (above LLOQ) sample.
AUC0-∞:	Area under the concentration versus time curve from 0 to infinity after single dosing.
AUC0-24hr:	Area under the concentration versus time curve, from 0 to 24 hours after dosing.
C24hr:	Plasma concentration at 24 hours.
CL/F:	Apparent clearance after extravascular administration.
Cmax:	Maximum observed plasma concentration after the administration of a given dose.
fu:	Fraction of unbound drug in plasma.
Tmax:	Time to maximum observed plasma drug concentration.
t½:	(Apparent) terminal half-life.
Vz/F:	Apparent volume of distribution during the terminal phase after extravascular administration.

No value for AUC0-∞, CL/F, Vz/F, or apparent terminal t½ will be reported for cases that do not exhibit a terminal log-linear phase in the concentration versus time profile.

Additional pharmacokinetic parameters may also be calculated for MK-8931 plasma protein binding in terms of unbound concentrations (e.g., Cmax_u, AUC0-∞_u, CLu/F).

11.2 Statistical Methods

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Pharmacology Sciences department at Celerion.

If, after the study has begun, changes are made to the statistical analysis plan stated below, then these deviations to the plan will be listed, along with an explanation as to why they occurred, in the Clinical Study Report (CSR).

Additional statistical analyses, other than those described in this section, may be performed if deemed appropriate.

11.2.1 Determination of Sample Size

The precision estimates presented below are based on a between subject log scale standard deviation estimate for MK-8931 AUC0-∞ and Cmax of 0.267 and 0.269, respectively, as observed in MK-8931 Protocol 023, the only study in which the preliminary market formulation has been administered and rich pharmacokinetic data are available.

AUC0-∞: With a sample size of 8 subjects with moderate hepatic insufficiency or N=8 with mild hepatic insufficiency (if Part 2 is conducted) and 8 subjects in the healthy control group, the half width of the 90% confidence interval for the AUC0-∞ geometric mean ratio (GMR; HI/healthy) on the log scale will be 0.24. The lower and upper 90% confidence limits for the GMR will be given by OBS/1.27 and OBS*1.27, where OBS is the observed GMR. Thus, if the observed AUC0-∞ GMR is 1.50, the 90% confidence interval would be [1.18, 1.91].

Cmax: With a sample size of 8 subjects with moderate hepatic insufficiency or N=8 with mild hepatic insufficiency (if Part 2 is conducted) and 8 subjects in the healthy control group, the half width of the 90% confidence interval for the Cmax GMR (HI/healthy) on the log scale will be 0.24. The lower and upper 90% confidence limits for the GMR will be given by OBS/1.27 and OBS*1.27, where OBS is the observed GMR. Thus, if the observed Cmax GMR is 1.50, the 90% confidence interval would be [1.18, 1.91].

11.2.2 Subjects to Analyze

The decision as to which plasma samples collected will be assayed for evaluation of pharmacokinetics will be collaboratively determined by the Departments of Pharmacokinetics, Pharmacodynamics, and Drug Metabolism and the appropriate department within Early-Stage Development. If indicated, these samples may also be assayed and/or pooled for assay in an exploratory manner for metabolites.

The following populations are defined for the analysis and reporting of data. All subjects will be reported, and their data analyzed, according to the treatment they actually received.

All Subjects as Treated: All subjects who received at least one dose of the investigational drug. This population will be used for assessments of safety and tolerability.

Per-Protocol: The set of data generated by the subset of subjects who comply with the protocol sufficiently to ensure that these data will be likely to exhibit the effects of treatment, according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements and absence of major protocol deviations. Any subjects or data values excluded from analysis will be identified, along with their reason for exclusion, in the CSR. At the end of the study, all subjects who are compliant with the study procedure as aforementioned and have available data will be included in the primary analysis dataset. This population will be used for the pharmacokinetic analyses.

11.2.3 Descriptive Statistics

Individual values will be listed for each plasma pharmacokinetic parameter 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

coefficient of variation (CV) (calculated as 100 x standard deviation/arithmetic mean), median, minimum, maximum, geometric mean, and geometric percent CV (calculated as 100 x sqrt(exp(s^2) - 1), where s^2 is the observed variance on the ln-scale). For Tmax, only median, minimum, and maximum will be provided.

