Official Protocol Title:	A 2-part, open-label, single-dose study to investigate the influence of hepatic impairment on the pharmacokinetics of MK-8189
NCT number:	NCT04676425
Document Date:	09-Feb-2021

Title Page

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Protocol Title: A 2-part, open-label, single-dose study to investigate the influence of hepatic impairment on the pharmacokinetics of MK-8189

This protocol amendment is applicable only to the United States.

Protocol Number: 012-01

Compound Number: MK-8189

Sponsor Name:

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
(hereafter referred to as the Sponsor or MSD)

Legal Registered Address:

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Regulatory Agency Identifying Number(s):

IND	118,986

Approval Date: 09 February 2021

Sponsor Signatory

Typed Name:
Title:

Date

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

Investigator Signatory

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

Typed Name:
Title:

Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 01/ Site 0001 Specific Amendment	09-FEB-2021	The protocol was amended to (1) include the site 0001-specific requirement of inclusion of the C-SSRS as required by the IRB for site 0001, (2) amend the Child-Pugh classification of the severity of disease, and (3) clarify the primary endpoints of the trial. Changes to the contraceptive language and QTC interval criteria were also updated to align with FDA feedback on other MK8189 protocols.
Original Protocol	24-NOV-2020	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 01

Overall Rationale for the Amendments:

The protocol was amended to (1) include the site 0001-specific requirement of inclusion of the C-SSRS as required by the IRB for site 0001, (2) amend the Child-Pugh classification of the severity of disease, and (3) clarify the primary endpoints of the trial. Changes to the contraceptive language and QTC interval criteria were also updated to align with FDA feedback on other MK8189 protocols.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 3 Hypotheses, Objectives, and Endpoints 9.3 Hypotheses/Estimation	• Primary endpoints were updated to include only AUC0-inf and Cmax • Estimation for primary endpoints updated to include only AUC0-inf and Cmax • Exploratory PK objectives and endpoints (e.g. AUC0-24, C24, Tmax, CL/F, Vz/F and apparent terminal t½) were added	While the other PK parameter values will be reported as exploratory endpoints, only AUC0-inf and Cmax are considered primary endpoints
5.1 Inclusion Criteria	• Clarify language regarding WOCBP and abstinence	To align with FDA feedback on other MK-8189 protocols

Section # and Name	Description of Change	Brief Rationale
10.7 Appendix 7: Country/Site-specific Requirements	• Added the C-SSRS - Baseline Version and C-SSRS - Since Last Assessment Version to the schedule of activities as well as further explanation of monitoring procedures. • Exclusion criteria for healthy and hepatically impaired participants have both been updated for the standard C-SSRS and suicidality related text. • Added information on how safety data will be collected and reported based on addition of the standard C-SSRS.	Inclusion of site specific requirements for site 0001, per the request of IRB for site 0001 to include C-SSRS to evaluate participant safety. Standard information surrounding the C-SSRS were added and updated as a result.
10.9 Appendix 9 12-Lead Electrocardiogram Abnormalities	• Update QTc interval criteria	Update QTc interval criteria to align with exclusion criteria
10.11 Appendix 11 Child-Pugh classification of the severity of liver disease	• Added a footnote to Child-Pugh classification table in relation to assessment of ascites which indicates that if a participant has ascites controlled by 2 medications they may be assigned 2 points.	When diuretics are used to control ascites it is common for a combination of a potassium sparing and potassium wasting diuretics to be used to mitigate issues with potassium imbalance, thus the use of 2 medications may not necessarily indicate more severe ascites and 2 points, as opposed to 3 points, may be assigned based on the modified Child-Pugh classification method.
10.12 Appendix 12: Abbreviations	• Added C-SSRS as an abbreviation	Inclusion of the C-SSRS as a new abbreviation used throughout the document

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A 2-part, open-label, single-dose study to investigate the influence of hepatic impairment on the pharmacokinetics of MK-8189

Short Title: The effect of hepatic impairment on MK-8189 pharmacokinetics

Acronym: Not Applicable

Hypotheses, Objectives, and Endpoints:

The study population includes male and female participants with moderate and mild hepatic impairment between the ages of 18 and 75 (inclusive) and healthy controls.

Primary Objectives	Primary Endpoints
Part 1 - To compare MK-8189 pharmacokinetics after single dose administration of 4 mg MK-8189 to participants with moderate hepatic impairment and healthy control participants. - Estimation: The AUC0-inf and Cmax in participants with moderate hepatic impairment will be estimated and compared to those obtained from healthy control participants. Part 2 - To compare MK-8189 pharmacokinetics after single dose administration of 4 mg MK-8189 to participants with mild hepatic impairment and healthy control participants. - Estimation: The AUC0-inf and Cmax in participants with mild hepatic impairment will be estimated and compared to those obtained from healthy control participants in Part 1.	Part 1 and Part 2 - AUC0-inf and Cmax

Secondary Objectives	Secondary Endpoints
Part 1 - To evaluate the safety and tolerability of MK-8189 in patients with moderate hepatic impairment and in healthy control participants after single dose administration of 4 mg MK-8189. Part 2 - To evaluate the safety and tolerability of MK-8189 in patients with mild hepatic impairment after single dose. administration of 4 mg MK-8189.	Part 1 and Part 2 • Adverse experiences, laboratory safety tests, electrocardiograms and vital signs
Tertiary/Exploratory Objectives	**Tertiary/Exploratory Endpoints**
Part 1 and Part 2 - To investigate the relationship between CYP2C9 genetic polymorphisms and the PK of MK-8189. Genetic variation in CYP2C9 may be analyzed for association with any laboratory or clinical data collected in this study. - To explore the relationship between genetic variation and response to the treatment administered, and mechanisms of disease. Variation across the human genome may be analyzed for association with clinical data collected in this study. - To compare additional MK-8189 pharmacokinetic parameter values after single dose administration of 4 mg MK-8189 to participants with moderate hepatic impairment, mild hepatic impairment, and healthy control participants.	Part 1 and Part 2 - Germline genetic variation in CYP2C9 and association to clinical data collected in this study - Germline genetic variation and association to clinical data collected in this study. - AUC0-24, C24, Tmax, CL/F, Vz/F and apparent terminal t½

Overall Design:

Study Phase	Phase 1
Primary Purpose	Treatment
Indication	Treatment of schizophrenia
Population	Participants with hepatic impairment and healthy participants
Study Type	Interventional
Intervention Model	Parallel This is a multi-site study.
Type of Control	Healthy matched -control participants
Study Blinding	Unblinded Open-label
Blinding Roles	No Blinding
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 6 months from the time the first participant signs the informed consent until the last participant's last study-related telephone call or visit.

Number of Participants:

Approximately 16 participants will be allocated/randomized in Part 1; a minimum of 6 participants with moderate hepatic impairment and 6 healthy participants will complete Part 1. Approximately 8 participants will be randomized/allocated in Part 2.; a minimum of 6 participants with mild hepatic impairment will complete Part 2.

Intervention Groups and Duration:

<table>
<tr><td>Intervention Groups</td><td>
<table>
<tr><th>Intervention Group Name</th><th>Drug</th><th>Dose Strength</th><th>Dose Frequency</th><th>Route of Adminis-tration</th><th>Regimen/ Treatment Period/ Vaccination Regimen</th><th>Use</th></tr>
<tr><td>Moderate Hepatic Impairment Group</td><td>MK-8189</td><td>4 mg</td><td>Single dose</td><td>Oral</td><td>Part 1 Day 1</td><td>Experi mental</td></tr>
<tr><td>Healthy Matched Control Group</td><td>MK-8189</td><td>4 mg</td><td>Single dose</td><td>Oral</td><td>Part 1 Day 1</td><td>Experi mental</td></tr>
<tr><td>Mild Hepatic Impairment Group</td><td>MK-8189</td><td>4 mg</td><td>Single dose</td><td>Oral</td><td>Part 2 Day 1</td><td>Experi mental</td></tr>
</table>
</td></tr>
<tr><td>Total Number of Intervention Groups/ Arms</td><td>There will be up to 3 groups each containing up to 8 participants.</td></tr>
<tr><td>Duration of Participation</td><td>Each participant will participate in the study for approximately 42 days, from the time the participant signs the Informed Consent Form through the final contact. After a screening phase of 28 days, each participant will be receiving assigned intervention for approximately 1 day. After the end of treatment each participant will be followed for 14 days.</td></tr>
</table>

Study Governance Committees:

Steering Committee	No
Executive Oversight Committee	No
Data Monitoring Committee	No
Clinical Adjudication Committee	No
Insert Other Oversight Committee	No
Study governance considerations are outlined in Appendix 1.	

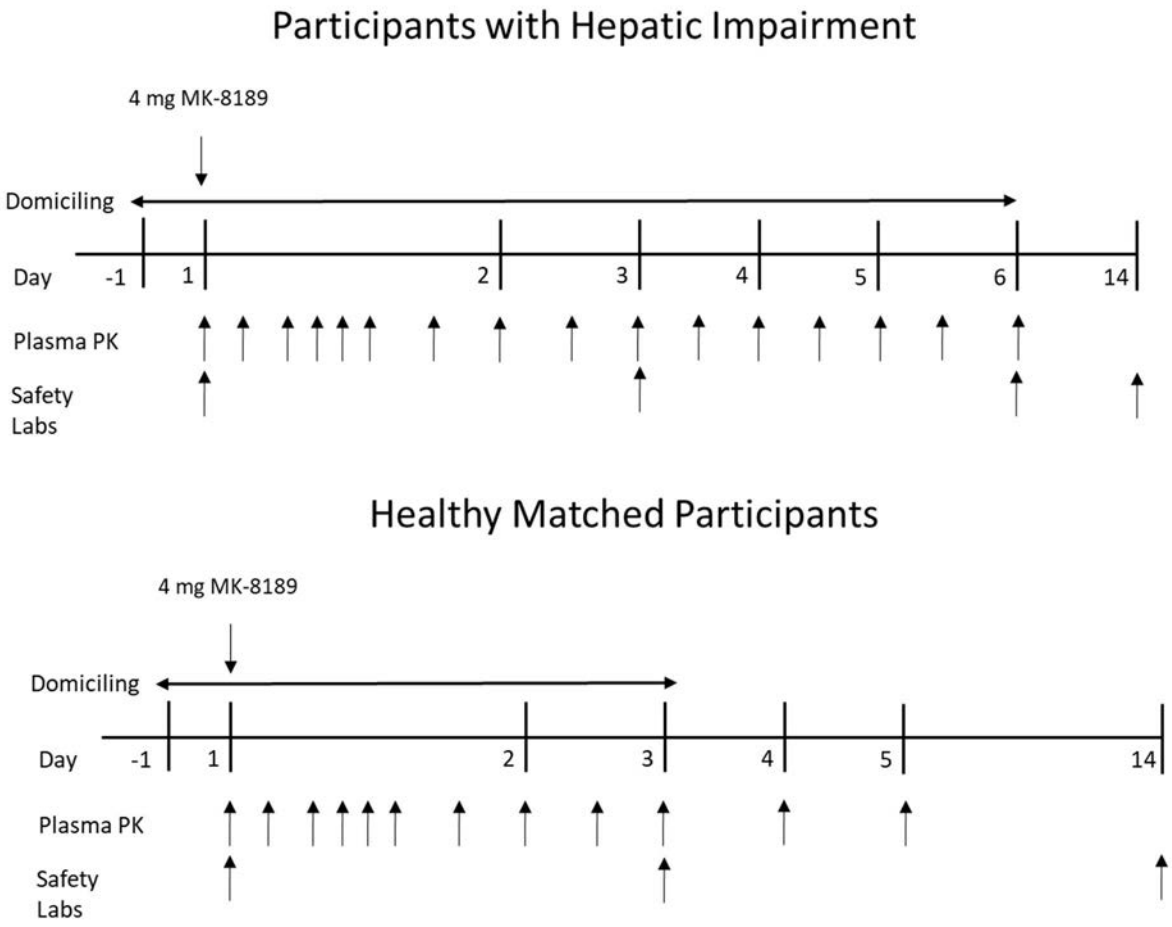
Study Accepts Healthy Volunteers: Yes

A list of abbreviations used in this document can be found in Appendix 12.

1.2 Schema

The study design is depicted in [Figure 1].

Figure 1 Study Design



1.3 Schedule of Activities

1.3.1 Hepatic Impairment Participants

Study Period:	Screening			Intervention																Post-study	Notes
Scheduled Day		-1	1	1	1	1	1	1	1	1	2	2	3	3	4	4	5	5	6	14	
Scheduled Hour	Screening	Check-in	Pre-dose	0	2	6	8	10	12	16	24	36	48	60	72	84	96	108	120	312	
Administrative Procedures																					
Informed Consent	X																				
Informed Consent for Future Biomedical Research	X																				
Participant Identification Card	X																				
Inclusion/Exclusion Criteria	X		X																		
Medical History	X																				Includes substance use (drugs, alcohol, tobacco and caffeine)
Prior/Concomitant Medication Review	X		X	X----------X																	*Refer to Section 8.1.5.*
Assignment of Screening Number	X																				*Refer to Section 8.1.6.*
Assignment of Treatment Number			X																		*Refer to Section 8.1.7*
Domiciling		X----------X																			*Refer to Section 8.1.11.*
Outpatient Visit	X																			X	
MK-8189 Administration				X																	To be dosed at approximately 8 AM

Study Period:	Screening			Intervention															Post-study	Notes
Scheduled Day		-1	1	1	1	1	1	1	1	1	2	2	3	3	4	4	5	5	6	14	
Scheduled Hour	Screening	Check-in	Pre-dose	0	2	6	8	10	12	16	24	36	48	60	72	84	96	108	120	312	
Standard Meals			X----------X																		Standard lunch and dinner will be provided at approximately 4 and 9 hours postdose, respectively. A snack will also be offered at approximately 12 hours postdose.
Safety Procedures																					
Full physical examination	X		X[a]																X		Directed PE may be performed at other times, at the Investigator's discretion. *Refer to Section 8.3.1.*
Height	X																				*Refer to Section 8.3.1.*
Weight	X																				BMI to be taken only at screening *Refer to Section 8.3.1.*
Vital Signs (heart rate, blood pressure)	X		X								X								X	X	*Refer to Section 8.3.2, Refer to Section 8.10.5 for timing*
Respiratory Rate	X		X																		*Refer to Section 8.3.2*
Body Temperature	X		X																		*Refer to Section 8.3.2*

Study Period:	Screening			Intervention																Post-study	Notes
Scheduled Day		-1	1	1	1	1	1	1	1	1	2	2	3	3	4	4	5	5	6	14	
Scheduled Hour	Screening	Check-in	Pre-dose	0	2	6	8	10	12	16	24	36	48	60	72	84	96	108	120	312	
12-lead ECG	X[b]		X[b]								X								X		*Refer to Section 8.3.3, Refer to Section 8.10.5 for timing*
Hepatitis B and C screen (per site SOP)	X																				
HIV-1, HIV-2 Screen	X																				
Serum/urine β-Human Chorionic Gonadotropin (β-hCG; WOCBP only)	X		X[a]																		Required for WOCBP. Serum or urine β-hCG at predose (per site SOP). Serum β-hCG required at Screening. *Refer to Section 10.2*
Serum FSH - (WONCBP only)	X																				For WONCBP. *Refer to Section 10.2 and 10.5*
Urine or Blood Drug Screen (UDS/BDS) (per site SOP)/alcohol screen	X		X[a]																		Any additional UDS/BDS and alcohol screen are conducted per site SOP. *Refer to Section 10.2*
Hematology, urinalysis, and chemistry	X		X[a]										X						X	X	*Refer to Section 8.3.4 and 10.2.*
INR Assessment	X																				
Assessment of Liver Function using Child-Pugh Classification	X																				*Refer to Section 5.1.2 and Appendix 11*

Study Period:	Screening			Intervention																Post-study	Notes
Scheduled Day		-1	1	1	1	1	1	1	1	1	2	2	3	3	4	4	5	5	6	14	
Scheduled Hour	Screening	Check-in	Pre-dose	0	2	6	8	10	12	16	24	36	48	60	72	84	96	108	120	312	
Creatinine Clearance Assessment	X		X																		*Refer to Section 5.2.2*
AE/SAE review	X----------																			X	*Refer to Section 8.4.*
Pharmacokinetics																					
Blood Collection for Plasma MK-8189			X[c]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		*Refer to Section 8.6.1*
Blood Collection for Plasma Protein Binding			X[c]																		*Refer to Section 4.2.1.2*
Biomarkers																					
Blood for Genetic Analysis			X																		Collect predose from enrolled participants only. *Refer to Section 8.8*

AE=adverse event; β-hCG=beta human chorionic gonadotropin; BDS=blood drug screen; FBR=future biomedical research; FSH=follicle stimulating hormone; ID=identification; SAE=serious adverse event; SOP=standard operating procedure; UDS=Urine Drug Screen
a. Pre-dose PE, urine drug screen, safety labs and pregnancy screen can be conducted/collected within 24 hours prior to study drug administration. Predose labs should be taken after an 8 hour fast. Results from predose safety labs and drug/alcohol screen must be reviewed prior to treatment allocation.
b. ECG measurements obtained in triplicate during Screening Visit and Day 1 pre-dose. All other measurements will be single measurements
c. Plasma for MK-8189 PK and plasma protein binding to be collected within 60 minutes prior to study drug administration.

