Official Protocol Title:	An Open-Label, Single-Dose Study to Evaluate the Pharmacokinetics of Islatravir (MK-8591) in Participants with Moderate Hepatic Impairment
NCT number:	NCT04515641
Document Date:	29-Apr-2021

Title Page

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Protocol Title: An Open-Label, Single-Dose Study to Evaluate the Pharmacokinetics of Islatravir (MK-8591) in Participants with Moderate Hepatic Impairment

Protocol Number: 030-01

Compound Number: MK-8591

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	128,595

Approval Date: 29 April 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
MK-8591-030-01	29-APR-2021	The original protocol is being amended to reduce the minimum number of required participants from 3 to 2 who have a score of 2 or higher on at least one of the laboratory parameters in inclusion criterion #2 in Section 5.1.2, in order to optimize recruitment of hepatically impaired participants. Additionally, the emergency unblinding call center and photograph of rash related text, as well as minor edits to the inform consent text in Section 8.4.1 are included in the amendment.
Original Protocol (MK-8591-030-00)	21-JULY-2020	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: [01]

Overall Rationale for the Amendments:

The original protocol is being amended to reduce (from 3 to 2) the minimum number of required participants with a score of 2 or higher on at least one of the laboratory parameters in inclusion criterion #2 in Section 5.1.2, in order to optimize recruitment of hepatically impaired participants. Additionally, the emergency unblinding call center and photograph of rash related text, as well as minor edits to the inform consent text in Section 8.4.1 are included in the amendment.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
5.1.2, Inclusion Criteria for Hepatically Impaired Participants	Reduced the minimum number of required participants with a score of 2 or higher on at least one of the laboratory parameters from 3 to 2 (inclusion criterion #2).	Potential participants with the lab abnormality criterion appear quite rare in the pool of recruitable subjects. In order to optimize recruitment of potential subjects with moderate hepatic insufficiency in general and facilitate the understanding of the effect of hepatic insufficiency, this requirement is being eased.
8.1.10, Participant Blinding/Unblinding	Added emergency unblinding call center related text. "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."	Text was added to clarify that an emergency unblinding call center is available for the study.

Section # and Name	Description of Change	Brief Rationale
8.3.5, Photograph of Rash	Added the new section for photographing skin reactions. "Photographs of any rash are highly recommended to be taken immediately, along with any additional information that may assist the investigator in the evaluation of the skin reaction, skin eruption or rash occurrence, in determining etiology and drug relationship."	Photographs are necessary to assist the investigator to evaluate the skin reaction, skin eruption or rash occurrence. As such, text was added regarding the recommended evaluation.
10.8, Appendix 8: Blood Volume Table	Removed "1" in prestudy column and added 1 to the count in the treatment period column for the following sample collection listed in the table: • Blood for Genetic Analysis • Blood for Plasma ISL • Blood for plasma M4	To correct typographic errors. There is no sample collection in prestudy for the three sample types per Section 1.3 Schedule of Activities.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: An Open-Label, Single-Dose Study to Evaluate the Pharmacokinetics of Islatravir (MK-8591) in Participants with Moderate Hepatic Impairment

Short Title: Islatravir (MK-8591, ISL) Hepatic Impairment Study

Acronym: Not applicable

Hypotheses, Objectives, and Endpoints:

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

Primary Objectives	Primary Endpoints
- To evaluate the plasma pharmacokinetics of ISL (e.g., AUC0-∞, AUC0-last, Cmax, Tmax, apparent terminal t½, CL/F, and Vz/F) after a single oral dose of 60 mg ISL in participants with moderate hepatic impairment compared to healthy control participants. Estimation: In participants with moderate hepatic impairment, plasma pharmacokinetics (AUC0-∞, Cmax) of ISL following a single 60 mg ISL dose will be estimated and compared to those observed in healthy mean matched control participants.	- AUC0-∞, AUC0-last, Cmax, Tmax, apparent terminal t½, CL/F, and Vz/F of plasma ISL
Secondary Objectives	Secondary Endpoints
- To evaluate the safety and tolerability of ISL in participants with moderate hepatic impairment.	- Adverse experiences, laboratory safety tests, ECGs, and VSs.
- To evaluate the intracellular pharmacokinetics (e.g., AUC0-∞, AUC0-last, Cmax, C24, C168, C672, Tmax, and apparent terminal t½) of ISL triphosphate (ISL-TP) in peripheral blood mononuclear cells (PBMCs) after a single oral dose of 60 mg ISL in participants with moderate hepatic impairment compared to healthy control participants.	- AUC0-∞, AUC0-last, Cmax, C24, C168, C672, Tmax, and apparent terminal t½ of ISL-TP in PBMC

Overall Design:

Study Phase	Phase 1
Primary Purpose	Treatment
Indication	Treatment and prevention of HIV Infection
Population	Participants with Moderate Hepatic Impairment and Healthy Participants
Study Type	Interventional
Intervention Model	Single Group This is a single-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 12 participants will be allocated.

Intervention Groups and Duration:

Intervention Groups	<table><tr><th>Intervention Group Name</th><th>Drug</th><th>Dose Strength</th><th>Dose Frequency</th><th>Route of Administration</th><th>Use</th></tr><tr><td>Moderate Hepatic Impairment Group</td><td>MK-8591 (ISL)</td><td>60 mg</td><td>Single dose</td><td>Oral</td><td>Experimental</td></tr><tr><td>Healthy Matched Control Group</td><td>MK-8591 (ISL)</td><td>60 mg</td><td>Single dose</td><td>Oral</td><td>Experimental</td></tr></table>
Total Number of Intervention Groups/ Arms	2
Duration of Participation	Each participant will participate in the study for approximately 2 months from the time the participant signs the Informed Consent Form through the final contact.

Study Governance Committees:

Steering Committee	No
Executive Oversight Committee	No
Data Monitoring Committee	No
Clinical Adjudication Committee	No
There are no governance committees in this study.	