11.2.4 Analysis Overview

Pharmacokinetics

Part 1:

Individual AUC0-∞ values of MK-8931 after single-dose administration of 40 mg MK-8931 to subjects with moderate HI and healthy matched control subjects enrolled in Part 1 will be ln-transformed and evaluated with an ANCOVA model. The ANCOVA model will contain a categorical factor for population (subjects with moderate HI, healthy matched control subjects) and gender, and continuous covariates age and BMI. Gender will be included only if there are at least three males and three females from each population. A 90% confidence interval for the AUC0-∞ difference in least-squares means (subjects with moderate HI - healthy matched control subjects) will be computed from the model. These confidence limits will then be exponentiated to obtain a confidence interval for the GMR of AUC0-∞ (subjects with moderate HI / healthy matched control subjects).

The pharmacokinetic condition to initiate Part 2 of the study will be met if the point estimate for the AUC0-∞ ratio of geometric means (subjects with moderate HI / healthy matched control subjects) exceeds 1.5.

AUC0-last, AUC0-24hr, Cmax, and C24hr, will be analyzed in a similar fashion as AUC0-∞.

Part 2:

If Part 2 is conducted, the pharmacokinetic parameters of MK-8931 after single-dose administration of 40 mg MK-8931 to subjects with mild HI and healthy control subjects matched to subjects with mild HI (from Part 1 and/or Part 2, as applicable) will be analyzed in a similar fashion as the pharmacokinetic parameters in Part 1.

Parts 1 and 2:

Plots of the individual values of AUC0-∞, AUC0-last, AUC0-24hr, Cmax, and C24hr for each population will be provided.

11.2.5 Other Analyses

The relationship between MK-8931 pharmacokinetics and hepatic insufficiency may be examined in an exploratory manner via a scatter plot of MK-8931 AUC0-∞ versus the Child-Pugh score, including the data from subjects with moderate HI and, if conducted, subjects with mild HI, and healthy subjects as reference.

Relationships between MK-8931 AUC0-∞ and the baseline laboratory components of the Child-Pugh score (i.e., bilirubin, albumin levels, and prothrombin time) may also be assessed graphically.

11.3 Safety Evaluation

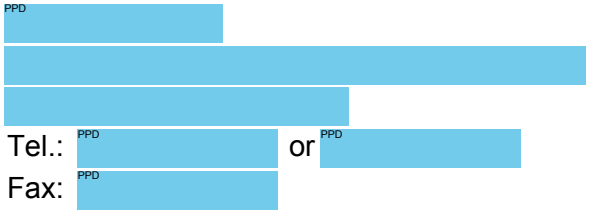
The safety and tolerability of MK-8931 will be evaluated by clinical assessment of adverse events and other safety measurements. Summary statistics for the laboratory safety tests, ECGs, and/or vital signs may also be computed and provided, as deemed clinically appropriate.

12 STUDY ADMINISTRATION

12.1 Ethics

12.1.1 Institutional Review Board

This protocol will be reviewed by an IRB and the study will not start until the IRB has approved the protocol or a modification thereof. The IRB is constituted and operates in accordance with the principles and requirements described in the US Code of Federal Regulations (21 CFR Part 56). The IRB is with the International Conference on Harmonization (ICH) compliant and may be reached at:



12.1.2 Ethical Conduct of the Study

This research will be carried out in accordance with the protocol, US Code of Federal Regulations, Good Clinical Practices (GCP), 21 CFR Parts 50, 56, and 312, the ethical principles set forth in the Declaration of Helsinki, and the ICH harmonized tripartite guideline regarding GCP (E6 Consolidated Guidance, April 1996).

12.1.3 Subject Information and Consent

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

Subjects will be given a copy of their ICF.

The initial ICF, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB approval/favorable opinion in advance of use. The subject 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.

The informed consent will adhere to IRB/Ethics Research Committee (ERC) requirements, applicable laws and regulations and Sponsor requirements.

12.1.4 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.

12.2 Termination of the Study

Celerion, the Investigator, and/or Merck reserve the right to terminate the study in the interest of subject welfare.

12.2.1 Clinical Criteria for Early Trial Termination

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

12.3 Data Quality Assurance

Standard operating procedures are available for all activities performed at Celerion relevant to the quality of this study. Designated personnel of Celerion will be responsible for implementing and maintaining quality assurance and quality control systems to ensure that the trial is conducted, and that data are generated, documented and reported in compliance with the study protocol, GCP and Good Laboratory Practice requirements as well as applicable regulatory requirements and local laws, rules and regulations relating to the conduct of the clinical study.