1.3.2 Healthy Matched Participants

Study Period:	Screening			Intervention												Post-study	Notes
Scheduled Day		-1	1	1	1	1	1	1	1	1	2	2	3	4	5	14	
Scheduled Hour.	Screening	Check-in	Pre-dose	0	2	6	8	10	12	16	24	36	48	72	96	312	
Administrative Procedures																	
Informed Consent	X																
Informed Consent for Future Biomedical Research	X																
Participant Identification Card	X																
Inclusion/Exclusion Criteria	X		X														
Medical History	X																Includes substance use (drugs, alcohol, tobacco and caffeine)
Prior/Concomitant Medication Review	X		X	X----------												-X	*Refer to Section 8.1.5.*
Assignment of Screening Number	X																*Refer to Section 8.1.6.*
Assignment of Treatment Number			X														*Refer to Section 8.1.7.*
Domiciling		X----------											-X				*Refer to Section 8.1.11.*
Outpatient Vist	X													X	X	X	
MK-8189 Administration				X													To be dosed at approximately 8 AM
Standard Meals		X----------															Standard lunch and dinner will be provided at approximately 4 and 9 hours postdose, respectively. A snack will also be offered at approximately 12 hours postdose.

Study Period:	Screening			Intervention												Post-study	Notes
Scheduled Day		-1	1	1	1	1	1	1	1	1	2	2	3	4	5	14	
Scheduled Hour.	Screening	Check-in	Pre-dose	0	2	6	8	10	12	16	24	36	48	72	96	312	
Safety Procedures																	
Full physical examination	X		X[a]												X		Directed PE may be performed at other times, at the Investigator's discretion. *Refer to Section 8.3.1.*
Height	X																*Refer to Section 8.3.1.*
Weight	X																BMI to be taken only oat screening *Refer to Section 8.3.1.*
Vital Signs (heart rate, blood pressure)	X		X								X				X	X	*Refer to Section 8.3.2, Refer to Section 8.10.5 for timing*
Respiratory Rate	X		X														*Refer to Section 8.3.2*
Body Temperature	X		X														*Refer to Section 8.3.2*
12-lead ECG	X[b]		X[b]								X				X		*Refer to Section 8.3.3, Refer to Section 8.10.5 for timing*
Hepatitis B and C screen (per site SOP)	X																
HIV-1, HIV-2 Screen	X																
Serum/urine β-Human Chorionic Gonadotropin (β-hCG; WOCBP only)	X		X[a]														Required for WOCBP. Serum or urine β-hCG at predose (per site SOP). Serum β-hCG required at Screening. *Refer to Section 10.2*
Serum FSH - (WONCBP only)	X																For WONCBP. *Refer to Section 10.2 and 10.5*

Study Period:	Screening			Intervention												Post-study	Notes
Scheduled Day		-1	1	1	1	1	1	1	1	1	2	2	3	4	5	14	
Scheduled Hour.	Screening	Check-in	Pre-dose	0	2	6	8	10	12	16	24	36	48	72	96	312	
Urine or Blood Drug Screen (UDS/BDS) (per site SOP)/alcohol screen	X		X[a]														Any additional UDS/BDS and alcohol screen are conducted per site SOP. *Refer to Section 10.2*
Hematology, urinalysis, and chemistry	X		X[a]										X			X	*Refer to Section 8.3.4 and 10.2.*
Creatinine Clearance Assessment	X		X														*Refer to Section 5.2.1*
AE/SAE review	X----------															-X	*Refer to Section 8.4.*
Pharmacokinetics																	
Blood Collection for Plasma MK-8189			X[c]		X	X	X	X	X	X	X	X	X	X	X		*Refer to Section 8.6.1*
Blood Collection for Plasma Protein Binding			X[c]														*Refer to Section 4.2.1.2*
Biomarkers																	
Blood for Genetic Analysis			X														Collect predose from enrolled participants only. *Refer to Section 8.8*

AE=adverse event; β-hCG=beta human chorionic gonadotropin; BDS=blood drug screen; FBR=future biomedical research; FSH=follicle stimulating hormone; ID=identification; SAE=serious adverse event; SOP=standard operating procedure; UDS=Urine Drug Screen
a. Pre-dose PE, urine drug screen, safety labs and pregnancy screen can be conducted/collected within 24 hours prior to study drug administration. Predose labs should be taken after an 8 hour fast. Results from predose safety labs and drug/alcohol screen must be reviewed prior to treatment allocation.
b. ECG measurements obtained in triplicate during Screening Visit and Day 1 pre-dose. All other measurements will be single measurements
c. Plasma for MK-8189 PK and plasma protein binding to be collected within 60 minutes prior to study drug administration.

2 INTRODUCTION

2.1 Study Rationale

The liver is involved in the clearance of many drugs through a variety of oxidative and conjugative metabolic pathways and/or through biliary excretion of the unchanged drug or metabolites. Alterations of these excretory and metabolic activities by hepatic impairment can lead to drug accumulation. Hepatic disease can alter the absorption and disposition of drugs as well as their efficacy and safety.

Patients with schizophrenia have a higher incidence of co-morbid conditions and are at greater risk for multiple co-morbidities as compared to individuals without schizophrenia. Liver disease is among the co-morbidities for which there is increased prevalence in the schizophrenia population. In fact, it has been reported in the literature that the co-morbidity with the highest OR is viral hepatitis (OR 3.98, 95% CI 2.81 to 5.64), which can lead to hepatic impairment. Consistent with this, the OR for liver disease in patients with schizophrenia compared to controls is also significant (OR 1.66, 95% CI 1.19 to 2.31) [Smith, D. J., et al 2013].

MK-8189 undergoes oxidative metabolism primarily via CYP3A4, with a lesser contribution by CYP2C9 and a minor contribution from CYP1A2. A human absorption, metabolism and excretion study has not yet been conducted. However, in both rats and monkeys, biotransformation was the major mechanism of elimination with only trace levels of unchanged parent compound detected in the excreta. Since hepatic metabolism plays an important role in the elimination of MK-8189, and hepatic impairment may affect the PK of MK-8189, it is appropriate to evaluate the effect of hepatic impairment on the PK of MK-8189.

2.2 Background

Refer to the IB/approved labeling for detailed background information on MK-8189

2.2.1 Pharmaceutical and Therapeutic Background

MK-8189 is a potent and selective inhibitor of PDE10A that is being developed as a novel therapeutic for the treatment of schizophrenia. The PDE10A enzyme metabolically inactivates the ubiquitous second messengers, cAMP and cGMP [Bender, A. T. and Beavo, J. A. 2006] and is highly expressed in the target nucleus of the corticostriatal pathway, the striatum [Seeger, T. F., et al 2003]. Preclinical pharmacology studies demonstrate that PDE10A inhibition increases cAMP/cGMP signaling in pathways that have been associated with underlying pathology (glutamate) as well as clinically validated therapeutics (dopamine D2 receptor antagonists) for schizophrenia. Enhanced signaling in these pathways is hypothesized to restore behavioral inhibition that is impaired in schizophrenia [Grauer, S. M., et al 2009] [Schmidt, C. J., et al 2008]. PDE10A inhibitors may potentially be an alternative treatment as monotherapy and/or adjunct treatment in schizophrenia patients who have inadequate response to first line AAP treatment.

2.2.2 Preclinical and Clinical Studies

Preclinical and clinical study information can be found in the MK-8189 IB.

2.2.2.1 Preclinical PK

MK-8189 exhibited low to moderate plasma clearance in rats (21.3 mL/min/kg) and monkeys (9.3 mL/min/kg). In both species, the terminal half-life in plasma was approximately 4 hrs and the oral bioavailability ranged from 41 to 46%. MK-8189 was significantly bound to plasma proteins in rat, monkey, and human with unbound fraction (expressed as percent) as 8.2, 8.7, and 4.0%, respectively. The compound did not preferentially distribute to red blood cells from any of the three species. In both rats and monkeys, the major mechanism of elimination is biotransformation with oxidation as the dominant pathway. Oxidative metabolism of MK-8189 is catalyzed primarily via CYP3A, with a lesser contribution by CYP2C9 and a minor contribution from CYP1A2.

2.2.2.2 Clinical Studies

To date, completed studies in the Phase 1 program include 3 single-dose clinical studies, 1 DDI study and 1 multiple-dose clinical study conducted with MK-8189. A total of 104 participants were enrolled in the Phase 1 studies with 59 healthy participants and 33 participants with schizophrenia receiving at least 1 dose of MK-8189. Twelve participants received placebo. Single doses up to 6 mg (IR formulation) and multiple increasing doses up to 16 mg (CR formulation) over 14 days have been administered to date in these completed studies.

Overall, single and multiple doses of MK-8189 were generally well tolerated. The most frequently (≥5%) reported treatment emergent AEs following administration of MK-8189 (across all completed 5 Phase 1 studies) were headache, somnolence, fatigue, dystonia (includes dystonia, torticollis, oromandibular dystonia, spasmodic dysphonia and blepharospasm), diarrhea, akathisia, anxiety, dizziness, insomnia, nausea and decreased appetite. No deaths occurred in any of the 5 Phase 1 trials. A total of 9 participants were discontinued due to AEs. No treatment-related SAEs were reported across these studies.

There were no clinically meaningful changes in laboratory investigations, ECGs or VS related to MK-8189.

In a Phase 2 POC trial (P005), MK-8189 was generally well tolerated up to 12 mg QD. Adverse Events that occurred in ≥5% of participants in the MK-8189 intervention group and had greater incidence than placebo were diarrhea, nausea, vomiting, decreased appetite, akathisia, dystonia, headache, sedation, somnolence, anxiety, and insomnia. No deaths were reported in the P005 study. No SAEs were reported for participants on MK-8189.

In P005, for the primary endpoint of PANSS total score change from baseline at Week 4, although the MK-8189 group showed meaningful improvement in symptoms, the improvement missed statistical significance (difference [95% CI] in LS mean change was -4.7 [-9.8, 0.5]; p=0.074). Risperidone was superior to placebo with respect to this endpoint

(difference [95% CI] in LS mean change was -7.3 [-14.0, -0.6]; p=0.033). There was no difference in magnitude of effect between MK-8189 and risperidone (difference [95% CI] in LS mean change was 2.6 [-4.0, 9.2]; p=0.440). For the exploratory endpoint of PANSS positive subscale score at Week 4, both MK-8189 and risperidone were superior to placebo. There was no significant difference in effect between MK-8189 and risperidone. Neither risperidone nor MK-8189 demonstrated significant improvement in the CGI-S.

Following multiple doses of the controlled release formulation, MK-8189 exposure increased approximately proportionally with dose over the range of doses tested (2 to 16 mg) in all populations. Median Tmax of MK-8189 as monotherapy ranged from 10 to 20 hours with a t1/2 of approximately 8.4 hours (37.8% GCV).

Based on completed studies, data suggest that the exposures at steady state for a given dose are generally comparable between healthy participants and participants with schizophrenia administered MK-8189 as monotherapy.

In a DDI study (P006) the coadministration of extended release 240-mg diltiazem increased MK-8189 AUC and Cmax by approximately 2-fold and 1.3-fold, respectively, confirming that MK-8189 is a CYP3A substrate.

2.2.3 Ongoing Clinical Studies

P007 is a 4- panel (A, B, C and D) randomized (3:1), placebo-controlled, multiple-dose safety, tolerability and PK study of MK-8189 monotherapy in participants with schizophrenia and healthy participants. The study is clinically complete and data are unblinded. In this study, 16 healthy participants (Japanese and non-Japanese) were enrolled in Panel A and 16 participants with schizophrenia were enrolled in Panel B. Participants were washed off their standard of care during screening. The treatment regimen for Panel A and Panel B was as follows: MK-8189 4- mg/placebo Days 1-3, MK-8189 8- mg/placebo Days 4-6, MK-8189 12- mg/placebo Days 7-9, MK-8189 16- mg/placebo Days 10-12, MK-8189 20- mg/placebo Days 13-15 and MK-8189 24- mg/Days 16-18.

Safety data from Panel A and Panel B indicated that MK-8189 at doses up to and including 24 mg were generally well tolerated and tolerability was similar across the populations (healthy Japanese, healthy non-Japanese and participants with schizophrenia). No SAEs or deaths were reported and no AEs of dystonia were reported.

In Panel A, of the 16 participants enrolled, 14 completed treatment and 2 discontinued due to an AE: 1 Japanese participant discontinued due to a treatment-related headache of moderate intensity following administration of the MK-8189 16 mg dose and 1 Japanese participant discontinued due to treatment-related exacerbation of a preexisting motor tic disorder of moderate severity. The AE began following administration of the 4 mg dose and the participant was discontinued following treatment with MK- 8189 8 mg x 2 days. This AE resolved approximately 3 weeks following cessation of therapy. This participant was also reported to have moderate akathisia at the MK-8189 4-mg dose which resolved 1 day following discontinuation of drug.

Ten of 12 (83.3%) and 3 of 4 (75%) participants reported at least 1 AE following treatment with MK-8189 and placebo, respectively. The most common AEs (reported by ≥2 participants) following treatment with MK-8189, regardless of causality, were headache (n=6, 50% vs. placebo n=1, 25%), dizziness (n=4, 33% vs placebo n=0), decreased appetite (n=3, 25% vs placebo n=1, 25%), insomnia (n=3, 25% vs placebo n=0), anxiety (n=2, 16.7% vs placebo n=1, 25%), restlessness (n=2, 16.7% vs. placebo n=0), and abdominal discomfort (n=2, 16.7% vs placebo n=0).