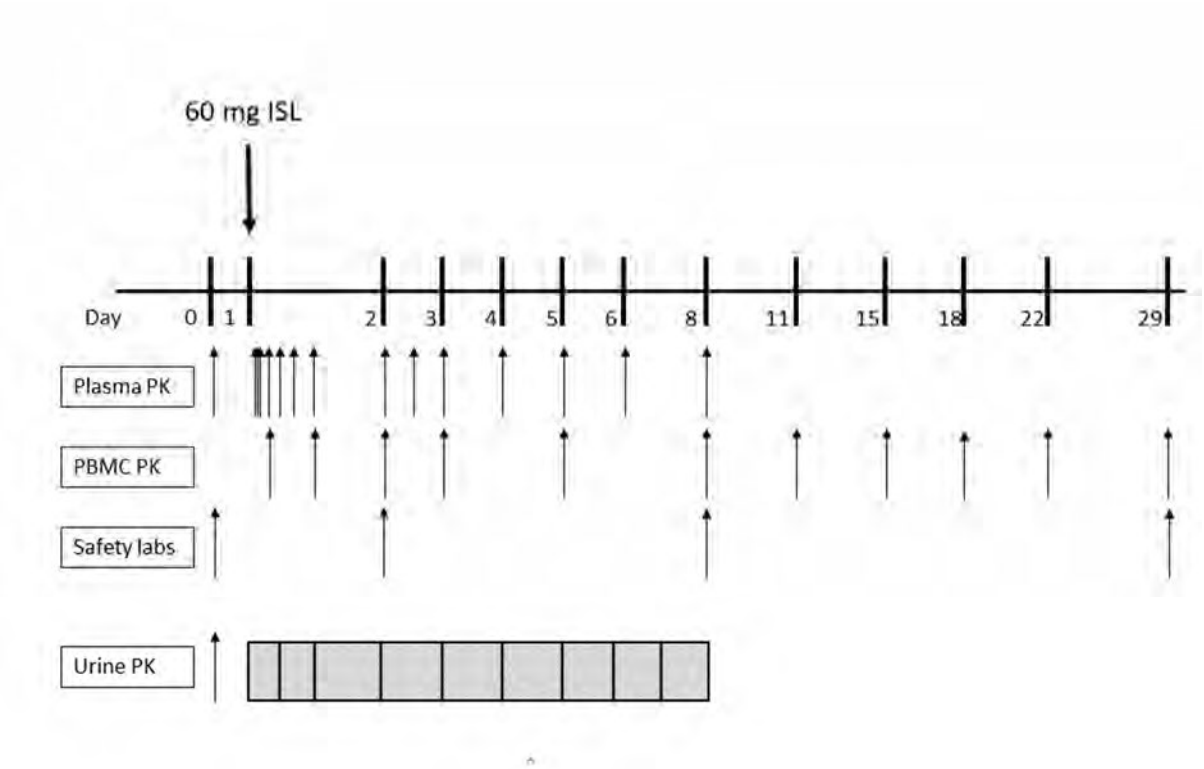
Study Accepts Healthy Volunteers: Yes

A list of abbreviations used in this document can be found in Appendix 11.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Study Design



1.3 Schedule of Activities

All Participants																				
				Intervention																Notes:
Scheduled Day				1									2	2	3	4	5	6	8	
Scheduled Hour	Screening	Check-in	Pre-dose	0	0.25	0.5	1	2	4	6	8	12	24	36	48	72	96	120	168	
Administrative/Study 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																	
Domiciling		X----------																	X	*Refer to Section 8.1.11.*
MK-8591 (ISL) Administration				X																
Safety Procedures																				
Full physical examination	X		X[a]																	Symptom-driven 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																			*Refer to Section 8.3.1.*
Assessment of Liver Function using Child-Pugh Classification	X																			To be performed in participants with Hepatic impairment only.
Vital Signs (heart rate, blood pressure)	X		X										X						X	*Refer to Section 8.3.2*
Respiratory Rate	X		X																	*Refer to Section 8.3.2*
Body Temperature	X		X																	*Refer to Section 8.3.2*
12-lead ECG	X		X										X						X	*Refer to Section 8.3.3*
Hepatitis B and C screen (per site SOP)	X																			For healthy participants only
HIV-1, HIV-2 Screen	X																			

All Participants																				
				Intervention																Notes:
Scheduled Day				1									2	2	3	4	5	6	8	
Scheduled Hour	Screening	Check-in	Pre-dose	0	0.25	0.5	1	2	4	6	8	12	24	36	48	72	96	120	168	
Serum/urine β-Human Chorionic Gonadotropin (β-hCG)	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 Follicle Stimulating Hormone (FSH)	X																			For WONCBP. *Refer to Section 10.2 and 10.5*
GC/CT (gonorrhea + chlamydia) screen	X																			Per site SOP
Syphilis serologic screening	X																			Per site SOP
Trichomonas testing	X																			If available, per site SOP
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.*
AE/SAE review	X----------																		----------X	*Refer to Section 8.4.*
Pharmacokinetics/Biomarkers																				
Blood Collection for Plasma ISL			X[a]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	*Refer to Section 8.6.1.*
Blood collection for M4 metabolite			X[a]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Blood for PBMC ISL-TP[b]			X[a]						X				X		X		X		X	
Urine collection for ISL and M4 metabolite			X[c]	X----------						X-------X		X------X		X------X		x-x	x-x	x--x	x--x	Urine intervals: Predose, 0-4, 4-8, 8-24, 24-48,48-72, 72-96,96-120,120-144, 144-168 hr
Blood for Genetic Analysis			X																	Collect predose from enrolled participants only. *See Section 8.8*

a. Pre-dose PE, pregnancy test, urine drug screen, safety labs, and blood sample for plasma ISL/M4 metabolite/PBMC ISL-TP can be conducted/collected within 24 hours prior to study drug administration. Results from predose safety labs and drug/alcohol screen must be reviewed prior to treatment allocation.
b. PBMC samples will also be analyzed for ISL diphosphate (ISL-DP) to check that sample stabilization is performed properly. No ISL-DP concentrations or PK parameters will be reported.
c. A spot urine sample will be collected prior to study drug administration.