The CSR will be audited by the quality assurance (QA) department and the QA audit certificate will be included in the study report.

All clinical data will undergo a 100% quality control check prior to clinical database lock. Edit checks are then performed for appropriate databases as a validation routine using SAS® to check for missing data, data inconsistencies, data ranges etc. Corrections are made prior to database lock.

Case Report Forms (CRFs) are printed off directly from the database. Each CRF is reviewed and signed by the Investigator.

12.4 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 will be outlined in Celerion Data Management Plan.

12.5 Direct Access to Source Data/Documents

Celerion will ensure that the Sponsor, IRB and inspection by domestic and foreign regulatory authorities will have direct access to all trial-related sites, source data/documents, and reports for the purpose of monitoring and auditing (ICH[E6] 5.1.2 & 6.10). In the event that other trial-related monitoring should be done by other parties, they will be required to sign a confidentiality agreement prior to any monitoring and auditing.

12.6 Drug Supplies, Packaging and Labeling

The Sponsor will supply sufficient quantities of the study formulations to allow completion of this study. The lot numbers and expiration dates (where available) of the drugs supplied will be recorded in the final report.

Records will be made of the receipt and dispensing of the drugs supplied. At the conclusion of the study, any unused MK-8931 drugs will be returned to the Sponsor unless otherwise specified by the Sponsor. If no supplies remain, this fact will be documented in the pharmacy product accountability records.

12.7 Data Handling and Record Keeping

Celerion's Merck library CRFs will be supplied.

12.8 Report Format

According to the ICH Harmonized Tripartite Guideline (Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use M4 and the ICH M2 Expert Working Group), the final report will be written according to the ICH E3 Guideline (Structure and Content of Clinical Study Reports).

12.9 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 GCP (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 Appendix 1.

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 GCP 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 GCP 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 [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.

12.10 Publication Policy

The Sponsor will provide separate guidance on the criteria for publication of clinical trial data when contacted for permission to publish.

12.11 Privacy Notice

In order to comply with government regulations governing clinical studies, as well as ICH GCP 3.2.1, Merck & Co., Inc., and its corporate affiliates ("Sponsor"), is required to record the name and address of each IRB or IEC member that reviews and approves this study. The Sponsor is also required to document that each IRB or 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 (ICH GCP 8.2.8).

13 REFERENCES

1 National Institute of Health, National Institute on Aging, Alzheimer's disease education and referral center, Alzheimer's disease fact sheet [online], 2015.

2 Mangoni AA and Jackson SHD. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. Br J Clin Pharmacol. 2004; 57(1): 6–14.

3 FDA Draft Guidance: Pharmacokinetics in Patients With Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling. 2003.

4 Pugh RNH, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the esophagus for bleeding esophageal varices. Brit J Surg 1973;60(8):646-649.

Appendix 1: 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.

Appendix 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 10.4 – 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. CRF Documentation for Future Biomedical Research Specimens

Documentation of subject consent for Future Biomedical Research will be captured in the Case Report Forms (CRFs). 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 (PPD). 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 PPD

13. References

1. National Cancer Institute: http://www.cancer.gov/dictionary/?searchTxt=biomarker
2. International Conference on Harmonization Guidance: DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES E15; http://www.ich.org/LOB/media/MEDIA3383.pdf
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

Appendix 3: PAXgene™ Blood for DNA Analysis

Clinical Biomarker Specimen Management

Business Confidential use only

Merck Research Laboratories

SCP-124-00

PAXgene™ BLOOD FOR DNA ANALYSIS SPECIMEN COLLECTION PROCEDURE

SPECIMEN COLLECTION NOTES*

***NOTE**: Refer to protocol flow chart or Specimen Collection Overview Chart for scheduled collection time points.

***NOTE:** Collection of specimens from vascular access devices and heparin or saline locks is not recommended due to the potential for specimen contamination. This specimen should be collected as a peripheral blood draw.

Supplies and Materials (per patient, per time point)

Provided to the Institution

- Requisition form/card
- "PAXgene Blood DNA" labels
- One 8.5 mL PAXgene™ Blood DNA collection tube (Cat#761115)

Precautions

*** SAFETY PRECAUTION:** Contents of the PAXgene™ tube are irritating to skin. Wear disposable gloves, safety glasses or goggles and a laboratory coat and follow standard laboratory safety procedures while working with these tubes. If inhaled, supply fresh air; consult doctor in case of complaints. If skin contact, immediately wash with water and soap, and rinse thoroughly. If contents make eye contact, rinse opened eye for 15 minutes under running water, then consult a doctor. If swallowed, immediately call a doctor.