In Panel B, of the 16 participants enrolled, 3 participants discontinued due to AEs; 1 participant discontinued after administration of placebo due to a psychotic disorder. The participant was reported to have mild psychosis prior to dosing and the AE of moderate psychosis began following administration of placebo on Day 4. The AE resolved within 4 weeks. Another participant was discontinued due to a panic attack, psychosis and dissociation following administration of MK-8189 16 mg which were all assessed as severe in intensity and treatment-related. The participant was restarted on their antipsychotic medication, and within 15 hours the intensity of these AEs abated and was considered mild. The psychosis and panic attack resolved within 6 days and the dissociation resolved within 1.3 weeks. In addition, 1 participant discontinued due to mild dyspepsia, considered unrelated to treatment, following administration of MK-8189 4 mg.

Ten of 12 participants (93.8%) and 4 of 4 participants (100%) reported at least 1 AE following treatment with MK-8189 and placebo, respectively. The most common AEs (reported by ≥2 participants) regardless of causality were headache (n=7, 58.3% vs placebo n=1, 25%), constipation (n=5, 41.7%, vs placebo n=1, 25%), dyspepsia (n=3, 25% vs placebo n=0), anxiety (n=3, 25% vs placebo n=0), neck pain (n=3, 25% vs placebo n=0), nausea (n=2, 16.7 % vs placebo n=1, 25%), and insomnia (n=2, 16.7% vs placebo n=1, 25%).

Panel C was conducted to evaluate the multiple-dose safety, tolerability and PK of MK-8189 as add-on therapy in participants with schizophrenia. Participants were randomized to MK-8189 or placebo (3:1) and titrated up to doses of 24 mg while remaining on their antipsychotic standard of care. The titration schedule was the same as that evaluated in Panel A and Panel B. Seventeen participants were enrolled in Panel C and safety data suggest that MK-8189 was generally well tolerated up to including doses of 24 mg when administered as add-on therapy. No SAEs or deaths occurred, and 1 AE of dystonia considered unrelated to treatment was reported and is described as part of the safety summary below.

In Panel C, 10 participants completed study treatment and 7 discontinued treatment. One participant withdrew consent and one participant was discontinued from treatment for a protocol deviation, as the participant had a history of seizures (exclusion criteria) not disclosed during Screening. Five participants discontinued due to an AE: One participant discontinued due to moderate treatment-related akathisia following administration of MK-8189 8-mg. One participant discontinued due to treatment-related mild nausea and moderate vomiting which began following treatment with the MK-8189 12 mg and treatment-related mild headache and moderate hypertension which began following treatment with MK-8189 16 mg. One participant discontinued due to treatment-related moderate abdominal pain and muscles spasms following treatment with MK-8189 4 mg. One participant discontinued due to mild treatment-related chest pain following treatment with MK-8189 12 mg. One

participant discontinued due to treatment-related mild palpitations following treatment with MK-8189 12 mg.

One participant experienced dystonia following treatment with MK-8189 4 mg. The AE of dystonia was considered unrelated as it was determined the participant had previously experienced dystonia while taking lurasidone, which had been reinitiated during the trial. This participant was discontinued for failure to disclose a history of seizures as mentioned above.

In Panel C, 13 of 13 participants (100%) and 1 of 4 (25%) participants experienced at least 1 adverse event following MK-8189 and placebo, respectively. The most common AEs (≥2 participants) regardless of causality were decreased appetite (n=5, 38.5% vs placebo, n=0), dizziness (n=4, 30.8% vs placebo n=1, 25%), headache (n=4, 30.8% vs placebo n=0) nausea (n=3, 23.1% vs placebo n=0), vomiting (n=3, 23.1% vs placebo. n=0), abdominal pain upper (n=2, 15.4% vs placebo n=0), anxiety (n=2, 15.4% vs placebo n=0), constipation (n=2, 15.4% vs. placebo n=0), and restlessness (n=2, 15.4% vs placebo n=0).

Panel D was conducted to evaluate the multiple-dose safety, tolerability and PK of supratherapeutic doses of MK-8189 monotherapy in participants with schizophrenia. The planned enrollment for Panel D was 20 participants with schizophrenia or schizoaffective disorder. Participants were washed off their antipsychotic medication during the screening phase. During the treatment period, participants were titrated up to 48 mg or received placebo in a ratio of 3:2. The titration regimen was MK-8189 8-mg/placebo Days 1-3, MK-8189 16 mg/placebo Days 4-6, MK-8189 24 mg/placebo Days 7-9, MK-8189 36 mg/placebo Days 10-12 and MK-8189 48-mg/placebo Days 13-15.

Safety data from Panel D indicate that MK-8189 at doses up to and including 48 mg is generally well tolerated. No deaths have been reported and 1 SAE of treatment-related psychotic disorder was reported. This SAE is described below as part of the AE summary. In addition, two participants experienced dystonia. However, as dystonia occurred following cessation of MK-8189 dosing and following re-initiation of the participants pre-trial atypical antipsychotic treatment, these AEs were not considered related to MK-8189.

Twenty-six (26) participants were enrolled in Panel D. Eighteen of 26 participants completed study treatment and 8 participants discontinued treatment; six discontinuations were due to adverse events and 2 participants withdrew consent. One participant discontinued due to a treatment-related SAE of increased psychosis which resulted in hospitalization. The SAE occurred following treatment with the MK-8189 36 mg dose. The AE was considered severe and had a duration of 6 days. The SAE resolved following initiation of an antipsychotic and benzodiazepine. No other AEs were reported by this participant. In addition, one participant discontinued due to an AE of moderate psychosis on Day 14 following treatment with placebo; one participant discontinued due to AEs of moderate psychosis and severe anxiety following treatment with MK-8189 16 mg and neither AE was considered related to treatment; one participant was discontinued due to an AE of treatment-related, mild asymptomatic and intermittent atrial fibrillation following treatment with placebo; one participant discontinued due to mild treatment-related anxiety following treatment with MK-8189 16 mg. One participant discontinued due to several AEs following treatment with MK-

8189 including (dose at which AE began) moderate anxiety (16 mg), mild somnolence (8 mg), mild flank pain (16 mg), mild skin lesion (16 mg), mild vulvovaginal pruritis (16 mg), mild dermatitis (16 mg), and mild contact dermatitis (8 mg). Only somnolence and dermatitis were considered related to treatment.

In Panel D, 14 of 17 participants (82.4%) and 9 of 9 participants (100%) reported at least one AE following treatment with MK-8189 or placebo, respectively. The most common AEs (reported by ≥2 participants), regardless of causality, were anxiety (n=7, 41.2% vs. placebo n=1, 11.1%), headache (n=5, 29.4% vs. placebo n=2, 22.2%), nausea (n=5, 29.4 vs placebo n=1, 11.1%%), somnolence (n=4, 23.5% vs placebo n=1, 11.1%), back pain (n=3, 17.6%, vs placebo n=2, 22.2%), contact dermatitis (n=2, 11.8% vs placebo n=3, 33.3%), insomnia (n=2, 11.8% vs placebo n=1, 11.1%), psychotic disorder (n=2, 11.8% vs placebo n=1, 11.1%), dizziness (n=3, 17.6%, vs placebo n=0), decreased appetite (n=2, 11.8% vs placebo n=0), vomiting (n=2, 11.8% vs placebo n=0) and palpitations (n=2 (11.8% vs placebo n=0).

The observed proportion of participants reporting AEs was higher following the 48 mg dose (72.7%, n=8 of 11) when compared to the 8 mg (47.1%, n=8 of 17), 16 mg (50.0%, n=8 of 16), 24 mg (33.3%, n=5 of 15) and 36 mg (38.5%, n=5 of 13) dose groups. It should be noted that 11 participants (42.3%) reported at least one AE during screening. In general, there were no clear dose-related increases in specific AEs. However, all three participants with AEs of dizziness occurred at the 48 mg dose.

Overall, across P007 there were no clinically relevant trends for changes from baseline in vital signs, ECGs, or safety laboratory parameters. In Panel C, increases in ventricular rate/heart rate, appeared to be greater in the MK-8189 group when compared to placebo. In Panel D, while a few parameters such as ventricular rate/heart rate, resting diastolic blood pressure, and resting systolic blood pressure appeared to have some greater changes towards the end of dosing, these changes were within the range of changes observed 48 hours following completion of dosing (Day 17) when MK-8189 concentrations are expected to be significantly diminished, based on a half-life in participants with schizophrenia of approximately 8-11 hours.

In P007, at the same doses (16 mg and 24 mg), preliminary data from Panels A (healthy participants) and B (participants with schizophrenia) suggest that MK-8189 exposure appeared to be greater in participants with schizophrenia when compared with healthy participants; 1.6 - 2-fold and 1.5 - 1.7-fold for AUC0-24 and Cmax values, respectively at the 16 and 24 mg dose. However, when PK data from participants with schizophrenia dosed in Panel C (add-on therapy) and Panel D (monotherapy) were compared with Panel A, PK data were similar between healthy participants and participants with schizophrenia; the reason for the higher exposure observed in Panel B is currently unknown. CL/F (CV%) was found to be 3.65 L/hr (67%) with half-life (CV%) found to be 8.33 hr (21%).

2.3 Benefit/Risk Assessment

Healthy participants and participants with hepatic impairment in this trial will not receive direct benefit from treatment during participation as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine.

Additional details regarding specific benefits and risks for participants participating in this clinical study may be found in the accompanying IB and informed consent documents.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

The study population includes male and female participants with moderate and mild hepatic impairment between the ages of 18 and 75 (inclusive) and healthy controls.

Objectives	Endpoints
Primary	
<u>Part 1</u> • To compare MK-8189 pharmacokinetics after single dose administration of 4 mg MK-8189 to participants with moderate hepatic impairment and healthy control participants. • Estimation: The AUC0-inf and Cmax in participants with moderate hepatic impairment will be estimated and compared to those obtained from healthy control participants. <u>Part 2</u> • To compare MK-8189 pharmacokinetics after single dose administration of 4 mg MK-8189 to participants with mild hepatic impairment and healthy control participants. • Estimation: The AUC0-inf and Cmax in participants with mild hepatic impairment will be estimated and compared to those obtained from healthy control participants in Part 1.	<u>Part 1 and Part 2</u> • AUC0-inf and Cmax

Objectives	Endpoints
Secondary	
<u>Part 1</u> • To evaluate the safety and tolerability of MK-8189 in patients with moderate hepatic impairment and in healthy control participants after single dose administration of 4 mg MK-8189. <u>Part 2</u> • To evaluate the safety and tolerability of MK-8189 in patients with mild hepatic impairment after single dose. administration of 4 mg MK-8189.	<u>Part 1 and Part 2</u> • Adverse experiences, laboratory safety tests, electrocardiograms and vital signs
Tertiary/Exploratory	
<u>Part 1 and Part 2</u> • To investigate the relationship between CYP2C9 genetic polymorphisms and the PK of MK-8189. Genetic variation in CYP2C9 may be analyzed for association with any laboratory or clinical data collected in this study. • To explore the relationship between genetic variation and response to the treatment administered, and mechanisms of disease. Variation across the human genome may be analyzed for association with clinical data collected in this study. • To compare additional MK-8189 pharmacokinetic parameter values after single dose administration of 4 mg MK-8189 to participants with moderate hepatic impairment, mild hepatic impairment, and healthy control participants.	<u>Part 1 and Part 2</u> • Germline genetic variation in CYP2C9 and association to clinical data collected in this study • Germline genetic variation and association to clinical data collected in this study. • AUC0-24, C24, Tmax, CL/F, Vz/F and apparent terminal t½

4 STUDY DESIGN

4.1 Overall Design

This is a 2-part, non-randomized, open-label, single-dose study to compare, in Part 1, the PK of MK-8189 in participants with moderate hepatic impairment (based on the Child-Pugh classification) to healthy control participants reasonably matched to the demographics (age, weight, sex) of the group with hepatic impairment. Following a review of the safety and PK data from Part 1, a decision will be made as to whether Part 2 will be initiated; if there is a clinically meaningful higher exposure of MK-8189 in participants with hepatic impairment as compared to healthy participants, Part 2 will be conducted. Part 2 of the study will compare the PK of MK-8189 in participants with mild hepatic impairment to the healthy participants enrolled in Part 1. On Day 1, a single oral dose of MK-8189 will be administered and followed by PK sampling for 96 hours in the healthy control participants and for 120 hours in the mild and moderate hepatic impaired participants. Safety will be monitored through physical examination, vital signs, 12-lead electrocardiograms (ECGs), adverse events and clinical laboratory tests.

The clinic will attempt to contact participants (including participants who terminate the study early) using their standard procedures approximately 14 days after study drug administration to determine if any adverse events have occurred since dosing.

In Part 1, a total of up to 16 adults male and female participants will be enrolled. Up to 8 participants with moderate hepatic impairment (a score of 7 to 9, on the Child-Pugh scale) and up to 8 healthy control participants matched to the mean demographic of the moderate hepatic impairment group (see Section 5 for matching criteria) .

In Part 2, up to 8 participants with mild hepatic impairment (a score of 5 to 6 on the Child-Pugh scale) will be enrolled. The healthy control group in Part 1 will be used for the PK comparison in Part 2.

Because this is a Phase 1 assessment of MK-8189 in humans, the PK, pharmacodynamic, and safety profiles of the compound are still being elucidated. This protocol is therefore written with flexibility to accommodate the inherent dynamic nature of Phase 1 clinical studies. Refer to Section 8.11.6 for examples of modifications permitted within the protocol parameters.

Specific procedures to be performed during the study, as well as their prescribed times and associated visit windows, are outlined in the SoA in Section 1.3. Details of each procedure are provided in Section 8.

4.2 Scientific Rationale for Study Design

A 2-part, open-label study design has been selected to evaluate the effect of hepatic impairment on the PK of MK-8189. Though hepatic elimination may be important for MK-8189, the magnitude of the preclinical and clinical safety margins support a reduced design with an evaluation of participants with moderate hepatic impairment first; in the clinic a

starting dose 2-fold and a top dose 12-fold the proposed dose have been evaluated and found to be generally well tolerated (Panel D, P007). It has been recognized that, in general, low clearance compounds (CL < 20 L/h) are less affected by hepatic impairment [Heimbach, T., et al 2020].Though MK-8189 is primarily eliminated through hepatic metabolism, the low clearance of MK-8189 (CL/F < 5 L/hr) may limit the effect of moderate hepatic impairment on MK-8189 PK.

Following a review of the safety and PK data from moderately hepatic impaired patients and healthy control participants (Part 1), a decision will be made by the Sponsor whether to conduct Part 2 in mildly hepatic impaired participants. If a clinically meaningful increase in MK-8189 exposure is observed in participants with moderate hepatic impairment (Part 1) when compared to healthy participants, Part 2 will be initiated. The effect of mild hepatic impairment on MK-8189 PK will not need to be assessed if a clinically meaningful increase in MK-8189 exposure is not observed in moderate hepatic impairment patients. Following enrollment of the moderate hepatic cohort, a control group will be enrolled with demographics which are reasonably matched to the mean demographic parameters to control for the influence of covariates. The Child-Pugh classification will be used to categorize hepatic impairment due to its widespread use and acceptance by regulatory agencies including the U.S. Food and Drug Administration [S 2003] and the European Committee for Medicinal Products for Human Use). [Guideline on the evaluation of... 2005]

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 [Pugh, R. N. H., et al 1973] has been subsequently found useful in classifying a patient's level of hepatic impairment for PK studies. The Child-Pugh scale has been shown to correlate with hepatic (i.e., metabolic) clearance for several compounds. [S 2003]

In the current study, patients with chronic, stable hepatic impairment due to any etiology will be enrolled, and the Child-Pugh scale will be used to classify the severity of liver disease (see Child-Pugh classification of the severity of liver disease presented in Appendix 10.11). The Child-Pugh scale used in this trial takes into account the medications/treatments being used to treat complications of cirrhosis, in order to accurately describe the severity of encephalopathy and ascites [Garcia-Tsao, G., et al 2007]. Patients' 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, as the laboratory parameters specified in the Child-Pugh scale (e.g., reduced serum albumin, increased serum bilirubin, and increased INR) may be better associated with the capacity of the liver to eliminate drugs, in comparison to ascites and encephalopathy, [Guideline on the evaluation of... 2005] at least four (4) patients with moderate hepatic impairment (Part 1 only) will be required to have a score of at least 2 on one of the laboratory parameters on the Child-Pugh scale.