All Participants						
	Intervention					Notes
Scheduled Day	11	15	18	22	Post-trial visit/ Day 29 [d]	
Scheduled Hour	240	336	408	504	672	
Administrative/ Study Procedures						
Concomitant Medication Review	X	X	X	X	X	
Safety Procedures						
Vital Signs (heart rate, blood pressure)	X	X	X	X	X	Refer to Section 8.3.2
AE/SAE review	X	X	X	X	X	
Hematology, urinalysis, and chemistry					X	
HIV-1, HIV-2					X	
Pharmacokinetics						
Blood for PBMC ISL-TP PK	X	X	X	X	X	
d. Post-trial study procedures will be conducted on Day 29 of the study						

2 INTRODUCTION

Islatravir (MK-8591, ISL) is a novel, potent NRTTI being developed both for treatment of HIV-1 infection and for prevention of HIV-1 infection in uninfected individuals at high risk. Currently, ISL is being evaluated in Phase 2 and Phase 3 trials at a dose of 0.75 mg QD (in combination with 100 mg doravirine, DOR; NCT03272347, NCT04223778, NCT04223791, NCT04233216, NCT04233879) and in a Phase 2 trial at doses of 60 mg and 120 mg QM (NCT04003103). Additional programs, with other doses and administration frequencies within the range of 0.75-120 mg, are being considered as well.

2.1 Study Rationale

The liver is involved in drug clearance through multiple oxidative and conjugative metabolic pathways and through biliary excretion. Hepatic insufficiency from acute or chronic liver disease may affect excretion and metabolism, leading to accumulation of drug and metabolites. Hepatic disease can therefore alter the levels of drugs, potentially leading to an effect on efficacy and/or safety.

Islatravir will be administered to HIV patients with liver disease, including those co-infected with hepatitis C virus (HCV). Based on the evidence to date, a major effect of hepatic insufficiency on islatravir PK seems unlikely, but possible. In preclinical studies, hepatic metabolic pathways do not appear to play an important role in islatravir metabolism. The major metabolite of islatravir, M4 (4'-ethynyl-2-fluoro-2'deoxyinosine), is formed by adenosine deaminase (ADA), which is a ubiquitously expressed enzyme with relatively high activity in liver. Therefore, hepatic insufficiency could result in decreased ADA activity, potentially leading to modestly higher levels of islatravir in participants with hepatic insufficiency. A greater understanding of the effects of hepatic insufficiency on islatravir PK is thus considered important.

This Phase 1 study will evaluate the general tolerability and pharmacokinetics (PK) of a single 60 mg dose of ISL in participants with moderate hepatic insufficiency, compared to participants in good health.

2.2 Background

Refer to the IB/approved labeling for detailed background information on MK-8591 (islatravir, ISL).

HIV-1 infection remains a global health challenge, with close to 37 million people living with HIV/AIDS worldwide. The use of ever-improving highly effective ARVs has greatly improved the natural history of HIV infection, such that HIV infection has become a chronic illness, provided patients remain adherent in taking ARV therapy. Globally, almost two million people yearly become newly infected with HIV, thus demonstrating a need for effective prevention strategies that could reduce this infection rate. There are numerous barriers for many individuals in taking daily medication, including access to medication and stigma. Several recent advances in the field, including simplification from 3- to 2-drug

regimens and long-acting formulations that potentially allow for less frequent dosing, are attempting to address these needs in order to improve adherence and outcomes for patients.

Islatravir is differentiated from other ARVs because of its high potency, long half-life, favorable drug resistance profile and broad pharmacological distribution. Because of these properties, ISL is well-suited as a compound to be delivered in less frequent dosing regimens. Understanding the effect of intrinsic factors, such as hepatic insufficiency, on ISL is an important aspect of clinical development of the compound.

2.2.1 Pharmaceutical and Therapeutic Background

Islatravir is a highly potent HIV-1 NRTTI. The inactive parent is phosphorylated to the active ISL-TP in PBMCs and other cells. Unlike conventional NRTIs, ISL acts via multiple mechanisms, leading to both immediate and delayed chain termination. In in vitro studies in PBMCs, ISL-TP demonstrated antiviral activity, with an IC50 of 0.21 nM, while other NRTIs demonstrated IC50s ranging from 10.1 to 144 nM. ISL demonstrates a favorable mutant selection profile compared to other NRTIs.

In vitro studies in monkey and human blood indicated that ISL is efficiently phosphorylated to the mono-, di-, and triphosphate anabolites (ISL-MP, ISL-DP, and ISL-TP, respectively) in PBMCs. These phosphorylated anabolites of ISL were not detected extracellularly and are therefore not directly excreted or metabolized. Phosphorylated ISL may become dephosphorylated in PBMCs, at which point ISL may then exit the cell and return to the pool of extracellular ISL that is subject to renal excretion and metabolism via ADA. [redacted]

2.2.2 Preclinical and Clinical Studies

Potential systemic effects of ISL have been extensively evaluated in nonclinical safety studies, including repeat-dose oral toxicity and PK studies in rats (up to 6 months) and monkeys (up to 9 months). These studies are described in detail in the ISL IB. Overall, target organ/system toxicities identified in enteral ISL exploratory and/or GLP studies in rats and monkeys were considered not relevant at the anticipated human Cmax and AUC exposure for a 240 mg dose of ISL, based on the safety margins (1X and 5X) at the NOAELs over the expected clinical exposures. [redacted]

Orally administered ISL has been evaluated in 8 completed and 2 ongoing Phase 1 trials, 2 ongoing Phase 2 trials and 4 ongoing Phase 3 trials. Across the 10 Phase 1 studies, as of 31-Mar-2020, 206 adult participants (including 30 participants with HIV-1 infection) received an ISL single dose (up to 400 mg orally) or multiple doses (up to 100 mg QW for 3 weeks and up to 5 mg QD for 6 weeks orally). In the Phase 1 studies, single and multiple doses of ISL have been generally well tolerated, with no drug-related SAEs and no

discontinuations due to a drug-related AE. For all Phase 1 studies with oral administration, the most frequently reported drug-related AE (≥2% of participants in any protocol) was headache.

Following oral administration, plasma PK data indicate that ISL was rapidly absorbed with a median Tmax of 0.5 hr, and an apparent terminal t½ of 47 to 64 hr after single doses. Intracellular ISL-TP levels reached C_{max} between 6 to 24 hr and declined with an apparent terminal t½ of 79 to 214 hr. Over the entire Phase 1 clinical program, ISL plasma exposure and ISL-TP levels appeared to increase in an approximately dose-proportional manner between ISL doses of 0.25 and 400 mg. M4 levels, when assessed, correspond to ~30-40% of ISL plasma parent levels at all dose levels tested. Following administration of 30 mg ISL with a high-fat meal, PK of ISL-TP in PBMCs were largely unaffected. Examinations of DDIs between ISL and DTG/TDF, ISL and LNG/EE, ISL and DOR, and ISL and pantoprazole demonstrated no clinically meaningful interactions.