Required Equipment

- Freezer for -20°C for PAXgene™ tube storage (For storage exceptions/monthly batch shipments).

Clinical Biomarker Specimen Management

Business Confidential use only

Merck Research Laboratories

SCP-124-00

Labeling

1. Place patient-specific label on the PAXgene Blood DNA tube.
2. If required: Fill out the requisition form/card appropriately (ensure that you follow specific processing instructions per the protocol specific Laboratory Procedure Manual).

Preparation

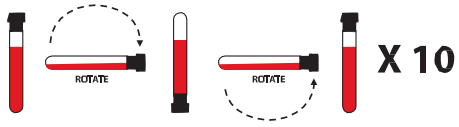
1. Ensure the patient has signed the appropriate IRB/ERC-approved consent for genetic specimen collection prior to collecting the specimen.
2. Ensure the PAXgene™ Blood DNA collection tubes are at room temperature prior to collecting blood.

***NOTE:** Do not use tubes after the expiration date printed on the label.

3. The PAXgene™ Blood DNA collection tubes should not be the first tubes drawn during venipuncture. **It should be the last tube collected**.

Specimen Collection

1. Collect blood into each PAXgene™ Blood DNA collection tube via your institution's recommended standard procedure for venipuncture.
    - Ensure that the blood has stopped flowing into the tube before removing the tube from the holder.
    - Each tube holds approximately 8.5 mL of blood.
    - Under-filling of the tubes could result in an incorrect blood-to-additive ratio and may lead to poor performance (e.g. poor quality or low quantity)
2. Immediately after collection, completely and gently invert the tube 10 times to mix uniformly.



***NOTE: After each tube is collected, it is CRITICAL to gently invert PAXgene™ 10 times to ensure proper mixing of blood & PAXgene™ proprietary reagent.**

Clinical Biomarker Specimen Management

Business Confidential use only

Merck Research Laboratories

SCP-124-00

Specimen Processing & Handling

1. Within 5-10 minutes of the blood draw, place tubes upright in a wire or hard plastic rack at ambient temperature (18-25°C).

2. Tubes **must be shipped within 24 hrs of collection** to the laboratory at ambient temperature.

Storage Exceptions (special circumstances only)

If storing specimens for batch shipment: Specimen tubes MUST be transferred to a -20°C freezer, in a wire or hard plastic rack in the upright position, after collection. **Specimen tubes may be stored frozen upright at -20°C for no longer than 4 weeks at -20°C.** Tubes stored at -20°C must be shipped on dry ice to the Laboratory.

***NOTE**: Any storage time and temperature excursions must be documented and communicated upon specimen shipment within the shipment inventory documents.

***NOTE:** Frozen PAXgene™ Blood DNA collection tubes are subject to breakage on impact. To reduce the risk of breakage during handling and shipment, frozen tubes should be treated in the same manner as glass tubes. If freezing is required, a wire or hard plastic rack should be used (**NO STYROFOAM**) as the tubes may crack.

Clinical Biomarker Specimen Management

Business Confidential use only

Merck Research Laboratories

SCP-124-00

Packaging and Shipping

1. It is the responsibility of the primary investigator to ensure that all staff personnel who will be handling, packaging, and/or shipping clinical specimens are trained and certified as required by National and International regulations and they ship materials in accordance with all current regulations relating to the handling and shipping of hazardous goods.

2. Follow packing and shipping instructions for **AMBIENT** shipments.

3. Contact shipping courier to obtain any required documentation/forms required for shipment.

4. Ship to the Laboratory **within 24 hr of the blood draw**.

5. **Shipping schedule** – Select overnight or priority delivery and ensure that shipments are received at the destination vendor Monday through Friday, except on U.S. holidays. Shipments can be received on Saturday with advanced notification. **Contact the Vendor if you are uncertain about the shipping or receiving schedule.**

***NOTE:** For storage exceptions where ambient shipment was not possible, and specimens were frozen (-20°C), always ship frozen specimens on DRY ICE.