4.2.1 Rationale for Endpoints

4.2.1.1 Safety Endpoints

Safety and tolerability will be assessed throughout the study by monitoring participants for clinical AEs as well as through the conduct of physical and 12 lead ECGs, VS, and laboratory safety tests.

4.2.1.2 Pharmacokinetic Endpoints

An objective of this study is to characterize the PK of MK-8189 in participants with hepatic impairment. Therefore, individual plasma concentration and actual sample collection times of MK-8189 will be used to derive the PK parameter values such as AUC0-24, AUC0-inf, Cmax, Tmax, C24hr, CL/F, Vd/F and apparent t1/2. Protein binding for MK-8189 will also be analyzed. As MK-8189 is highly protein bound, the fraction unbound PK parameters (at a minimum CL/F, Vd/F) will be provided in healthy participants and participants with hepatic impairment.

4.2.1.3 Planned Exploratory Biomarker Research

4.2.1.3.1 Planned Genetic Analysis

Genetic variation may impact a participant's response to therapy, susceptibility to, severity, and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug ADME; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a sample will be collected for DNA analysis from consenting participants.

DNA samples may be used for research related to the study intervention(s), the disease under study, or related diseases. They may also be used to develop tests/assays including diagnostic tests related to the disease under study, related diseases, and study intervention(s). Genetic research may consist of the analysis of 1 or more candidate genes, the analysis of genetic markers throughout the genome, or analysis of the entire genome. Analysis may be conducted if it is hypothesized that this may help further understand the clinical data.

The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to understand study disease or related conditions.

In addition to studying variation across the human genome, polymorphisms of CYP2C9 will specifically be investigated for association with the PK of MK-8189 since MK-8189 is partially metabolized by CYP2C9. Genetic variation in CYP2C9 may be analyzed for association with any laboratory or clinical data collected in this study

4.2.1.4 Future Biomedical Research

The Sponsor will conduct FBR on DNA specimens for which consent was provided during this clinical study.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for FBR 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 participants receive the correct dose of the correct drug/vaccine at the correct time. The details of FBR are presented in Appendix 6.

4.3 Justification for Dose

A single-dose of 4 mg will be administered in this trial. The highest likely clinical dose of MK-8189 is expected to be 24 mg. While multiple doses up to 48 mg of MK-8189 have been found to be generally well tolerated, a titration scheme has been used to step up to this supratherapeutic dose. The titration approach has been used to mitigate dystonia which was observed in P001 with an immediate release formulation and the need to continue the titration approach with the CR formulation has not yet been evaluated. To date, the highest generally well tolerated starting dose evaluated is 8 mg, providing a 2-fold clinical margin to the 4 mg dose to be administered in this trial. While hepatic impairment may increase the exposure of MK-8189, this effect may be modest due to its low intrinsic clearance [Heimbach, T., et al 2020]. MK-8189 is a BCS class 1 compound up to doses of 16 mg and BCS class 2 at 24 mg. In addition, PK of MK-8189 generally increases dose proportionally in subjects with schizophrenia over the dose range evaluated (2 mg to 48 mg). Thus, the effect of hepatic impairment at a low dose of 4 mg is expected to be extrapolatable, within reasonable variability, to the highest likely clinical dose of 24 mg.

4.3.1 Rationale for Dose Interval and Study Design

As MK-8189 PK is linear, single-dose PK will be predictive of multiple-dose PK and therefore, only a single-dose evaluation of MK-8189 in hepatic impairment is required.

4.4 Beginning and End of Study Definition

The overall study begins when the first participant signs the ICF. The overall study ends when the last participant completes the last study-related telephone-call or visit, withdraws from the study, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

A study may be paused during review of newly available preclinical/clinical safety, PK, pharmacodynamic, efficacy, or biologic data or other items of interest, prior to a final decision on continuation or termination of the study. It may be necessary to keep the study open for gathering/reviewing of additional supportive data to optimally complete the objective(s) of the study. If necessary, the appropriate amendment(s) to the protocol and/or appropriate communication(s) will be generated. If the decision has been made to end the study following this review period, the study end will be defined as the date of the Sponsor decision, and this end of study date supersedes the definitions outlined above. The Competent Authority(ies) and IRB(s)/IEC(s) will be apprised of the maximum duration of the study beyond the last participant out and the justification for keeping the study open.

4.4.1 Clinical Criteria for Early Study Termination

There are no prespecified criteria for terminating the study early.

5 STUDY POPULATION

In Part 1 male and female participants with moderate hepatic impairment and healthy participants between the ages of 18 and 75 years of age may be enrolled. If Part 2 is conducted, male and female participants with mild hepatic impairment between the ages of 18 and 75 will be enrolled.

The individual age and weight of the healthy participants is aimed to be within the range ± 15 years and ± 20% of the mean age and weight of participants with moderate hepatic impairment. In addition, the numbers of males and females of the healthy participants will be generally matched to the numbers of hepatic insufficient participants within ± 1; i.e., if there are 4 males and 4 females in the hepatic insufficient group, every effort will be made to ensure a 4:4 ratio in the healthy participants, but 3:5 or 5:3 would be acceptable as well.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

A participant will be eligible for inclusion in the study if the participant:

Type of Participant and Disease Characteristics

5.1.1 Inclusion Criteria for Healthy Participants

1. Is in good health based on medical history, physical examination, VS measurements and ECGs performed prior to randomization.

   Appendix 9 provides a table of the 12-Lead Electrocardiogram Abnormality Criteria.

2. Is in good health based on laboratory safety tests obtained at the screening visit. Appendix 2 provides a table of laboratory safety tests to be performed. Appendix 10 provides an algorithm for the assessment of out of range laboratory values.

3. Have a BMI≥18.5 and ≤40 kg/m^2, inclusive. See Section 8.3.1 for criteria on rounding to the nearest whole number. BMI = weight (kg)/height $(m)^2$.

4. Continuous non-smokers or moderate smokers (of fewer than 20 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.

Demographics

5. Is male or female, from 18 years to 75 years of age inclusive, at the time of signing the informed consent.

Female Participants

6. A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:

- Is not a WOCBP

  OR

- Is a WOCBP and using an acceptable contraceptive method, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 5 during the intervention period and for at least 14 days after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention. Note: participants intending to rely on abstinence as a birth control method should agree to use double-barrier birth control methods if they engage in intercourse.

  - A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 48 hours before the first dose of study intervention.

  - If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

  - Additional requirements for pregnancy testing during and after study intervention are in Appendix 2.

  - The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

  - Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Informed Consent

7. The participant has provided documented informed consent/assent for the study. The participant may also provide consent/assent for FBR. However, the participant may participate in the study without participating in FBR.

5.1.2 Inclusion Criteria for Hepatically Impaired Participants

The following inclusion criteria apply to all hepatically impaired participants. A hepatically impaired participant will be eligible for inclusion in the study if the participant:

Type of Participant and Disease Characteristics

1. Has a diagnosis of chronic (> 6 months), stable (no acute episodes of illness within the previous 2 months due to deterioration in hepatic function) hepatic impairment with features of cirrhosis due to any etiology.

2. Part 1 only: Has a score on the Child-Pugh scale ranging from 7 to 9 (moderate hepatic impairment) at screening. At least 4 (or at least 3 in the situation where only 6 participants are enrolled or complete the study) of the participants must have a score of 2 or higher on at least one of the laboratory parameters (i.e., albumin, INR, and bilirubin) at screening on the Child-Pugh scale.

3. Part 2 only: Patient's score on the Child-Pugh scale must range from 5 to 6 (mild hepatic impairment).

4. With the exception of hepatic impairment, is in generally good health based on medical history, physical examination, VS measurements and ECGs performed prior to randomization. Appendix 9 provides a table of the 12-Lead Electrocardiogram Abnormality Criteria. Participants with stable, chronic medical or psychiatric conditions may be included at the discretion of the investigator and the Sponsor.

5. With the exception of hepatic impairment, is in good health based on laboratory safety tests obtained at the screening visit and prior to randomization. Appendix 2 provides a table of laboratory safety tests to be performed. Appendix 10 provides an algorithm for the assessment of out of range laboratory values.

6. Has a BMI $\geq$ 18.5 and $\leq$ 40 kg/m^2. See Section 8.3.1 for criteria on rounding to the nearest whole number. BMI = weight (kg)/height (m)^2.

Demographics

7. Is male or female, from 18 years to 75 years of age inclusive, at the time of signing the informed consent.

Female Participants

8. A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:

- Is not a WOCBP

  OR

- Is a WOCBP and using an acceptable contraceptive method, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 5 during the intervention period and for at least 14 days after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention. Note: participants intending to rely on abstinence as a birth control method should agree to use double-barrier control methods if they engage in intercourse.

    - A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 48 hours before the first dose of study intervention.

    - If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

    - Additional requirements for pregnancy testing during and after study intervention are in Appendix 2.

    - The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Informed Consent

9. The participant has provided documented informed consent/assent for the study. The participant may also provide consent/assent for FBR. However, the participant may participate in the study without participating in FBR.

5.2 Exclusion Criteria

The participant must be excluded from the study if the participant:

5.2.1 Exclusion Criteria for Healthy Participants

The following exclusion criteria apply to all healthy participants. The participant must be excluded from the study if the participant:

Medical Conditions

1. Has a history of clinically significant endocrine, gastrointestinal, cardiovascular, hematological, hepatic, immunological, renal, respiratory, genitourinary, or major neurological (including stroke and chronic seizures) abnormalities or diseases. Participants with a remote history of uncomplicated medical events (eg, uncomplicated

kidney stones, as defined as spontaneous passage and no recurrence in the last 5 years, or childhood asthma) may be enrolled in the study at the discretion of the investigator. Subjects with stable chronic conditions that are adequately controlled by medication may be enrolled upon discussion with the Sponsor.

2. Is mentally or legally incapacitated, has significant emotional problems at the time of prestudy (screening) visit or expected during the conduct of the study or has a history of clinically significant psychiatric disorder of the last 5 years. Participants who have had situational depression may be enrolled in the study at the discretion of the investigator.

3. Has a history of cancer (malignancy).

   Exceptions: (1) Adequately treated non-melanomatous skin carcinoma or carcinoma in situ of the cervix or; (2) Other malignancies which have been successfully treated with appropriate follow up and therefore unlikely to recur for the duration of the study, in the opinion of the investigator and with agreement of the Sponsor (eg, malignancies which have been successfully treated ≥10 years prior to the prestudy [screening] visit).

4. Has known hypersensitivity to the active substance of any of the excipients of the study drug.

5. Has a history of significant multiple and/or severe allergies (eg, food, drug, latex allergy), or has had an anaphylactic reaction or significant intolerability (ie, systemic allergic reaction) to prescription or non-prescription drugs or food.

6. Is positive for hepatitis B surface antigen, hepatitis C antibodies or HIV.

7. Had major surgery, donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks prior to the prestudy (screening) visit.

8. Participant has an estimated CrCl ≤70 mL/min based on the CG Equation at Screening.

Cockcroft-Gault Equation:

$$CrCl = \frac{(140-age[yr])(body\ wt\ [kg])}{(72)(serum\ creatinine\ [mg/dL])}$$

[When creatinine is measured in µmol/L, use this formula]

$$CrCl = \frac{(140-age[yr])(body\ wt[kg])}{(72)(serum\ creatinine\ [\mu mol/L] \times 0.0113)}$$

For females, multiply the result by 0.85.

At the discretion of the investigator a measured CrCl, as determined by a 24-hour urine collection, may be used in place of, or in conjunction with, the estimate of the CrCl.

Participants who have a measured CrCl of up to 10% below 70 mL/min may be enrolled in the study at the discretion of the investigator.

Prior/Concomitant Therapy

9. Has taken any drugs known to be moderate or strong inhibitors of CYP3A, CYP2C9 or P-gp for 14 days (or 5 half-lives, whichever is greater) or CYP3A or CYP 2C9 inducers, including St. John's Wort, for 28 days (or 5 half-lives, whichever is greater) prior to dosing of study drug and throughout the study. Use of weak CYP3A/2C9 inhibitors/inducers or P-gp inhibitors may be deemed acceptable following consultation with the Sponsor Clinical Monitor and the Investigator. Acetaminophen (up to 2 g per 24-hour period) may be permitted during the study. In addition, participants who are taking medications (excluding inhibitors or inducers discussed above) for stable diseases for ~1 month prior to dosing may be allowed to participate in the study at the discretion of the Investigator and following consultation with the Sponsor.

Prior/Concurrent Clinical Study Experience

10. Has participated in another investigational study within 4 weeks (or 5 half-lives of the investigational drug, whichever is greater) prior to the prestudy (screening) visit. The window will be derived from the date of the last visit in the previous study.

Diagnostic Assessments

11. Has a mean QTc interval >450 msec, has a history of risk factors for Torsades de Pointes (eg, heart failure/cardiomyopathy or family history of long QT syndrome), has uncorrected hypokalemia or hypomagnesemia, is taking concomitant medications that prolong the QT/QTc interval.

Other Exclusions

12. Is under the age of legal consent.

13. Does not agree to follow the smoking restrictions as defined by the CRU.

14. Consumes greater than 3 glasses of alcoholic beverages (1 glass is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce]) per day. Participants who consume 4 glasses of alcoholic beverages per day may be enrolled at the discretion of the investigator.

15. Consumes excessive amounts, defined as greater than 6 servings (1 serving is approximately equivalent to 120 mg of caffeine) of coffee, tea, cola, energy drinks, or other caffeinated beverages per day.

16. Is a regular user of cannabis, any illicit drugs or has a history of drug (including alcohol) abuse within approximately 2 years. With the exception of cannabis, participants must have a negative UDS prior to randomization.

17. Presents any concern by the investigator regarding safe participation in the study or for any other reason the investigator considers the participant inappropriate for participation in the study.

18. Is unwilling to comply with the study restrictions (see Section 5.3 for a complete summary of study restrictions).

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

5.2.2 Exclusion Criteria for Hepatically Impaired Participants

The following exclusion criteria apply to all hepatically impaired participants.

The participant must be excluded from the study if the participant:

Medical Conditions

1. Has a history of any illness that, in the opinion of the Investigator, might confound the results of the study or poses an additional risk to the participant by their participation in the study.

2. Is institutionalized or mentally or legally incapacitated at the time of prestudy (screening) visit or expected during the conduct of the study.

3. Has a history of cancer (malignancy).

4. Exceptions: (1) Adequately treated nonmelanomatous skin carcinoma or carcinoma in situ of the cervix or; (2) Other malignancies which have been successfully treated with appropriate follow up and therefore unlikely to recur for the duration of the study, in the opinion of the investigator and with agreement of the Sponsor (eg, malignancies which have been successfully treated ≥10 years prior to the prestudy [screening] visit).