After ISL administration to treatment-naïve participants with HIV-1 infection at doses of 0.5 mg, 1 mg, 2 mg, 10 mg, and 30 mg, viral load reduction data show greater than 1.0 log drop on average at all doses tested. Pharmacokinetic data in participants infected with HIV-1 generally were consistent with the data in healthy participants.

2.2.3 Ongoing Clinical Studies

There are ten ongoing trials involving oral ISL.

Protocol 015 (P015) is a multiple panel double-blind placebo-controlled trial in 76 healthy adult Japanese males, examining PK and general safety and tolerability of ISL up to 120 mg and 100 mg DOR. In P015, which remains blinded, ISL (or placebo) appears to be generally well tolerated at all doses examined to date.

Protocol 026 (P026) is an open-label, single-dose trial to evaluate the pharmacokinetics of 60 mg ISL in 6 participants with severe renal impairment and 6 control participants. This trial initiated in July 2020 and information on general tolerability is not yet available.

Protocol MK-8591A 027 (P027) is an open-label clinical trial to evaluate the pharmacokinetics and relative bioavailability of three experimental presentations of the fixed dosed combination of 100 mg DOR and 0.75 mg ISL in 28 healthy participants. In this trial, ISL and DOR appear generally well tolerated.

Protocol MK-8558-004 is a multiple dose open label trial in 14 healthy adult participants, assessing the potential two-way DDI between 20 mg ISL and MK-8558, an investigational product that is a potential partner agent. In this trial, ISL appears generally well tolerated.

Protocol 011 (P011) is an ongoing Phase 2b trial (NCT03272347) in treatment-naive persons living with HIV-1 (PLWH), examining efficacy of daily ISL (0.25 mg, 0.75 mg, or 2.25 mg) initially in combination with DOR and 3TC, with 3TC discontinued based on interim analysis at 24 weeks, compared to participants on DOR/3TC/TDF throughout the study period. As of 31-Mar-2020, ISL has been administered to ~90 HIV-1 positive individuals for

at least 96 weeks. The 48-week analysis showed a numerically higher rate of drug-related AEs in participants who received DOR/3TC/TDF (19.4%) vs. participants on any dose of ISL (0%, 10%, 12.9% for 0.25 mg, 0.75mg, and 2.25 mg, respectively). Among the 90 participants who received any dose of ISL, there was no specific drug-related AE that occurred in more than 5% of the participants.

Protocol 016 (P016) is a double-blind, placebo-controlled Phase 2 trial (NCT04003103) in low-risk otherwise healthy individuals, examining general tolerability and PK of QM administration of oral ISL alone, to establish greater understanding of potential doses for a QM PrEP indication. This trial is examining doses of 60 mg and 120 mg (and placebo); the first participants were dosed in November 2019. As of 31-Mar-2020, approximately 50 individuals considered at low risk for HIV infection have been administered at least one dose of ISL in this trial.

Protocols 017-020 (P017-P020) are Phase 3 trials in persons living with HIV-1 switching from current therapy (P017, P018), are heavily treatment experienced (P019), or are naïve to therapy (P020). All four of these trials initiated in early 2020; information on general tolerability is limited.

2.3 Benefit/Risk Assessment

Healthy participants in clinical studies 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 hepatic impairment between the ages of 18 and 75 years (inclusive) and healthy matched controls.

Objectives	Endpoints
Primary	
• To evaluate the plasma pharmacokinetics of ISL (e.g., AUC0-∞, AUC0-last, Cmax, Tmax, apparent terminal t½, CL/F, and Vz/F) after a single oral dose of 60 mg ISL in participants with moderate hepatic impairment compared to healthy control participants. Estimation: In participants with moderate hepatic impairment, plasma pharmacokinetics (AUC0-∞, Cmax) of ISL following a single 60 mg ISL dose will be estimated and compared to those observed in healthy mean matched control participants.	• AUC0-∞, AUC0-last, Cmax, Tmax, apparent terminal t½, CL/F, and Vz/F of plasma ISL
Secondary	
• To evaluate the safety and tolerability of ISL in participants with moderate hepatic impairment.	• Adverse experiences, laboratory safety tests, ECGs, and VSs.
• To evaluate the intracellular pharmacokinetics (e.g., AUC0-∞, AUC0-last, Cmax, C24, C168, C672, Tmax, and apparent terminal t½) of ISL triphosphate (ISL-TP) in peripheral blood mononuclear cells (PBMCs) after a single oral dose of 60 mg ISL in participants with moderate hepatic impairment compared to healthy control participants.	• AUC0-∞, AUC0-last, Cmax, C24, C168, C672, Tmax, and apparent terminal t½ of ISL-TP in PBMC
Tertiary/Exploratory	
• To evaluate the plasma pharmacokinetics of the metabolite M4 (e.g., AUC0-∞, AUC0-last, Cmax, and Tmax,) after a single oral dose of 60 mg ISL in participants with moderate hepatic impairment compared to healthy control participants.	• AUC0-∞, AUC0-last, Cmax, and Tmax, of plasma M4

Objectives	Endpoints
• To evaluate urinary excretion of ISL and M4 after a single oral dose of 60 mg ISL in participants with moderate hepatic impairment and in healthy control participants.	• Ae, CLr, and fe of ISL and M4 in urine
• To explore the relationship between genetic variation and response to the treatment(s) administered, and mechanisms of disease. Variation across the human genome may be analyzed for association with clinical data collected in this study.	• Germline genetic variation and association to clinical data collected in this study

4 STUDY DESIGN

4.1 Overall Design

This is a nonrandomized, multi-group, open-label, single-dose study of ISL in adult male and female participants with moderate hepatic insufficiency (N=6) and in matched healthy adult male and female participants (N=6). Once all participants with moderate hepatic insufficiency are enrolled, the healthy matched control participants will be enrolled. Individual age and weight of healthy matched control participants will be within the range ± 10 years and ± 2.0 kg/m^2 of the mean age and body mass index (BMI) of participants with hepatic insufficiency. 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.