Shipping Address:
BioProcessing Solutions Alliance
Attn: CommStaff
Nelson Biological Laboratories
604 Allison Road, C120
Piscataway, New Jersey 08854, USA
Tel: PPD
Fax: PPD
Email: PPD

Appendix 4: Procedures for the Collection Handling, Storage and Shipping of MK-8931 Pharmacokinetic Samples

Supplies and Equipment

1. Plastic Lavender Topped Vacutainers Containing K_2EDTA as the anticoagulant: Capable of holding 4 mL of whole blood. (e.g., Vacutainer #367861 or Fisher #02-683-99C)

2. Sample Tubes: 3.6 mL NUNC Cryotube starfoot, 12.5x72mm Internal thread; screw cap, Polypropylene Sterile (Fisher Part # 10070731 or NUNC Part # 379189)

   Note: *These tubes (3.6 mL NUNC cryotubes) should not be substituted by other tubes based on the proper functioning of the automated liquid handling system. Substitution of tubes results in (strong) delays.*

3. Centrifuge: Capable of rotating between 1000-3000 RCF (x g) for 10 minutes. Note that RCF varies according to the centrifuge rotor radius. The formula for computing RCF from rotation speed and centrifuge radius is RCF = $11.2r(RPM/1000)^2$, where r is rotor radius, in cm, and RPM is the rotations per minute setting of the centrifuge. A typical refrigerated centrifuge (GH-3.8 model from Beckman) yields 1150 RCF at 2500 RPM, for example.

4. -20 ± 10°C Sample Storage Freezer

Collection of Blood

For specific time points of sample collection, please refer to the Study Flow Chart (Section 6).

Sample Labeling

1. Whole Blood Samples. Vacutainers containing whole blood should be labeled (non-barcoded) as appropriate.

2. Plasma Samples. NUNC tubes containing plasma samples should be labeled with the pre-printed barcoded labels with the allocation number, day, date and time (hours postdose) provided by the Sponsor. Labels should be vertically attached and placed on the NUNC tubes toward the top of the tube in order for the level of plasma in the tube to be viewed. Preferably only **one (1)** layer of label should be placed on the tube (not 2). This is critical for the proper functioning of the automated liquid handling station.

Procedure

1. Draw approximately 4 mL whole blood into plastic (PET) vacutainer containing K_2EDTA as the anticoagulant and invert 6 times. The vacutainer should be labeled as appropriate (see above).

2. Immediately after collection, the blood containing tubes should be placed in an ice bath and centrifuged promptly between 1000-3000 RCF (x g) for 10 minutes. A refrigerated (4 to 10°C) or non-refrigerated centrifuge may be used. Note that RCF varies according to the centrifuge rotor radius. The formula for computing RCF from rotation speed and

centrifuge radius is RCF = 11.2r (RPM/1000)^2, where r is rotor radius, in cm, and RPM is the rotations per minute setting of the centrifuge. If the samples cannot be centrifuged immediately, the tubes should be kept in an ice bath and centrifuged within 30 minutes of collection.

Note: *Be sure to account for rotor size variations by adjusting the revolutions per minute (RPM) for the specific centrifuge to yield between 1000-3000 RCF (xg) as noted in the Supplies and Equipment section.*

3. Immediately after separation of the whole blood, carefully transfer 1.0-2.0 mL plasma into a 3.6 mL NUNC cryotube identified with pre-printed barcoded labels (see above) and store at -20 ± 10°C until transfer to the analytical laboratory on DRY ICE.

   Note(s): *In the event that the whole blood samples cannot be processed immediately the samples should be kept in an ice bath. No more than 60 minutes should elapse between blood draw and the freezing of plasma samples.*

Sample Shipping

Sample Preparation for Shipment

- Samples are to be packaged and prepared for shipment in compliance with US Department of Transportation, Nuclear Regulatory Commission, International Air Transport Association, international, state, local, and any other applicable regulations

- Sort samples by subject (all samples from one subject together) and arrange in sequence according to collection time. As appropriate, samples should be placed in grid boxes and bundled together and placed in freezer/plastic bags. Small vials vulnerable to leakage or damage should be placed in divided trays or boxes.