5. Has a history of significant multiple and/or severe allergies (eg, food, drug, latex allergy), or has had an anaphylactic reaction or significant intolerability (ie, systemic allergic reaction) to prescription or non-prescription drugs or food.

6. Has known hypersensitivity to the active substance or any of the excipients of the study drug.

7. Is positive for HIV.

8. Had major surgery, donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks prior to the prestudy (screening) visit.

9. Participant has an estimated CrCl ≤60 mL/min based on the CG Equation at Screening.

Cockcroft-Gault Equation:

$$CrCl = \frac{(140\text{-age[yr]})(\text{body wt [kg]})}{(72)(\text{serum creatinine [mg/dL]})}$$

[When creatinine is measured in µmol/L, use this formula]

$$CrCl = \frac{(140\text{-age[yr]})(\text{body wt[kg]})}{(72)(\text{serum creatinine [µmol/L]} \times 0.0113)}$$

For females, multiply the result by 0.85.

At the discretion of the investigator a measured CrCl, as determined by a 24-hour urine collection, may be used in place of, or in conjunction with, the estimate of the CrCl.

Participants who have a measured CrCl of up to 10% below 60 mL/min may be enrolled in the study at the discretion of the investigator.

Prior/Concomitant Therapy

10. Has taken any drugs known to be moderate or strong inhibitors of CYP3A, CYP2C9 or P-gp for 14 days (or 5 half-lives, whichever is greater) or CYP3A or CYP 2C9 inducers, including St. John's Wort, for 28 days (or 5 half-lives, whichever is greater) prior to dosing of study drug and throughout the study. Use of weak CYP3A/2C9 inducers or P-gp inhibitors may be deemed acceptable following consultation with the Sponsor Clinical Monitor and the Investigator. Acetaminophen (up to 2 g per 24 hour period) may be permitted during the study. In addition, participants who are taking medications (excluding inhibitors or inducers discussed above) for stable diseases for ~1 month prior to dosing may be allowed to participate in the study at the discretion of the Investigator and following consultation with the Sponsor.

11. Is taking medications to treat chronic medical conditions and has not been on a stable regimen for at least 1 month and/or is unable to withhold the use of the medication(s) as specified in Section 6.5. Exceptions may be granted for participants in whom a medication regimen has been adjusted within the one-month window, at the discretion of the Investigator and following consultation with the Sponsor. See Section 5.1.2 for allowed medical conditions, and Section 6.5 for allowed medications.

Prior/Concurrent Clinical Study Experience

12. Has participated in another investigational study within 4 weeks (or 5 half-lives of the investigational drug, whichever is greater) prior to the prestudy (screening) visit. The window will be derived from the date of the last visit in the previous study.

Diagnostic Assessments

13. Has a mean QTc interval >450 msec, has a history of risk factors for Torsades de Pointes (eg, heart failure/cardiomyopathy or family history of long QT syndrome), has uncorrected hypokalemia or hypomagnesemia, is taking concomitant medications that prolong the QT/QTc interval.

Other Exclusions

14. Is under the age of legal consent.

15. Does not agree to follow the smoking restrictions as defined by the CRU.

16. Consumes excessive amounts, defined as greater than 6 servings (1 serving is approximately equivalent to 120 mg of caffeine), of coffee, tea, cola, energy drinks, or other caffeinated beverages per day.

17. Is a regular user of cannabis, any illicit drugs or has a history of drug abuse within approximately 3 months. Participants must have a negative alcohol test and with the exception of cannabis, participants must have a negative UDS prior to randomization. Participants with hepatic impairment may be allowed for inclusion with a positive UDS for opiates or benzodiazepines if they have an active prescription from a licensed health care provider.

18. Is unwilling to comply with the study restrictions (see Section 5.3 for a complete summary of study restrictions.

19. Presents any concern by the investigator regarding safe participation in the study or for any other reason the investigator considers the participant inappropriate for participation in the study.

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

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

5.3.1.1 Diet Restrictions

In each treatment period, participants will fast from all food and drinks, except water, for at least 8 hours before study drug administration. Participants will fast from all food and drinks except water between study drug administration and the first scheduled meal. Meals and snack(s) will be provided by the investigator at time points indicated in the study flowchart. Participants will fast from all food and drinks except water between meals and snacks. After the 24-hour postdose procedures have been completed, subsequent meals and snacks will be unrestricted in caloric content, composition, and timing.

Water will be provided during study drug administration. Water will be restricted 1 hour before and 1 hour after study drug administration.

5.3.1.2 Fruit Juice Restrictions

Participants will refrain from the consumption of grapefruit juice, grapefruits, and grapefruit products beginning approximately 2 weeks prior to administration of the initial dose of study drug, throughout the study until the last PK sample is collected.

Participants also will refrain from the consumption of all fruit juices 24 hours prior to and after study drug administration. On all other days during the study, consumption of fruits and fruit juices (except for grapefruit, grapefruit juices, and grapefruit products) is allowed.

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

5.3.2.1 Caffeine Restrictions

Participants will refrain from consumption of caffeinated beverages or xanthine-containing products from 12 hours prior to the prestudy and poststudy visits and from 12 hours prior to and after study drug administration in each treatment period. At all other times, caffeinated beverages or xanthine-containing products will be limited to no more than 6 units per day (1 unit = 120 mg of caffeine).

5.3.2.2 Alcohol Restrictions

Participants will refrain from consumption of alcohol 24 hours prior to the prestudy and poststudy visits and from 24 hours prior to drug administration until participants are discharged in each treatment period. At all other times, alcohol consumption is limited to no more than approximately 3 alcoholic beverages or equivalent (1 glass is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce]) per day.

5.3.2.3 Tobacco Restrictions

Participants will follow the smoking restrictions (and if applicable, the use of nicotine/nicotine-containing products) defined by the CRU.

5.3.3 Activity Restrictions

Participants will avoid unaccustomed strenuous physical activity (ie, weight- lifting, running, bicycling, etc.) from the prestudy (screening) visit until administration of the initial dose of study drug, throughout the study (including washout intervals between treatment periods) and until the poststudy visit.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information may be

included, as outlined in the eCRF entry guidelines. Minimal information may include demography, screen failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements.

5.5 Participant Replacement Strategy

If a participant withdraws from the study a replacement participant may be enrolled if deemed appropriate by the investigator and Sponsor. The replacement participant will generally receive the same intervention or intervention sequence (as appropriate) as the participant being replaced. The replacement participant will be assigned a unique treatment/randomization number. The study site should contact the Sponsor for the replacement participant's treatment/randomization number.

The replacement participant may begin dosing at the subsequent dose level for that panel, based on investigator and Sponsor review and discussion.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Clinical supplies will be packaged to support enrollment and replacement participants as required. When a replacement participant is required, the Sponsor or designee needs to be contacted prior to dosing the replacement participant. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study intervention to be used in this study is outlined in [Table 1].

Table 1 Study Interventions

Arm Name	Arm Type	Intervention Name	Inter-vention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Adminis-tration	Regimen/Treatment Period/Vaccination Regimen	Use	IMP/ NIMP	Sourcing
Healthy Control	Experi mental	MK-8189	Drug	Tablet	4 mg	4 mg	Oral	Single Dose on Day 1	Experi mental	IMP	Provided by the sponsor
Moderate Hepatic Impairment Group	Experi mental	MK-8189	Drug	Tablet	4 mg	4 mg	Oral	Single Dose on Day 1	Experi mental	IMP	Provided by the sponsor
Mild Hepatic Impairment Group	Experi mental	MK-8189	Drug	Tablet	4 mg	4 mg	Oral	Single Dose on Day 1	Experi mental	IMP	Provided by the sponsor
The classification of Investigational Medicinal Product (IMP) and Non-Investigational Medicinal Product (NIMP) in this table is based on guidance issued by the European Commission and applies to countries in the European Economic Area (EEA). Country differences with respect to the definition/classification of IMP/NIMP may exist. In these circumstances, local legislation is followed.											

All supplies indicated in [Table 1] will be provided per the "Sourcing" column depending upon local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number where possible (eg, not applicable in the case where multiple lots or batches may be required due to the length of the study, etc).

Refer to Section 8.1.8 for details regarding administration of the study intervention.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

There are no specific calculations or evaluations required to be performed to administer the proper dose to each participant. The rationale for selection of doses to be used in this study is in Section 4.3.

6.2.2 Handling, Storage, and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

For all study sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product (if applicable) as per local guidelines unless otherwise instructed by the Sponsor.

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Participants will be assigned an AN for a single open-label treatment using the allocation schedule shown in [Table 2].

Table 2 Allocation of Participants to Treatment

Part 1[a]		
Hepatic Impairment Stage	N	Treatment
Moderate	6≤n≤8	MK-8189 4 mg
Healthy [b]	6≤n≤8	MK-8189 4 mg
Part 2[a]		
Mild	6≤n≤8	MK-8189 4 mg

[a] The participants in the groups defined by hepatic function should be reasonably similar to one another with respect to age, gender, and weight. However, participants with normal hepatic function should be matched at the group level. In order to make this matching possible, participants with normal hepatic function need to be enrolled after the participants with moderate hepatic impairment subjects have been recruited in Part 1. The participants with normal hepatic function in Part 1 also serve as control for mild hepatic category in Part 2.

[b] Participants with normal hepatic function are within ±15 years of the mean age and within ± 20% of the mean weight for the moderate hepatic function group. In addition, the numbers of males and females of the healthy participants will be generally matched to the numbers of hepatic insufficient participants within ± 1; i.e., if there are 4 males and 4 females in the hepatic insufficient group, every effort will be made to ensure a 4:4 ratio in the healthy participants, but 3:5 or 5:3 would be acceptable as well

6.3.2 Stratification

Not applicable

6.3.3 Blinding

This is an open-label study.

6.4 Study Intervention Compliance

When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study-site staff.

Participants will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant ID will be confirmed at the time of dosing by a member of the study-

site staff other than the person administering the study intervention. Study-site personnel will examine each participant's mouth to ensure that the study intervention was ingested.

6.5 Concomitant Therapy

Hepatic impairment and healthy participants: All prescription or non-prescription medications known to be moderate or strong inhibitors of CYP3A, CYP2C9 or P-gp or inducers of CYP3A or CYP2C9, will be prohibited throughout the study. Medications of particular concern include, but are not limited to azole antifungals (ketoconazole, itraconazole), macrolide antibiotics (erythromycin, clarithromycin), cimetidine, HIV protease inhibitors, nefazodone, rifampin, rifabutin, bosentan, modenafil, phenytoin, dexamethasone, troglitazone, barbiturates, and any drug or supplement (e.g., St. John's Wort). Weak CYP3A and/or CYP2C9 inhibitors or inducers or weak P-gp inhibitors may be deemed acceptable following consultation with the Sponsor Clinical Monitor and the Investigator.

Participants who are taking medications for stable diseases that are on a steady dose and regimen for ~1 month prior to dosing on Day 1 may be allowed to participate in the study at the discretion of the Investigator, and following consultation with the Sponsor Clinical Monitor.

Hepatically impaired participants only: Certain prescription medications used to treat manifestations of hepatic disease or medications needed to treat stable diseases (e.g., diuretics, lactulose, neomycin, etc.) will be allowed during the study, but the patient must be on a steady dose, drug, and regimen for ~1 month prior to dosing on Day 1. Lactulose should be restricted at least 24 hours prior to and 18 hours after dosing on Day 1 since it may potentially affect absorption of MK-8189. Neomycin, diuretics, beta-blockers and other approved concomitant medications should be restricted at least 4 hours prior to and 24 hours after dosing on Day 1. Any diuretics or beta-blockers that are significant CYP3A or CYP2C9 inhibitors or inducers (e.g., conivaptan) are not permitted.

Concurrent therapy with any medication during the course of the protocol including both prescription and non-prescription drugs must first be discussed with the Sponsor Medical Monitor prior to administration, unless appropriate medical care necessitates that therapy should begin before the Sponsor Medical Monitor can be consulted. Any medication used during the study conduct must be recorded on the appropriate case report form and include the name of the drug, dosage, date/time of and reason for administration.

6.5.1 Rescue Medications and Supportive Care

For the treatment of EPS, such as acute dystonia, all participants may be treated with an anticholinergic. If the symptoms are unresponsive to anticholinergic treatment, a benzodiazepine can be used.

In case the participant presents with signs of akathisia without signs of dystonia, the participant can be treated with a β-adrenergic blocker. If symptoms do not disappear with the β-adrenergic blocker, treatment with an anticholinergic may be used. An anticholinergic may

be used as first-line treatment in the case that a β-adrenergic blocker is not a preferred treatment based on a participant's medical history and/or concomitant medication.

Anticholinergics, benzodiazepines and β-adrenergic blockers are often used in the treatment of EPS and are considered standard practice. Oral anticholinergic treatment is also used as concomitant medication to prevent EPS symptoms with antipsychotic medication.

6.6 Dose Modification

Dose modifications are not applicable to this study

6.7 Intervention After the End of the Study

There is no study-specified intervention following the end of the study.

6.8 Clinical Supplies Disclosure

This study is open-label; therefore, the participant, the study-site personnel, the Sponsor, and/or designee are not blinded. Study intervention (name, strength, or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

In clinical studies with a single intervention, discontinuation of study intervention can only occur before the intervention. Therefore, participants who receive a single-dose intervention cannot discontinue study intervention.

7.2 Participant Withdrawal From the Study

A participant must be withdrawn from the study if the participant withdraws consent from the study.

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

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from future biomedical research, are outlined in Section 8.1.9. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

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

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

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

- Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the prespecified statistical data handling and analysis guidelines.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.

- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).

- All study-related medical decisions must be made by an investigator who is a qualified physician.

- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.

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

The maximum amount of blood collected from each participant over the duration of the study is outlined in Appendix 8.

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

8.1 Administrative and General Procedures

8.1.1 Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented consent from each potential participant or each participant's legally acceptable representative prior to participating in a clinical study or future biomedical research. If there are changes to the participant's status during the study (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate consent is in place.

8.1.1.1 General Informed Consent

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

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

The initial ICF, any subsequent revised written ICF, and any written information provided to the participant must receive the IRB/IEC's approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. 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 participant's dated signature or by the participant's legally acceptable representative's dated signature.

If the investigator recommends continuation of study intervention beyond disease progression, the participant or his/her legally acceptable representative will be asked to sign consent.

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

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

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or medically qualified designee will explain the FBR consent to the participant, or the participant's legally acceptable representative, answer all of his/her questions, and obtain documented informed consent before performing any procedure related to FBR. A copy of the informed consent will be given to the participant before performing any procedure related to FBR.

8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator, who is a qualified physician, to ensure that the participant qualifies for the study.

8.1.3 Participant Identification Card

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

The participant identification card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.4 Medical History

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

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 14 days before starting the study.

8.1.5.2 Concomitant Medications

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

8.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur prior to intervention allocation. Each

participant will be assigned only 1 screening number. Screening numbers must not be re-used for different participants.

8.1.7 Assignment of Treatment/Randomization Number

All eligible participants will be allocated, by nonrandom assignment, and will receive a treatment/randomization number. The treatment/randomization number identifies the participant for all procedures occurring after treatment randomization. Once a treatment/randomization number is assigned to a participant, it can never be reassigned to another participant.

A single participant cannot be assigned more than 1 treatment/randomization number.

8.1.8 Study Intervention Administration

Administration of study intervention(s) will be monitored by the investigator and/or study staff.