Assignment to a group will be as follows:

Impairment Stage	N	Child-Pugh score[a]
Moderate	6	7-9
Healthy	6	0

[a] Child-Pugh score based on standard scoring (see below). Baseline Child-Pugh will be obtained twice (at least 72 hours apart as part of participant screening) and the mean of the two values will be used. The second Child-Pugh score may be calculated at the time of check-in.

[b] At least 3 participants with a score of at least 2 on one of the laboratory parameters (reduced serum albumin, increased serum bilirubin, or increased INR) will be enrolled.

On Day 1, participants will receive a single oral dose of 60 mg ISL, followed by PK sampling until 168 hours postdose (in both the healthy control group and the moderate hepatic impairment group). There will be additional visits at hours 240, 336, 408, 504, 672

postdose for the collection of PBMCs. Safety will be monitored throughout the study by repeated clinical and laboratory evaluations.

As noted, the Child-Pugh classification will be used to categorize hepatic insufficiency. The Child-Pugh scale is utilized by clinicians to categorize chronic liver disease and cirrhosis and is also used to categorize participants with hepatic insufficiency for PK studies. In the current study, patients with chronic, stable hepatic insufficiency with features of cirrhosis due to any etiology will be enrolled, and the Child-Pugh scale will be used to classify the severity of liver disease (Table 1). The points from each row are summed, leading to the final Child-Pugh score. Scores of 5-6, 7-9, and 10-15 are classified as having mild, moderate, or severe hepatic insufficiency, respectively. To insure an adequate number of study participants with laboratory abnormalities consistent with hepatic dysfunction, at least 3 participants will be required to have a score of at least 2 on one of the laboratory parameters (reduced serum albumin, increased serum bilirubin, or increased INR).

Table 1 Severity of Liver Disease Classification

	Points Score for Increasing Abnormality		
Assessment	**1**	**2**	**3**
Encephalopathy[†]	None	1 or 2	3 or 4
Ascites	Absent	Slight	Moderate
Albumin (g/dL)	>3.5	2.8 to 3.5	<2.8
International normalized ratio (INR)	<1.7	1.7 to 2.3	>2.3
Bilirubin (mg/dL)—not PBC[‡§] Bilirubin (mg/dL)—only for PBC[‡§]	<2 <4	2 to 3 4 to 10	>3 >10

[†] Portal-system encephalopathy is Staged 0 to 4.
[‡] PBC=Primary Biliary Cirrhosis.
[§] Select only one dependent on type of cirrhosis.

The Child-Pugh classification will be used due to its widespread use and acceptance by regulatory agencies, including the U.S. Food and Drug Administration and the European Committee for Medicinal Products for Human Use. This study design is supported by FDA guidelines for drugs which undergo substantial hepatic metabolism and for which an indication is sought for patients with hepatic insufficiency.

Because this is a Phase 1 assessment of MK-8591 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

An open-label study design has been selected to evaluate the effect of hepatic impairment on the pharmacokinetics of ISL and will adequately address the objectives of the study. Although hepatic elimination is unlikely to lead to marked changes in ISL levels, the magnitude of the preclinical and clinical safety margins supports a reduced design with an evaluation of patients with moderate hepatic impairment. Individuals without hepatic impairment will serve as a control group. In order to adequately assess the impact of hepatic impairment, enrolled participants with reasonably matched demographics to mean demographic parameters will be enrolled.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

There are no efficacy endpoints in this trial.

4.2.1.2 Safety Endpoints

Multiple trials have evaluated oral ISL in human participants, including a Phase 1 trial with doses as high as 400 mg, and a Phase 2 trial in which participants have received monthly doses of 60 mg or 120 mg. To date, oral ISL appears generally well tolerated, and there have been no concerning safety signals. A standard safety monitoring plan consisting of adverse event monitoring, physical examinations, vital signs (heart rate and blood pressure), 12-lead ECGs and laboratory tests (hematology, serum chemistry and urinalysis), obtained pre- and post-dosing, has been deemed adequate to assess tolerability of ISL in this trial.

4.2.1.3 Pharmacokinetic Endpoints

In order to evaluate the pharmacokinetics of ISL administered to patients with moderate hepatic impairment, the following pharmacokinetic parameters will be evaluated: AUC0-∞, AUC0-last, Cmax, Tmax, apparent terminal t½, CL/F, and Vz/F of plasma ISL. In addition to assessing parent ISL levels, the following ISL-TP PK parameters will be evaluated in PBMCs: AUC0-∞, AUC0-last, Cmax, C24, C168, C672, Tmax, and apparent terminal t½ of ISL-TP. This intracellular evaluation will allow a more complete understanding of ISL-TP levels in this population.

Assessment of these PK parameters for both ISL and ISL-TP has been consistently performed throughout the entire Phase 1 clinical development program. The relationship between ISL and ISL-TP levels has been well characterized in healthy study participants and in HIV+ study participants. This assessment, however, will allow greater understanding of that relationship in hepatically impaired individuals, and can therefore determine whether ISL-TP levels, which are key to defining the PK threshold for efficacy, will also be sufficient in this population.

In addition, the PK of M4, the major circulating metabolite of ISL, will be evaluated as an exploratory endpoint. As noted, there is a theoretical possibility that M4 levels could be

lower in individuals with hepatic insufficiency due to lower hepatic activity of ADA. This assessment, therefore, will allow determination of M4 plasma and urine concentrations in these participants.

4.2.1.4 Pharmacodynamic Endpoints

No pharmacodynamic endpoints will be evaluated.

4.2.1.5 Planned Exploratory Biomarker Research

4.2.1.5.1 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 absorption, distribution, metabolism, and excretion; 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.

4.2.1.6 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 (as part of the main study) 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 that participants receive the correct dose of the correct drug/vaccine at the correct time. The details of FBR are presented in Appendix 6.

4.2.2 Rationale for the Use of Comparator/Placebo

Not applicable

4.3 Justification for Dose

A dose of 60 mg has been selected to be administered as a one-time oral dose in this trial. This dose level is currently the highest oral dose being considered for pivotal trials, as it is the dose being considered for Phase 3 evaluations of QM ISL for pre-exposure prophylaxis. As noted, the PK for both parent ISL and ISL-TP has been dose-proportional over the entire dose range evaluated to date (0.25-400 mg), and thus the effects of hepatic impairment are not likely to vary with dose. A one-time dose of ISL, as being performed here, will be able to inform on other dose administration frequencies, as the PK parameter values obtained in this trial can be used to model potential effects at other doses.