- Enclose a detailed specimen inventory, sealed in a Zip-Loc™ bag (or equivalent brand), in the shipment box:

  Specimen Inventory Sheet/Form/Log

  The following information will be included on the specimen inventory sheet/form/log which will accompany the sample shipment:

  - MK number
  - Study number
  - Randomization number
  - Period
  - Nominal time
  - Specimen type
  - Date(s) of sample collection
  - Total number of samples in shipment
  - Merck barcodes (if feasible)

- For frozen samples, there must be sufficient temperature maintenance material (e.g., dry ice, icepack) to maintain the samples in a frozen state for at least 72 hours. All shipments will be made in freezer boxes containing sufficient DRY ICE.

- It is the responsibility of the primary investigator to ensure that all staff personnel who will be handling, packaging, and/or shipping clinical specimens act in conformance with International Air Transport Association (IATA) regulations, US Department of Transportation, Nuclear Regulatory Commission, International Air Transport Association, international, state, local, and any other applicable regulations relating to the handling and shipping of hazardous goods.

- Shipments should be sent on MONDAY or TUESDAY (unless prior approval from SPONSOR to ship WEDNESDAY) to assure receipt by FRIDAY.

- Samples should be sent at intervals to be determined by the Sponsor and the investigator. Samples should be shipped using World Courier. The Shipment address is:

- **SAMPLES Shipping Address**

  Analytical Laboratory
  Pharma Medica Research Inc.
  6100 Belgrave Road
  Mississauga, Ontario, Canada
  L5R 0B7
  Tel.: PPD
  Fax: PPD
  PPD
  E-mail: PPD

  Note: Sample storage for this study is -20 ± 10°C.

- The following papers are to accompany the shipment:
  - Airway Bill
  - Specimen Inventory

- Notify recipient noted above, Early Clinical Scientist (ECS), and Clinical Research Associate (CRA) by FAX or email, immediately after the samples leave your premises. Provide the following information in the FAX or email:

  - MK/protocol number
  - Randomization number
  - Name of courier or transport company.
  - Name of contact at shipment point of origin
  - Time and date the shipment left your premises.
  - A copy of the Airway Bill.

- Upon arrival, the shipment will be unpacked, and the contents documented. The individual responsible at the shipment point of origin will be notified as to sample disposition.

These procedures may be altered with an administrative letter from the Sponsor.

Appendix 5: Sample Handling Instructions for MK-8931 Protein Binding

In Vitro Protein Binding Plasma Assay — Sample Collection, Handling, Labeling, Storage, and Shipment

Blood for In Vitro Protein Binding

1. Collection of Blood

   For specific time points of sample collection, please refer to the Study Flow Chart (Section 6).

2. Sample Labeling

   Spray-dried EDTA VACUTAINER tubes should be labeled with allocation number, period, day, date, and actual time (hours postdose). Bar-coded labels will also be provided by Sponsor for plasma samples.

3. Procedures

   a. Collect 10 mL of whole blood in a K_2EDTA (lavender-top) tube or equivalent, either by venipuncture or saline-lock.

   b. Centrifuge for 15 minutes at 3000 rpm at 4°C, remove the plasma and transfer to 3.6-cc NUNC cryotubes or equivalent (2 aliquots per subject). If centrifugation cannot be performed immediately, the blood-containing tubes should be placed in an ice bath.

   c. All plasma samples should be immediately placed into a -80±15°C or lower freezer and stored frozen at -80±15°C or lower until transfer to Merck on DRY ICE.

      Blood should be centrifuged and all plasma separated and frozen within 30 minutes from the time the blood is drawn. The entire process from collection to separation of the plasma must be done as carefully as possible to minimize hemolysis of red blood cells and release of proteases, which can complicate sample analysis.

4. Shipping Procedures for In Vitro Protein Binding Plasma (Archive)

   All shipments will be made in freezer boxes containing sufficient DRY ICE and labeled as HUMAN SAMPLES. Ship tube(s) in a leak-proof plastic bag.

   Please include a sample inventory sheet with each shipment.

   Call or fax the Sample Receipt Department at Merck Research Laboratories when the shipment has been made and give the appropriate airbill number. Fax: PPD Tel.: PPD

   Shipment should be sent on MONDAY or TUESDAY to assure receipt by Friday.

Ship for next-day delivery to:

PPD

MRL, Division of Merck & Co., Inc.
770 Sumneytown Pike
Building No. 75B, LAB 1210
West Point, Pennsylvania 19486, USA

Note: *Sample storage for this study is -80±15°C or lower.*

These procedures may be altered with an administrative letter from the Sponsor.