Participants will fast from all food and drinks, except water, for at least 8 hours prior to study drug administration. Participants will remain fasted for 4 hours post dose. Approximately 240 mL of water will be provided during study drug administration, but will be restricted 1 hour prior to and 1 hour post dose.

8.1.8.1 Timing of Dose Administration

Participants will be dosed according to the SoA (Section 1.3).

8.1.9 Discontinuation and Withdrawal

The investigator or study coordinator must notify the Sponsor when a participant has been discontinued/withdrawn from the study . If a participant discontinues for any reason at any time during the course of the study, the participant may be asked to return to the clinic (or be contacted) for a poststudy visit as per the number of days described in Section 1.3 to have the applicable procedures conducted. However, the investigator may decide to perform the poststudy procedures at the time of discontinuation or as soon as possible after discontinuation. If the poststudy visit occurs prior to the safety follow-up time frame as specified in Section 8.4.1, the investigator should perform a follow-up telephone call at the end of the follow-up period (Section 8.4.1) to confirm if any AEs have occurred since the poststudy clinic visit. Any AEs that are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.9.1 Withdrawal From Future Biomedical Research

Participants may withdraw their consent for future biomedical research. Participants may withdraw consent at any time by contacting the investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the participant'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 participant 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 study data and results. No new analyses would be generated after the request is received.

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

8.1.10 Participant Blinding/Unblinding

This is an open-label study; there is no blinding for this study. The emergency unblinding call center will be available so that a health care provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.11 Domiciling

Hepatic Impairment participants will report to the CRU on Day -1 before the scheduled day of study intervention administration on Day 1 and remain in the unit until 120 hours postdose. At the discretion of the investigator, participants may be requested to remain in the CRU longer.

Healthy matched participants will report to the CRU on Day-1 before the scheduled day of study intervention administration on Day 1 and remain in the unit until 48 hours postdose. At the discretion of the investigator, participants may be requested to remain in the CRU longer.

8.1.12 Calibration of Equipment

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

8.2 Efficacy/Immunogenicity Assessments

There are no direct efficacy assessments in this study.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. The total amount of blood/tissue to be drawn/collected over the course of the study (from prestudy to poststudy visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant, can be found in Appendix 8.

Planned time points for all safety assessments are provided in the SoA.

8.3.1 Physical Examinations

A complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) as per institutional standard. Height and weight will also be measured and recorded.

A brief directed physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

BMI

BMI equals a person's weight in kilograms divided by height in meters squared ($BMI=kg/m^2$). BMI will be rounded to the nearest whole number according to the standard convention of 0.1 to 0.4 round down and 0.5 to 0.9 round up.

Body weight and height will be obtained with the participant’s shoes off and jacket or coat removed.

8.3.2 Vital Signs

- Body temperature, via contactless forehead thermometer, heart rate, respiratory rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Vital signs will be measured in a semirecumbant position after 10 minutes rest and will include temperature, systolic and diastolic blood pressure, and pulse

8.3.2.1 Resting Vital Signs

Vital Sign Measurements (Heart Rate and Blood Pressure)

Participants should be resting in a quiet setting without distractions in a semirecumbent position for at least 10 minutes before having VS measurements obtained. Semirecumbent VS will include HR, systolic and diastolic BP, RR, and body temperature at timepoints indicated in the SoA. The correct size of the BP cuff and the correct positioning on the participants' arm is essential to increase the accuracy of BP measurements.

The predose (baseline) HR and BP will be triplicate measurements obtained at least 1-2 minutes apart within 3 hours of dosing MK-8189/placebo. The mean of these measurements will be used as the baseline to calculate change from baseline for safety evaluations (and for rechecks, if needed). Postdose VS measurements will be single measurements.

Participants will continue to rest semirecumbent from dosing until 4 hours postdose except to stand for other study-related procedure.

Body Temperature

Body temperature will be measured via contactless forehead thermometer. The same method must be used for all measurements for each individual participant and should be the same for all participants.

8.3.3 Electrocardiograms

- Triplicate and single 12-lead ECG will be obtained and reviewed by an investigator or medically qualified designee (consistent with local requirements) as outlined in the SoA (Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Appendix 9 for evaluation and withdrawal criteria and additional QTc readings that may be necessary.

- At each time point when triplicate ECG are required, 3 individual ECG tracings should be obtained at least 1 to 2 minutes apart, but no more than 2 minutes apart. The full set of triplicates should be completed in no more than 6 minutes.

- Special care must be taken for proper lead placement by qualified personnel. Skin should be clean and dry before lead placement. Participants may need to be shaved to ensure proper lead placement. Female participants may need to remove interfering garments.

- Participants should be resting in the semirecumbent for at least 10 minutes before each ECG measurement.

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

- Screening and Predose ECGs will be obtained in triplicate at least 1 to 2 minutes apart within 3 hours before dosing MK-8189. The mean of the predose (Day 1) measurements will be used as the baseline to calculate change from baseline for safety evaluations (and for rechecks, if needed).

- During the treatment period, if a participant demonstrates an increase in QTc interval ≥60 msec compared with predose baseline measurement, the ECG will be repeated twice within 5 minutes. The mean value of the QTc interval from the 3 ECGs will represent the value at that time point. If the QTc interval increase from baseline for any postdose time point is ≥60 msec, the participant will continue to be monitored by repeat 12-lead ECGs every 15 minutes for at least 1 hour or until the QTc is within 60 msec of baseline. If prolongation of the QTc interval ≥60 msec persists, a consultation with a study cardiologist may be appropriate and the Sponsor should be notified.

- If the QTc interval is ≥500 msec on any postdose ECG, the Sponsor should be notified and the ECGs should be reviewed by a cardiologist. The participant should be telemetry-

monitored (until the QTc is <500 msec) or should be considered for transfer to a location where closer monitoring and definitive care (eg, a CCU or ICU) is available.

- If the participant has unstable hemodynamics, or has any clinically significant dysrhythmias noted on telemetry, the participant should be immediately transferred to an acute care setting for definitive therapy.

- If prolongation of the QTc is noted, concomitant medications that prolong QTc should be held until the QTc is within 60 msec of baseline and the QTc is <500 msec.

- A cardiologist will be consulted by the investigator as needed to review ECG tracings with significant abnormalities.

8.3.4 Clinical Safety Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

- If laboratory values from nonprotocol-specified laboratory assessments performed at the institution’s local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).

- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 5 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

8.4 Adverse Events, Serious Adverse Events, and Other Reportable Safety Events

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE, and other reportable safety event reports can be found in Appendix 3.

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

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3.

The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity and causality.

8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information

AEs, SAEs, and other reportable safety events that occur after the participant provides documented informed consent but before intervention allocation, must be reported by the investigator for randomized participants only if the event is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo, or a procedure.

From the time of intervention allocation through 14 days following cessation of intervention, all AEs, SAEs and other reportable safety events must be reported by the investigator.

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

Investigators are not obligated to actively seek AEs or SAEs or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in [Table 3].

Table 3 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	Reporting Time Period: Consent to Randomization/ Allocation (Randomized participants only)	Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period	Reporting Time Period: After the Protocol-specified Follow-up Period	Time Frame to Report Event and Follow-up Information to Sponsor:
NSAE	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
SAE	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/ Lactation Exposure	Report if: - participant has been exposed to any protocol-specified intervention (eg, procedure, washout or run-in treatment including placebo run-in)	Report all	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event
ECI (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - potential DILI - require regulatory reporting	Not required	Within 24 hours of learning of event
ECI (do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event
Cancer	Report if: - due to intervention - causes exclusion	Report all	Not required	Within 5 calendar days of learning of event (unless serious)
Overdose	Report if: - receiving placebo run-in or other run-in medication	Report all	Not required	Within 24 hours of learning of event

DILI=drug-induced liver injury; ECI=event of clinical interest; NSAE=nonserious adverse event; SAE=serious adverse event

8.4.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events

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

8.4.3 Follow-up of AE, SAE, and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events, including pregnancy and exposure during breastfeeding, ECIs, cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in allocated participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements and global laws and regulations relating to safety reporting to regulatory authorities, IRB/IECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAE) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee) that occurs during the study are reportable to the Sponsor.

All reported pregnancies must be followed to the completion/termination of the pregnancy.

Any pregnancy complication will be reported as an AE or SAE.

The medical reason (example: maternal health or fetal disease) for an elective termination of a pregnancy will be reported as an AE or SAE. Prenatal testing showing fetus will be born with severe abnormalities/congenital anomalies that leads to an elective termination of a pregnancy will be reported as an SAE for the fetus.

Pregnancy outcomes of ectopic pregnancy, 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.

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

Not applicable.

8.4.7 Events of Clinical Interest

Selected serious and nonserious AEs are also known as ECIs and must be reported to the Sponsor.

Events of clinical interest for this study include:

1. An overdose of Sponsor's product, as defined in Section 8.5.

2. Dystonia

3. An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

   *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that must trigger an additional evaluation for an underlying etiology. The study site guidance for assessment and follow up of these criteria can be found in the Investigator Study File Binder (or equivalent).

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

8.5 Treatment of Overdose

For purposes of this study, an overdose will be defined as any dose of any drug administered as part of the study exceeding the dose 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.

8.6 Pharmacokinetics

The decision as to which plasma and/or urine samples collected will be measured for evaluation of PK/pharmacodynamics will be collaboratively determined by the Sponsor (eg, samples at lower doses may not be measured if samples at higher doses reveal undetectable drug concentrations). If indicated, these samples may also be measured and/or pooled for assay in an exploratory manner for metabolites and/or additional pharmacodynamic markers.

8.6.1 Blood Collection for Plasma MK-8189

Sample collection, storage, and shipment instructions for plasma samples will be provided in the operations manual.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Biomarkers

Collection of samples for other biomarker research is also part of this study. The following samples for biomarker research are required and will be collected from all participants as specified in the SoA:

- Blood for Genetic Analysis

8.8.1 Planned Genetic Analysis Sample Collection

The planned genetic analysis sample will be drawn for CYP2C9 genotyping and for planned analysis of the association between genetic variants in DNA and drug response. If the IRB/IEC does not approve of the planned analysis of the association between DNA variation and drug response, or if there is a local law or regulation prohibiting the same, data analysis will be limited to CYP2C9. Leftover extracted DNA will be stored for FBR if the participant provides documented informed consent for FBR.

Sample collection, storage, and shipment instructions for planned genetic analysis samples will be in the operations/laboratory manual.

8.9 Future Biomedical Research Sample Collection

If the participant signs the FBR consent, the following specimens will be obtained as part of FBR:

- Leftover DNA for future research

8.10 Visit Requirements

Visit requirements are outlined in Section 1.3. Specific procedure-related details are provided in Section 8.

8.10.1 Screening

Approximately 4 weeks prior to intervention allocation/randomization, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.

Participants may be rescreened after consultation with the Sponsor. Rescreening should include all screening procedures listed in the SoA, including consent review. Rescreen procedures cannot be conducted the day prior to intervention allocation/randomization if there are Day -1 procedures planned per protocol.

8.10.2 Treatment Period

Refer to the Schedule of Activities (Section 1.3).

8.10.3 Discontinued Participants Continuing to be Monitored in the Study

At any point if a participant discontinues from treatment but continues to be monitored in the study, all of study procedures specified in the SoA may be completed at the discretion of the investigator and with Sponsor agreement.

8.10.4 Poststudy

Participants will be required to return to clinic approximately 14 days after the last dose of study intervention for the poststudy visit. If the poststudy visit occurs less than 14 days after the last dose of study intervention, a subsequent follow-up telephone call should be made at 14 days post the last dose of study intervention to determine if any AEs have occurred since the poststudy clinic visit.

8.10.5 Critical Procedures Based on Study Objectives: Timing of Procedure

For this study, the blood sampling for MK-8189 is the critical procedure.

At any postdose time point, the blood sample for MK-8189 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. Study procedures can be performed prior or after the prescribed/scheduled time.

The order of priority can be changed during the study with joint agreement of the investigator and the Sponsor Clinical Director. Blood samples should be taken after vital sign and ECG assessments or there should be a 10-minute window between a blood draw and the start of a vital sign or ECG assessment.

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

The following variance in procedure collection times will be permitted.

- PK Collection as outlined in [Table 4].

Table 4 Pharmacokinetic (Blood) Collection Windows

PK Collection	PK Collection Window
0 - <1 hr	5 min
1 - <24 hr	15 min
24 - 48 hr	30 min
>48 - 120 hr	30 min domiciled, 2 hrs outpatient visits

- Predose standard safety evaluations: vital signs and ECG (up to 3 hrs prior to dose) laboratory safety tests and physical exam (up to 24 hrs prior to dose)
- Postdose standard safety evaluations: vital signs, ECG, laboratory safety tests, and physical exam
  - <24 hr postdose may be obtained within 15 min of the theoretical sampling time
  - 24 hr - <48 hr postdose may be obtained within 1 hr of the theoretical sampling time
  - 48 hr – 120 hr postdose may be obtained within 2 hr of the theoretical sampling time

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

The dose and administration of the study intervention to any participant may not be modified. If necessary, a participant must be discontinued for the reasons described in Section 7.

The PK/pharmacodynamic sampling scheme currently outlined in the protocol may be modified during the study based on newly available PK or pharmacodynamic data (eg, to obtain data closer to the time of peak plasma concentrations). If indicated, these collected samples may also be assayed in an exploratory manner for metabolites and/or additional pharmacodynamic markers.

Up to additional 75 mL of blood may be drawn for safety, PK, and/or pharmacodynamic analyses. The total blood volume withdrawn from any single participant will not exceed the maximum allowable volume during his/her participation in the entire study (Appendix 8).

The timing of procedures for assessment of safety procedures (eg, vital signs, ECG, safety laboratory tests, etc) may be modified during the study based on newly available data. Additional laboratory safety tests may be added to blood samples previously drawn to obtain additional safety information. These changes will not increase the number of study procedures for a given participant during his/her participation in the entire study.

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 study objectives must be detailed by the Sponsor in a letter to the Study File and forwarded to the investigator for retention. The letter may be forwarded to the IRB/IEC at the discretion of the investigator.

9 STATISTICAL ANALYSIS PLAN

9.1 Statistical Analysis Plan Summary

Separately for each PK parameter, individual values of AUC0-24, Cmax, C24, AUC0-last, and AUC0-inf will be natural log-transformed and evaluated with a linear fixed effects model containing a fixed effect for population (each hepatic impairment group, and normal hepatic function). For each population, least-squares geometric means and their corresponding 95% CIs will be provided. Additionally, to compare participants with hepatic impairment to participants with normal hepatic function, a 2 sided 90% confidence interval for the true GMR (hepatic impairment/normal hepatic function) will be calculated for AUC0-24, Cmax, AUC0-last, and AUC0-inf.

The safety and tolerability of MK-8189 will be monitored by clinical assessment of adverse experiences and other safety measurements (e.g., labs, vital signs, ECGs).

9.2 Responsibility for Analyses

The statistical analysis of the data obtained from this study will be conducted by, or under the direct auspices of, the Early Clinical Development Statistics Department in collaboration with the Quantitative Pharmacology and Pharmacometrics Department and Translational Pharmacology Department of the Sponsor. 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.

9.3 Hypotheses/Estimation

Part 1 Estimation: The AUC0-inf and Cmax in participants with moderate hepatic impairment will be estimated and compared to those obtained from healthy control participants.