As this is a Phase 1 assessment of MK-8591 in humans, and the PK, pharmacodynamic and safety profiles of the compound are still being evaluated, modifications to the dose or dosing regimen may be required to achieve the scientific goals of the study objectives and/or to ensure appropriate safety monitoring of the study participants. Details of allowed modifications are provided in Section 8.11.6.

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

Male/Female participants with moderate hepatic impairment between the ages of 18 and 75 years (inclusive) and healthy matched controls will be enrolled in this study.

The individual age and weight of the healthy participants is aimed to be within the range ± 10 years and ± 10 kg of the mean age and weight of participants with hepatic insufficiency. 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 3 males and 3 females in the hepatic insufficient group, every effort will be made to ensure a 3:3 ratio in the healthy participants, but 2:4 or 4:2 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

5.1.1 Inclusion Criteria for Healthy Participants

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

Type of Participant and Disease Characteristics

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 and prior to administration of the initial dose of study drug. 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. Has a BMI ≥18.5 and ≤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

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

Male Participants

No measures are needed, but contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Female Participants

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 [4 weeks) after study intervention. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to study intervention.

- A WOCBP must have a negative highly sensitive pregnancy test ([urine or serum] as required by local regulations) within 24 hours before 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 located 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.

Informed Consent

5. Provides written informed consent/assent for the study. The participant may also provide consent/assent for future biomedical research. However, the participant may participate in the main study without participating in future biomedical research.

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 insufficiency with features of cirrhosis due to any etiology.

2. Has a score on the Child-Pugh scale ranging from 7 to 9 (moderate hepatic insufficiency) at screening. At least 2 of the participants must have a score of 2 or higher on at least one of the laboratory parameters (i.e., albumin, prothrombin time, and bilirubin) at screening on the Child-Pugh scale.

3. 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. Participants with stable, chronic medical or psychiatric conditions may be included at the discretion of the investigator and the Sponsor. Appendix 9 provides a table of the 12-Lead Electrocardiogram Abnormality Criteria.

4. With the exception of hepatic impairment, is in good health based on laboratory safety tests obtained at the screening visit and prior to study drug administration. 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.

5. 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

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

   Male Participants

   No measures are needed, but contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

   Female Participants

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

   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 4 weeks 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.

   - A WOCBP must have a negative highly sensitive pregnancy test ([urine or serum] as required by local regulations) within 24 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 located 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.

Informed Consent

7. Provides written informed consent/assent for the study. The participant may also provide consent/assent for future biomedical research. However, the participant may participate in the main study without participating in future biomedical research.

5.2 Exclusion Criteria

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.

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 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).

4. 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.

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

6. Is positive for hepatitis B surface antigen, hepatitis C antibodies, HIV-1 or HIV-2.

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

Prior/Concomitant Therapy

8. Is unable to refrain from or anticipates the use of any medication, including prescription and nonprescription drugs or herbal remedies beginning approximately 2 weeks (or 5 half-lives) prior to study drug administration, throughout the study, until the poststudy visit. There may be certain medications that are permitted (see Section 6.5).

Prior/Concurrent Clinical Study Experience

9. Has participated in another investigational study within 4 weeks (or 5 half-lives, 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

10. Has a QTc interval >470 for males or >480 ms for females, 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

11. Is not considered low risk of having HIV infection. Low risk for HIV infection is defined by all of the following, within 12 months prior to the screening visit (based on self-report by participant or medical history [if available]):

    a. No anal or vaginal intercourse with someone known to be HIV-infected, or with someone of unknown HIV infection status who is at increased risk of HIV infection.

    b. No stimulant use (cocaine [including crack], methamphetamine, or nonphysician prescribed pharmaceutical grade stimulants) or inhaled nitrous oxide.

    c. No illicit injection drug use of any kind.

    d. No new diagnosis of a sexually transmitted infection (STI) such as gonorrhea (GC), chlamydia (CT), incident syphilis, or trichomoniasis (if assessment is available). This includes, but is not exclusive to, any testing performed at screening.

    e. No greater than 3 different sexual partners for receptive or insertive vaginal or anal sex; and

    f. No history of antiretroviral therapy for HIV-1 infection, including for PrEP or for post-exposure prophylaxis. Note: individuals who have participated in studies of an antiretroviral, including Phase 1 studies, may be eligible after Sponsor consultation.

12. Is under the age of legal consent.

13. Is a smoker or user of electronic cigarettes and/or has used nicotine or nicotine-containing products (eg, nicotine patch) within 3 months of screening.

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 more than the daily limit 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. Participants must have a negative alcohol test and negative drug screen 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).

   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).

4. 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.

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

6. Is positive for HIV-1 or HIV-2.

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

Prior/Concomitant Therapy

8. 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) within 4 hours prior to and 8 hours after administration of the study drug. 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

9. Has participated in another investigational study within 4 weeks (or 5 half-lives, 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

10. Has a QTc interval >470 for males or >480 ms for females, has a history of risk factors for Torsades de Pointes (eg, heart failure/cardiomyopathy or family history of long QT syndrome) or is taking concomitant medications that prolong the QT/QTc interval.

Other Exclusions

11. Is not considered low risk of having HIV infection. Low risk for HIV infection is defined by all of the following, within 12 months prior to the screening visit (based on self-report by participant or medical history [if available]):

    a. No anal or vaginal intercourse with someone known to be HIV-infected, or with someone of unknown HIV infection status who is at increased risk of HIV infection.

    b. No stimulant use (cocaine [including crack], methamphetamine, or nonphysician prescribed pharmaceutical grade stimulants) or inhaled nitrous oxide.

    c. No illicit injection drug use of any kind.

d. No new diagnosis of a sexually transmitted infection (STI) such as gonorrhea (GC), chlamydia (CT), incident syphilis, or trichomoniasis (if assessment is available). This includes, but is not exclusive to, any testing performed at screening.

e. No greater than 3 different sexual partners for receptive or insertive vaginal or anal sex; and

f. No history of antiretroviral therapy for HIV-1 infection, including for PrEP or for post-exposure prophylaxis. Note: individuals who have participated in studies of an antiretroviral, including Phase 1 studies, may be eligible after Sponsor consultation.

12. Is under the age of legal consent.

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

14. 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.