Part 2 Estimation: The AUC0-inf and Cmax in participants with mild hepatic impairment will be estimated and compared to those obtained from healthy control participants in Part 1.

9.4 Analysis Endpoints

Primary Endpoints: MK-8189 PK variables (AUC0-inf and Cmax)

Secondary Endpoints: All types of adverse experiences, in addition to laboratory safety tests, 12-lead ECGs, and VS.

Exploratory Endpoints: AUC0-last, AUC0-24, C24hr, Tmax, CL/F, Vd/F and t1/2.

9.5 Analysis Populations

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

All Participants as Treated: The All Participants as Treated Population consists of all participants who received at least one dose of treatment. This population will be used for assessments of safety and tolerability.

Per-Protocol: The Per-Protocol Population consists of the set of data generated by the subset of participants 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 important protocol deviations. Important protocol deviations will be identified to the extent possible by individuals responsible for data collection/compliance, and its analysis and interpretation. Any participants 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 participants who are compliant with the study procedures as aforementioned and have available data from at least one treatment will be included in the per-protocol dataset. This population will be used for the PK analysis.

9.6 Statistical Methods

Pharmacokinetics:

At the end of the study, the final analysis will be run on pooled data from both study parts (if both parts are conducted).

Separately for each PK parameter, individual values of AUC0-24, Cmax, C24, AUC0-last, and AUC0-inf will be natural log-transformed and evaluated with a linear fixed effects model containing a fixed effect for population (each hepatic impairment group, and normal hepatic function). An unstructured covariance matrix will be used to allow for unequal population variances via the REPEATED and GROUP statement in SAS PROC MIXED. Kenward and Roger's method will be used to calculate the denominator degrees of freedom for the fixed effect (DDFM=KR). Ninety-five percent (95%) CIs for the least squares means for each population will be constructed on the natural log scale and will reference the t-distribution. Exponentiating the least-squares means and their corresponding 95% CIs will yield estimates for the population geometric means and confidence intervals about the geometric means on the original scale. Sample SAS code is given below:

```
proc mixed data=data;
  class population;
  model lnpk = population /ddfm=kr;
  repeated/ group= population;
  lsmeans population /cl alpha=0.05;
run;
```

To compare participants in each hepatic impairment population to participants with normal hepatic function, a two sided 90% confidence interval for the true difference in means (hepatic impairment – normal hepatic function) will be calculated for AUC0-24, Cmax, AUC0-last, and AUC0-inf using the mean square error from the model and referencing a t-distribution. These confidence limits will be exponentiated to obtain the 90% confidence interval for the true ratio of geometric means (hepatic impairment/normal hepatic function) for each PK parameter and each hepatic population.

Figures showing individual PK values with GMs (95% CIs) by population, plotted on the natural log scale, will be provided for PK parameters AUC0-24, Cmax, AUC0-last, and AUC0-inf. A figure showing the GMR (hepatic impairment/normal hepatic function) and corresponding 90% CI will be provided for PK parameters AUC0-24, Cmax, AUC0-last, and AUC0-inf.

The above analyses will be carried out for PK calculated from both total and unbound concentrations.

Individual values will be listed for each PK parameter (CL/F, Vd/F, AUC0-24, AUC0-last, AUC0-inf, C24, Cmax, Tmax, fraction unbound for PK parameters (at a minimum of CL/F, Vd/F), and terminal half-life (t1/2)) by population, and the following (non-model-based) descriptive statistics will be provided: N (number of participants with non-missing data), arithmetic mean, standard deviation, arithmetic percent CV (calculated as 100 x standard deviation/arithmetic mean), median, minimum, maximum, geometric mean, and geometric percent CV (calculated as 100 x sqrt(exp(s2) - 1), where s2 is the observed variance on the natural log-scale).

The relationship between MK-8189 PK and hepatic impairment will be examined in an exploratory manner via a scatter plot of PK values (AUC0-24, Cmax, AUC0-last, and AUC0-inf) versus the Child-Pugh score. Plots of PK values (AUC0-24, Cmax, AUC0-last, and AUC0-inf) and the baseline laboratory components of the Child-Pugh score (i.e., bilirubin, albumin levels, and INR time) may be provided. Plots of PK parameter values (AUC0-24, Cmax, AUC0-last, and AUC0-inf) vs age and body weight may also be provided.

Additionally, individual participant PK parameter values (AUC0-24, Cmax, AUC0-last, and AUC0-inf) may also be plotted against CrCL (estimated from Cockcroft-Gault Equation), using different symbols to identify participants from each population. Note: CrCL will be calculated as the mean of the two values determined at screening.

Safety: The safety and tolerability of MK-8189 will be monitored by clinical assessment of adverse experiences and other safety measurements (e.g., labs, vital signs, ECGs).

9.7 Interim Analyses

A preliminary analysis of Part 1 data may be conducted to inform on whether the study will proceed to Part 2.

9.8 Multiplicity

No multiplicity adjustment is needed as the study has no hypothesis testing.

9.9 Sample Size and Power Calculations

The sample size selected for each population to evaluate the effect of hepatic impairment on the PK of MK-8189 was not chosen to satisfy any a priori statistical requirement. This sample size (N=6-8 per group) has historically been shown to be sufficient for studies of this type and should provide adequate data to support the planned analyses. Nevertheless, estimates of the expected precision of the estimates, based on these sample sizes and the known variability obtained from hepatic PK studies are presented below.

The precision of the estimated ratios of geometric means (hepatic impairment / normal hepatic function) of PK parameters obtained from this study can be assessed by calculating the half-width of the 90% CIs expected for the given sample size and assumed variability. The pooled between-subject standard deviation (on the natural log scale) for AUC0-24 in participants with normal hepatic function and participants with schizophrenia on 4 mg MK-8189 was 0.29 ln(nM*hr) from P003. The pooled between-subject standard deviation for AUC0-24 was obtained using the between subject standard deviation of 0.16 ln(nM*hr) in healthy and between subject deviation of 0.39 ln(nM*hr) in participants with schizophrenia on 4 mg MK-8189 in P003. The variability for AUC0-inf in participants with moderate hepatic impairment is assumed to be similar to the variability in AUC0-24 in participants with schizophrenia for 4 mg dose from P003. The variability for AUC0-inf in participants with normal hepatic function is assumed to be similar to the variability in AUC0-24 in healthy participants for 4 mg dose from P003. Assuming a minimum sample size of 6 participants per population and observed between-subject standard deviation as given above, then the half width of the 90% CIs of GMRs for MK-8189 AUC0-inf on the log scale will be 0.30. The lower and upper 90% confidence limits for the true GMRs will be given by OBS/1.35 and OBS*1.35 for AUC0-inf, where OBS is the observed GMR. Thus, for example, if the observed GMR for AUC0-inf was 1.50, then the 90% CI for the GMR would be 1.11 to 2.03.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Code of Conduct for Clinical Trials

Merck Sharp and Dohme Corp., a subsidiary of Merck & Co., Inc. (MSD)

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, 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 participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (including all applicable data protection laws and regulations), and International Council for Harmonisation Good Clinical Practice (ICH-GCP), and also in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Highest ethical and scientific standards shall be endorsed for all clinical interventional investigations sponsored by MSD 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 that are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials, which are not under the full control of MSD.

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 MSD or comparator products. Alternatively, MSD may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine patient preferences, etc.

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial and shall respect the data protection rights of all participants, trial site staff and, where applicable, third parties. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel (or individuals acting on behalf of MSD) to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus

source documentation according to standard operating procedures. Per MSD policies and procedures, if potential fraud, scientific/research misconduct, privacy incidents/breaches or Clinical Trial-related Significant Quality Issues are reported, such matters are investigated. When necessary, appropriate corrective and/or preventative actions are defined and regulatory authorities and/or ethics review committees are notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish the primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the pre-specified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. 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 such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). 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. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

A. Regulatory Authority and Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

All protocols and protocol amendments will be submitted by MSD for regulatory authority acceptance/authorization prior to implementation of the trial or amendment, in compliance with local and/or national regulations.

The protocol, protocol amendment(s), informed consent form, investigator's brochure, and other relevant trial documents must be reviewed and approved by an IRB/IEC before being implemented at each site, in compliance with local and/or national regulations. Changes to the protocol that are required urgently to eliminate an immediate hazard and to protect participant safety may be enacted in anticipation of ethics committee approval. MSD will inform regulatory authorities of such new measures to protect participant safety, in compliance with local and/or national regulations.

B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants 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.

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Participants may withdraw from an MSD 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

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible, as well as all applicable data protection rights. Unless required by law, only the investigator, Sponsor (or individuals acting on behalf of MSD), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

Genomic research will only be conducted in accordance with a protocol and informed consent authorized by an ethics committee.

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

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

10.1.3 Data Protection

The Sponsor will conduct this study in compliance with all applicable data protection regulations.

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

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

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

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

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

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

10.1.3.3 Confidentiality of IRB/IEC Information

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

10.1.4 Publication Policy

The results of this study may be published or presented at scientific meetings. The Sponsor will comply with the requirements for publication of study results. In accordance with

standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

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

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

10.1.5 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the EMA clinical trial Directive 2001/20/EC, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study site contact information.

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

10.1.6 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GCP (eg, International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use GCP: Consolidated Guideline and other generally accepted standards of GCP); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical study.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by MSD, is provided in this appendix under the Code of Conduct for Clinical Trials.

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

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

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

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

10.1.7 Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

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

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

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

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

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

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

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during

the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's participants. Source documents and data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source documents are filed at the investigator's site.

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

10.1.9 Study and Site Closure

The Sponsor or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor or designee will promptly notify that study site's IRB/IEC as specified by applicable regulatory requirement(s).

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in [Table 5] will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 5 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Chemistry	Blood Urea Nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the upper limit of normal)
	Albumin	Bicarbonate or Total CO_2	Chloride	Phosphorous
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose (fasting)	Calcium	Alkaline phosphatase	
Coagulation	• INR (International normalized ratio, for hepatic impaired participants only)			
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, [bilirubin, urobilinogen, nitrite, leukocyte esterase] by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• Follicle-stimulating hormone (as needed in women of nonchildbearing potential only) • Serum or urine alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines). Alcohol breath test for alcohol screen is permitted. • Highly sensitive serum or urine human chorionic gonadotropin (β-hCG) pregnancy test (as needed for WOCBP) • Serology (HIV-1 and HIV-2 antibodies in all participants, HBsAg, and hepatitis C virus antibody in healthy participants only			
NOTES: The investigator (or medically qualified designee) must document their review of each laboratory safety report.				

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

- NOTE: For purposes of AE definition, study intervention (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, diagnostic agent, medical device, combination product, or protocol specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.

- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.

- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."

- Any new cancer or progression of existing cancer.

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened.
- Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.2 Definition of SAE

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

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

a. **Results in death**

b. **Is life-threatening**

- The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. **Requires inpatient hospitalization or prolongation of existing hospitalization**

- Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not an SAE.) A pre-existing condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant's medical history.

d. **Results in persistent or significant disability/incapacity**

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza,

and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. **Is a congenital anomaly/birth defect**

- In offspring of participant taking the product regardless of time to diagnosis.

f. **Other important medical events**

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3 Additional Events Reported

Additional events that require reporting

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor.

- Is a cancer
- Is associated with an overdose

10.3.4 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant

number, will be blinded on the copies of the medical records before submission to the Sponsor.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity/toxicity

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) reported during the study and assign it to 1 of the following categories:

  - Mild: An event that is easily tolerated by the participant, causing minimal discomfort, and not interfering with everyday activities (for pediatric studies, awareness of symptoms, but easily tolerated).

  - Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities (for pediatric studies, definitely acting like something is wrong).

  - Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category used for rating the intensity of an event; and both AE and SAE can be assessed as severe (for pediatric studies, extremely distressed or unable to do usual activities).

Assessment of causality

- Did the Sponsor's product cause the AE?

- The determination of the likelihood that the Sponsor's product caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information.

- **The following components are to be used to assess the relationship between the Sponsor's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the AE:

  - **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill

count, diary, etc), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?

- **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with investigational medicinal product)?

- **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.

- **Dechallenge:** Was the Sponsor's product discontinued or dose/exposure/frequency reduced?

    - If yes, did the AE resolve or improve?

    - If yes, this is a positive dechallenge.

    - If no, this is a negative dechallenge.

  (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the study is a single-dose drug study; or (4) Sponsor's product(s) is/are only used 1 time.)

- **Rechallenge:** Was the participant re-exposed to the Sponsor's product in this study?

    - If yes, did the AE recur or worsen?

    - If yes, this is a positive rechallenge.

    - If no, this is a negative rechallenge.

  (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the study is a single-dose drug study; or (3) Sponsor's product(s) is/are used only 1 time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND 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 PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR, AND IF REQUIRED, THE IRB/IEC.

- **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?

- The assessment of relationship will be reported on the case report forms/worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.

- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).

  - Yes, there is a reasonable possibility of Sponsor's product relationship:

    - There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.

  - No, there is not a reasonable possibility of Sponsor's product relationship:

    - Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)

- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

- New or updated information will be recorded in the CRF.

- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.5 Reporting of AEs, SAEs, and Other Reportable Safety Events to the Sponsor

AE, SAE, and other reportable safety event reporting to Sponsor via electronic data collection tool

- The primary mechanism for reporting to the Sponsor will be the EDC tool.
    - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
    - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
        - Reference Section 8.4.1 for reporting time requirements.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

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

10.4 Appendix 4: Medical Device and Drug-device Combination Products: Product Quality Complaints/Malfunctions: Definitions, Recording, and Follow-up

Not applicable.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below):

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraception Requirements

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency[b] *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen- only contraceptive implant[c,d] • IUS[c,e] • Non-hormonal IUD • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Contraceptive Methods That Are User Dependent[b] *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen- containing) hormonal contraception[c,d] - Oral - Intravaginal - Transdermal - Injectable
• Progestogen-only hormonal contraception[c,d] - Oral - Injectable
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
Methods That Are Not Considered Highly Effective *Failure rate of >1% per year when used consistently and correctly.*
• Progesterone-only hormonal contraception where inhibition of ovulation is not the primary mode of action • Male or female condom with or without spermicide • Cervical cap, diaphragm, or sponge with spermicide • A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double barrier methods)[f]
[a] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. [b] Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly). [c] Male condoms must be used in addition to female participant hormonal contraception. [d] If locally required, in accordance with CTFG guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. [e] IUS is a progestin releasing IUD. [f] A combination of male condom with either cap, diaphragm, or sponge with spermicide are considered acceptable, but not highly effective, birth control methods. Note: The following are not acceptable methods of contraception: - Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM. - Male and female condom should not be used together (due to risk of failure with friction).

10.6 Appendix 6: 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 study as outlined in Section 8.9 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 with which drugs/vaccines may interact
- 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. Participants for Enrollment

All participants enrolled in the clinical study will be considered for enrollment in future biomedical research.

b. Informed Consent

Informed consent for specimens (ie, DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all participants or legal guardians, at a study visit by the investigator or his or her designate. Informed consent for future biomedical research should be presented to the participants on the visit designated in the SoA. If delayed, present consent at next possible Participant Visit. Consent forms signed by the participant will be kept at the clinical study site under secure storage for regulatory reasons.

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

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of participant consent for future biomedical research will be captured in the eCRFs. Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen(s)

Collection of specimens for future biomedical research will be performed as outlined in the SoA. In general, if additional blood specimens are being collected for future biomedical research, these will usually be obtained at a time when the participant is having blood drawn for other study purposes.

4. Confidential Participant 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 participants' clinical information with future test results. In fact, little or no research can be conducted without connecting the clinical study data to the specimen. The clinical data allow specific analyses to be conducted. Knowing participant characteristics like sex, age, medical history and intervention 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 study 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 participant identifiers and this unique code will be held at the study 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 (eg, 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 future biomedical research protocol and consent. 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

Participants may withdraw their consent for future biomedical research and ask that their biospecimens not be used for future biomedical research. Participants may withdraw consent at any time by contacting the investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the participant'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 participant 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 study data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main study records) or the specimens have been completely anonymized, there will no longer be a link between the participant'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 study 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 study, the study 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 study 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 Participants

No information obtained from exploratory laboratory studies will be reported to the participant, family, or physicians. Principle reasons not to inform or return results to the participant include: Lack of relevance to participant 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 participants. Participants 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 participants diagnosed and treated on Sponsor clinical studies for future biomedical research.

11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the participant have been minimized and are described in the future biomedical research informed consent.

The Sponsor has developed strict security, policies, and procedures to address participant 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 emailed directly to clinical.specimen.management@merck.com.

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10.7 Appendix 7: Country/Site-specific Requirements

10.7.1 Site 0001-specific Requirements

Section 1.3.1 Schedule of Activities - Hepatic Impairment Participants

C-SSRS Baseline Version at screening is mandatory. Refer to Appendix 7 Section 8.3.5 for further information.

C-SSRS Since Last Assessment Version at the Day -1 predose, 48 hours postdose, and post-study visits are mandatory. Refer to Appendix 7 Section 8.3.5 for further information.

Section 1.3.2 Schedule of Activities - Healthy Matched Participants

C-SSRS Baseline Version at screening is mandatory. Refer to Appendix 7 Section 8.3.5 for further information.

C-SSRS Since Last Assessment Version at the Day -1 predose, 48 hours postdose, and post-study visits are mandatory. Refer to Appendix 7 Section 8.3.5 for further information.

Section 5.2.1 Exclusion Criteria for Healthy Participants

Exclusion Criteria: Is at imminent risk of self-harm, based on clinical interview and responses on the CSSRS, or of harm to others in the opinion of the investigator. Participants must be excluded if they report suicidal ideation with intent, with or without a plan or method (eg, positive response to item 4 or 5 in assessment of suicidal ideation on the CSSRS) in the past 5 years or suicidal behavior in their lifetime.

Section 5.2.2 Exclusion Criteria for Hepatically Impaired Participants

Exclusion Criteria: Is at imminent risk of self-harm, based on clinical interview and responses on the CSSRS, or of harm to others in the opinion of the investigator. Participants must be excluded if they report suicidal ideation with intent, with or without a plan or method (eg, positive response to item 4 or 5 in assessment of suicidal ideation on the CSSRS) in the past 5 years or suicidal behavior in their lifetime.

Section 8.3.5 Suicidal Ideation and Behavior Monitoring

Section 8.3.5.1 Clinical Assessments for Suicidal Ideation and Behavior Monitoring

Suicidal ideation and behavior will be prospectively assessed during this study using the C-SSRS. The C-SSRS should be administered by trained raters at the time points indicated in the SoA. In addition, C-SSRS will be administered at any unscheduled visit where safety assessments are performed. The C-SSRS will not be routinely administered at visits with a sole purpose of PK sampling and/or witnessed study intervention administration. Site staff should review the contents of the C-SSRS for completeness. If the C-SSRS is administered by someone other than the investigator, consider providing the completed C-SSRS to the investigator for review, before their assessment of the participant and to further inform their

evaluation. The C-SSRS is not explicit about whether the participant specifically has ideation at the time of screening. If a participant reports a prior history of ideation/behavior at screening, the assessor should also inquire and document if this is also present at the time of the Screening Visit.

Participants who at any time during this study report suicidal ideation or behavior that is considered to be an AE, either between visits or during visit interviews, must be assessed by the investigator. Participants who report suicidal ideation with intent, with or without a plan or method (ie, a positive response to items 4 or 5 in the assessment of suicidal ideation on the C-SSRS) or suicidal behavior must be evaluated that day by a psychiatrist or other trained mental health professional who is a licensed psychologist, social worker, or mental health nurse practitioner (or comparable professional qualification in countries outside the United States). After that evaluation, only those participants whose suicidal ideation is considered by the evaluator to be passive, and who expressly deny any intent to act, and who, after evaluation, are not judged to be at serious risk for self-harm during the course of the study may continue in the study; other participants must be discontinued from study participation and receive appropriate clinical follow-up care to ensure their safety.

Section 9.6 Statistical Methods

If the C-SSRS data are collected then the responses on the C-SSRS will be classified according to 11 prespecified categories as described in protocol Appendix 7. The most severe treatment-emergent event within each of three broad categories (suicidal ideation, suicidal behavior, and non-suicidal self-injurious behavior) reported at a visit will be used for reporting. An event is considered treatment-emergent during the assessment phase if it is either newly emerged or is more severe than the most severe event reported to have occurred in the trial-defined pre-treatment reference period.

Mapping Between the 11 Categories of Suicidal Ideation and Behavior and the C-SSRS

Category	C-SSRS Question (from eCRF)[†]
Suicidal ideation	
1. Passive	1. Wish to be dead
2. Active: Nonspecific (no method, intent, or plan)	2. Non-specific active suicidal thoughts
3. Active: Method, but no intent or plan	3. Active suicidal ideation with any methods (not plan) without intent to act
4. Active: Method and intent, but no plan	4. Active suicidal ideation with some intent to act, without specific plan
5. Active: Method, intent and plan	5. Active suicidal ideation with specific plan and intent
Suicidal behavior	
6. Preparatory actions toward imminent suicidal behaviors	Preparatory acts or behavior
7. Aborted attempt	Aborted attempt
8. Interrupted attempt	Interrupted attempt
9. Suicide attempt	Actual attempt
10. Completed suicide	Completed suicide
Self-injurious behavior, no suicidal intent	Has subject engaged in non-suicidal self-injurious behavior?
[†]Data are "yes" or "no"	

10.8 Appendix 8: Blood Volume Table

	Pre-study	Treatment Periods	Poststudy	Total Collections	mL Per Collection	Total mL/ Test
Participants with hepatic impairment						
Laboratory Safety Tests (all participants; includes FSH if applicable, β-hCG if applicable, and HIV/Hepatitis screen)	2	2	1	5	17	85
Blood for Planned Genetic Analysis	1	0	0	1	8.5	8.5
Blood for MK-8189	1	15	0	16	4	64
Blood for Protein Binding Plasma	1	0	0	1	10	10
Total Blood Volume per Participants with hepatic impairment for Part 1 and Part 2 [a]						167.5 mL
Healthy Matched Participants						
Laboratory Safety Tests (all participants; includes FSH if applicable, β-hCG if applicable, and HIV/Hepatitis screen)	2	1	1	4	17	68
Blood for Planned Genetic Analysis	1	0	0	1	8.5	8.5
Blood for MK-8189	1	11	0	12	4	48
Blood for Protein Binding Plasma	1	0	0	1	10	10
Total Blood Volume per Healthy matched participants for Part 1 [a]						134.5 mL

[a] If additional pharmacokinetic/pharmacodynamic and/or safety analysis is necessary, additional blood (up to 75 mL) may be obtained.

10.9 Appendix 9: 12-Lead Electrocardiogram Abnormality Criteria

12-Lead Electrocardiogram Abnormality Criteria		
	Screen Failure Criteria	Potentially Significant Postrandomization Findings (clarification on action to take)
RHYTHM		
Sinus Tachycardia	>110 bpm	HR >110 bpm and HR increase of ≥25 bpm from baseline
Sinus Bradycardia	<40 bpm	HR <40 bpm and HR decrease of ≥5 bpm from baseline
Sinus Pause/Arrest	>2.0 seconds	>2.0 seconds
Atrial Premature Complex	> 1 beat	≥ 3 beats
Ventricular Premature Complex	All	≥ 3 beats
Ectopic Atrial Rhythm	None	None
Junctional Rhythm	Junctional Rhythm with HR <40 bpm	Junctional Rhythm with HR <40 bpm
Idioventricular Rhythm	All	All
Atrial Fibrillation	All	All
Atrial Flutter	All	All
Supraventricular Tachycardia	All	All
Ventricular Tachycardia	All	All
AXIS		
Left Axis Deviation	RBBB With Left Anterior Hemiblock (LAHB)	New Onset LAHB
Right Axis Deviation	RBBB With Left Posterior Hemiblock (LPHB)	New Onset LPHB
CONDUCTION		
1st Degree AV Block	PR ≥230 ms	PR ≥ 230 ms + Increase of >15 ms; or PR Increase of >25%
2nd Degree AV Block	Mobitz Type II	Mobitz Type II
3rd Degree AV Block	All	All
LBBB	All	All
RBBB	RBBB With LAHB/LPHB as Defined Above	New Onset RBBB (Not Including Rate-related)
Incomplete Right BBB (ICRBBB) (QRS <120 ms)	No Exclusion	Nothing
Short PR/ Preexcitation Syndrome	Delta Wave + PR <120 ms	Delta Wave + PR <120 ms
Other Intra-Ventricular Conduction Delay	QRS ≥130 ms	QRS ≥130 ms + Increase of ≥10 ms
QTc		
Male	QTcF >450 ms	QTc (B or F) ≥500 ms or Increase of ≥60 ms From Baseline
Female	QTcF >450 ms	QTc (B or F) ≥500 ms or Increase of ≥60 ms From Baseline

12-Lead Electrocardiogram Abnormality Criteria		
	Screen Failure Criteria	Potentially Significant Postrandomization Findings (clarification on action to take)
HYPERTROPHY		
Atrial Abnormalities	Definite Evidence of P Mitrale or P Pulmonale	Definite Evidence of P Mitrale or P Pulmonale
Ventricular Abnormalities	Voltage Criteria for LVH Plus Strain Pattern	Voltage Criteria for LVH Plus Strain Pattern
MYOCARDIAL INFARCTION		
Acute or Recent	All	All
Old	All	All
ST/T MORPHOLOGY		
ST Elevation Suggestive of Myocardial Injury	In 2 or more contiguous leads	In 2 or more contiguous leads
ST Depression Suggestive of Myocardial Ischaemia	In 2 or more contiguous leads	In 2 or more contiguous leads
T-wave Inversions Suggestive of Myocardial Ischaemia	In 2 or more contiguous leads	In 2 or more contiguous leads
Non-specific ST-T Changes (In 2 or More Leads)	No exclusion	In 2 or more contiguous leads
PACEMAKER	All	All
Baseline is defined as Predose Day 1; ms=milliseconds, mm=millimeter		

10.10 Appendix 10: Algorithm for Assessing Out of Range Laboratory Values

For all laboratory values obtained at prestudy (screening) visit and/or predose evaluation:

A. If all protocol-specified laboratory values are normal, the participant may enter the study.

B. If a protocol specified laboratory value is outside of the parameter(s) outlined in the inclusion/exclusion criteria (including a repeat if performed), the participant will be excluded from the study.

C. If ≥1 protocol-specified laboratory value not specified in the inclusion/exclusion criteria is outside the normal range, the following choices are available:

    1. The participant may be excluded from the study;

    2. The participant may be included in the study if the abnormal value(s) is NCS (the investigator must annotate the laboratory value "NCS" on the laboratory safety test source document).

    3. The participant may be included in the study if the abnormality is consistent with a pre-existing medical condition which is not excluded per protocol (eg, elevated eosinophil count in a participant with asthma or seasonal allergies), the medical condition should be annotated on the laboratory report.

    OR

    4. The abnormal test may be repeated (refer items a. and b. below for continuation of algorithm for repeated values).

        a. If the repeat test value is within the normal range, the participant may enter the study.

        b. If the repeat test value is still abnormal, the study investigator will evaluate the potential participant with a complete history and physical examination, looking especially for diseases that could result in the abnormal laboratory value in question. If such diseases can be ruled out, and if the abnormal laboratory value is not clinically relevant, then the participant may enter the study.

D. If there is any clinical uncertainty regarding the significance of an abnormal value, the participant will be excluded from the study.

10.11 Appendix 11: Child-Pugh classification of the severity of liver disease

Finding	Points Scored for Each Observed Finding		
	1	2	3
Encephalopathy [a]	None	1 or 2 (or suppressed with medication)	3 or 4 (or refractory)
Ascites [b]	Absent	Slight or Subject on 1 or 2[c] medication to control ascites	Moderate or Severe or Subject on 2[c] or more medications to control ascites or requires paracentesis
Bilirubin (mg/dL)	<2	2 to 3	>3
Albumin (g/dL)	>3.5	2.8 to 3.5	<2.8
INR	<1.7	1.7 to 2.3	>2.3

a. Grade 0: normal consciousness, personality, neurological examination, electroencephalogram

Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cycles per second waves

Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves

Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves

Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2-3 cycles per second delta activity

b. Ascites is graded according to the following criteria:

Absent: No ascites detectable by manual investigation.

Slight: Ascites palpation doubtful

Moderate: Ascites detectable by palpation

Severe: Necessity of paracentesis, does not respond to medication treatment.

c. If a combination of 2 medications are used primarily to minimize adverse effects (e.g. potassium imbalance), ascites may be scored as 2 per the investigator's clinical judgement.

10.12 Appendix 12: Abbreviations

Abbreviation	Expanded Term
AAP	Atypical Antipsychotic
ADME	Absorption, distribution, metabolism, and excretion
AE	adverse event
ALT	Alanine transaminase
AN	Allocation number
AST	Aspartate transaminase
AUC	Area under the curve
β-hCG	β-human chorionic gonadotropin
BCS	Biopharmaceutics Classification System
BMI	body mass index
BP	blood pressure
cAMP/cGMP	Adenosine 3',5'-cyclic monophosphate/Guanosine 3',5'-cyclic monophosphate
CCU	Critical Care Unit
CG	Cockcroft-Gault
CGI-S	Clinical Global Impression, Severity of Illness
CI	Confidence Interval
CL	Clearance
Cmax	Maximum plasma concentration
CrCl	creatinine clearance
CR	Controlled Release
CRF	Case Report Form
CRU	clinical research unit
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
CTFG	Clinical Trial Facilitation Group
CYP	Cytochrome P450
DDI	Drug-Drug Interaction
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
EDC	electronic data collection
EMA	European Medicines Agency
EPS	Extrapyramidal symptoms
FBR	Future Biomedical Research
FDAAA	Food and Drug Administration Amendments Act
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GCV	Generalized cross validation
GMR	Geometric Mean Ratio
HBsAg	Hepatitis B surface antigen
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICU	Intensive Care Unit
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee

Abbreviation	Expanded Term
INR	International Normalized Ratio
IR	Immediate Release
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
LS	Least Squares
NCS	not clinically significant
OR	Odds Ratio
PDE10A	cAMP and cAMP-inhibited cGMP 3',5'-cyclic phosphodiesterase 10A
P-gp	P-glycoprotein 1
PANSS	Positive and Negative Syndrome Scale
PK	pharmacokinetic
POC	Proof of Concept
QD	Once daily
RNA	ribonucleic acid
SAE	serious adverse event
SoA	schedule of activities
SUSAR	suspected unexpected serious adverse reaction
t1/2	Half-life
Tmax	Time to maximum plasma concentration
UDS	urine drug screen
Vd	volume of distribution
VS	vital sign
WBC	white blood cell
WOCBP	woman/women of childbearing potential
WONCBP	woman/women of nonchildbearing potential

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