15. 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 negative UDS prior to randomization. Participants with hepatic impairment may be allowed for inclusion with a positive UDS for opiates if they have an active prescription from a licensed health care provider.

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

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 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

Participants will fast from all food and drinks, except water, for at least 8 hours prior to laboratory safety evaluations and study drug administration. Participants will fast from all food and drinks except water between study drug administration and the first scheduled meal, which will occur approximately 2 hours after dosing. Thereafter, there will be no restrictions (other than those provided in Section 5.3.3.) regarding meals and snack(s). While in the CRU, participants will fast from all food and drinks except water between meals and snacks. Otherwise, there are no dietary restrictions other than those defined below.

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

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. 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 and after study drug administration. 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

Smoking or the use of electronic cigarettes, or the use of nicotine/nicotine-containing products is not permitted for participants in the healthy control group.

Participants in the moderate hepatic impairment group will follow the smoking restrictions (and if applicable, the use of electronic cigarettes or 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 randomized 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(s) to be used in this study is outlined in Table 2.

Table 2 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP/ NIMP	Sourcing
Healthy Control Group	Experi-mental	MK-8591 (ISL)	Drug	Capsule	30 mg	60 mg	Oral	Single Dose on Day 1	Experimental	IMP	Provided by the Sponsor
Moderate Hepatic Impair-ment Group	Experi-mental	MK-8591 (ISL)	Drug	Capsule	30 mg	60 mg	Oral	Single Dose on Day 1	Experimental	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 2 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 in order to administer the proper dose to each participant. The rationale for selection of doses to be used in this study is provided 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 allocation number (AN) for a single open-label treatment using the allocation schedule shown in Table 3.

Table 3 Allocation of Participants to Treatment

Hepatic Impairment Stage	N	Treatment
Moderate	6	MK-8591 (ISL) 60 mg
Healthy	6	MK-8591 (ISL) 60 mg

6.3.2 Stratification

No stratification based on age, sex, or other characteristics will be used in this study.

6.3.3 Blinding

This is an open-label study; therefore, the Sponsor, investigator, and participant will know the intervention administered.

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.

When participants are dosed at the site, they 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

If a participant does not discontinue all prior medications within 14 days or 5 half-lives of the first dose of study intervention (whichever is longer), they may be included in the study if the investigator can rationalize that the specific use of a prior medication is not clinically relevant within the context of the study.

Concurrent use of any prescription or nonprescription medication, or concurrent vaccination, during the ongoing study (ie, after intervention allocation) must first be discussed between the investigator and Sponsor prior to administration, unless appropriate medical care

necessitates that therapy or vaccination should begin before the investigator and Sponsor can consult. The participant will be allowed to continue in the study if both the Sponsor and the investigator agree.

Ibuprofen may be used for minor ailments without prior consultation with the Sponsor. Paracetamol/acetaminophen use for minor ailments requires consultation with the Sponsor.

For Participants with Moderate Hepatic Impairment:

Participants who are taking medications to treat general medical conditions and/or conditions associated with hepatic disease (e.g., hypertension, non-insulin dependent diabetes mellitus, hypercholesterolemia, hypo- or hyperthyroidism, gout, depression) will be allowed to participate in the study at the discretion of the Investigator and following consultation with the Sponsor Clinical Monitor. Participants must be on a stable regimen for at least 1 month prior to study drug administration and is able to withhold the use within 4 hours prior to and 8 hours after study drug administration. Any exceptions to this must first be discussed between the Investigator and Sponsor.

Certain prescription medications used to treat manifestations of hepatic disease (e.g., 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 6 hours prior to and after dosing on Day 1 since it may potentially affect absorption.

Examples of types of medications that would be used for chronic medical conditions that would be allowed include (but are not limited to) the following:

- Angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists, diuretics
- Beta blockers
- Metformin, thiazolidinediones, sulfonylureas, DPP-4 inhibitors, alpha-glucosidase inhibitors, incretin mimetics
- Statins
- Levothyroxine
- Colchicine, allopurinol
- Selective serotonin uptake inhibitors (SSRIs), tricyclic antidepressants
- Proton pump inhibitors

Any medication (including over-the-counter) that, by the determination of the Investigator, might interfere with the study (e.g., cimetidine) must be discontinued at least 2 weeks (or 5 half-lives of the compound, whichever is longer) prior to the dosing of study drug.

6.5.1 Rescue Medications and Supportive Care

No rescue or supportive medications are specified for use in this study.

6.6 Dose Modification (Escalation/Titration/Other)

Dose modifications are not applicable to this study.

6.6.1 Stopping Rules

The following stopping rules will be employed during the conduct of this study.

If any of the below stopping rules are met, the study will be paused and no further dosing will occur until the Sponsor has reviewed the totality of data available. In order to continue the study (upon joint agreement with the Sponsor and investigator), an amendment will be submitted for approval.

1. An individual participant reports an SAE considered related to the study drug by the investigator.

2. Two (2) or more participants report Severe Non-serious Adverse Events considered related to the study drug by the investigator.

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 prior to the intervention and generally represents withdrawal from the study.

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 or participant's legally acceptable representative 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 will not exceed 382 mL (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.

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 future biomedical research consent to the participant, answer all of his/her questions, and obtain written informed consent before performing any procedure related to future biomedical research. A copy of the informed consent will be given to the participant.

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 randomization, 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 randomization. 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 randomly allocated 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 re-assigned to another participant.

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

In a situation where rerandomization of the participants is planned (eg, study extension periods), the rerandomization will be based on a new randomization schedule; however, each participant will retain his/her original treatment/randomization number. Only the study intervention regimen associated with the rerandomization period or phase may change.

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

Participants will report to the CRU on Day -1 prior to the scheduled day of study intervention administration on Day 1 and remain in the unit until 168 hours post dose for healthy matched controls and participants with moderate hepatic impairment. At the discretion of the investigator, participants may be requested to remain in the CRU longer. Participants may be permitted to leave the unit, for emergency situations only, during the domiciling period at the discretion of the investigator after discussion with the Sponsor. The decision how to monitor the participant will be at the discretion of the investigator after discussion with the Sponsor. Domiciling of participants will facilitate PK collection and safety assessments while ISL and metabolite levels are expected to be highest, ensuring that these assessments are performed in a timely fashion.

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

BMI

Body Mass Index equals a person's weight in kilograms divided by height in meters squared (BMI=kg/m^2). Body Mass Index 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, HR, RR, and BP will be assessed.
- Body temperature will be measured with an appropriate thermometer.
- 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 semi-recumbent position after 10 minutes rest.

8.3.2.1 Resting Vital Signs

Vital Sign Measurements (Heart Rate and Blood Pressure)

Participants should be resting in a semirecumbent position for at least 10 minutes prior to having VS measurements obtained. Semirecumbent VS will include HR and BP. The correct size of the BP cuff and the correct positioning on the participants' arm is essential to increase the accuracy of BP measurements.

Predose HR and BP will be in triplicate measurements, obtained at least 1 to 2 minutes apart within 3 hours of study drug administration. 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.

Body Temperature

Body temperature will be measured. 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 measurements will be obtained and reviewed by an investigator or medically qualified designee (consistent with local requirements) as outlined in the SoA using an ECG machine that automatically calculates the HR and measures PR, QRS, QT, and QTc intervals.
- The model of ECG machine will remain consistent for each individual participant.
- Special care must be taken for proper lead placement by qualified personnel. Skin should be clean and dry prior to 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 position for at least 10 minutes prior to each ECG measurement.
- The correction formula to be used for QTc is Fridericia.
- If repeat ECGs are required, the clinical site will decide whether to leave the electrodes in place or mark the position of the electrodes for subsequent ECGs. To mark the position of the electrodes, 12-lead electrode sites will be marked on the skin of each participant with an ECG skin marker pen to ensure reproducible electrode placement.
- Predose ECGs will be obtained in triplicate at least 1-2 minutes apart within 3 hours prior to administration of ISL. The mean of these measurements will be used as the baseline to calculate change from baseline for safety evaluations (and for rechecks, if needed). Post-dose ECG measurements will be single measurements.

- If a participant demonstrates an increase in QTc interval ≥60 msec compared with mean 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 mean 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, 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 cardiac or intensive care unit) 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 study cardiologist will be consulted by the investigator as needed to review ECG tracings with 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 28 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.

8.3.5 Photograph of Rash

Photographs of any rash are highly recommended to be taken immediately, along with any additional information that may assist the investigator in the evaluation of the skin reaction, skin eruption or rash occurrence, in determining etiology and drug relationship.

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 consent form is signed 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 28 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 4.

Table 4 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. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

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

8.6.1 Blood Collection for Plasma ISL and PBMC ISL-TP

Blood collection time points for plasma ISL and M4 and PBMC ISL-TP are outlined in the SoA (Section 1.3). Sample collection, storage, and shipment instructions for plasma samples will be provided in the Study Operations Manual.

8.6.2 Urine Collection for Urinary MK-8591 and M4

Urine collection intervals for urinary ISL and M4 are outlined in the SoA (Section 1.3). Sample collection, storage, and shipment instructions for urine samples will be provided in the Study 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 should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at the site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for future biomedical research. If the planned genetic analysis is not approved, but future biomedical research is approved, this sample will be collected for the purpose of future biomedical research.

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

8.9 Future Biomedical Research Sample Collection

If the participant signs the future biomedical research consent, the following specimens will be obtained as part of future biomedical research:

- 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 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 if there are Day -1 procedures planned per protocol.

8.10.2 Treatment Period/Visit

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 the study procedures specified in the SoA may be completed at the discretion of the investigator and with Sponsor agreement. The subset of study procedures completed will be communicated in a PCL.

8.10.4 Poststudy

Poststudy procedures will be conducted on Day 29 of the study.

8.10.5 Critical Procedures Based on Study Objectives: Timing of Procedure

For this study, the blood sample for ISL is the critical procedure.

At any postdose time point, the blood sample for ISL 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.

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 5.

Table 5 Pharmacokinetic (Blood) Collection Windows

PK Collection	PK Collection Window
0 - <1 hr	5 min
1 - <24 hr	15 min
24 - <48 hr	1 hr
48 - ≤120 hr	2 hr
120 – 168 hr	6 hr
> 168 hr	24 hr

- Predose standard safety evaluations: vital signs and ECG up to 3 hrs; laboratory safety tests and physical exam up to 24 hrs
- 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
  - 120 – 168 hr postdose may be obtained within 6 hr of the theoretical sampling time
  - > 168 hr postdose may be obtained within 24 hr of the theoretical sampling time

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

This is a Phase 1 assessment of ISL in humans, and the PK, pharmacodynamic, and safety profiles of the compound are still being elucidated. This protocol is written with some flexibility to accommodate the inherent dynamic nature of Phase 1 clinical studies. Modifications to the dose, dosing regimen, and/or clinical or laboratory procedures currently outlined may be required to achieve the scientific goals of the study objectives and/or to ensure appropriate safety monitoring of the study participants.

As such, some alterations from the currently outlined dose and/or dosing regimen may be permitted based on newly available data, but the maximum daily dose may not exceed those currently outlined in the protocol.

- Decrease in the dose of the study intervention administered
- Modification of the PK sample processing and shipping details based on newly available data

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 50 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

This section contains a summary of the statistical analyses for this trial. Full detail is in the Statistical Methods (Section 9.6).

Pharmacokinetics: Separately for each of the following PK parameters, after a single dose administration of 60 mg ISL to participants with moderate hepatic impairment and healthy control participants, will be natural log-transformed and evaluated with a linear fixed effects model containing a fixed effect for population (participants with moderate hepatic impairment, and healthy control participants): individual values of plasma ISL AUC0-∞, AUC0-last, and Cmax; PBMC ISL-TP AUC0-∞, AUC0-last, Cmax, C24, C168, and C672; and plasma M4 AUC0-∞, AUC0-last, and Cmax. 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.

To address the primary estimation objective and compare participants with moderate hepatic impairment to participants with normal hepatic function, a two sided 90% confidence interval for the true difference in means (moderate hepatic impairment – normal hepatic function) will be calculated for each PK parameter 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 (moderate hepatic impairment/ normal hepatic function) for each PK parameter.

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

Sample Size and Power Calculations: The between-subject standard deviations (on the natural log scale) for plasma ISL AUC0-∞ and Cmax, PBMC MK-8951-TP AUC0-∞ and Cmax after administration of ISL observed in a previous study (PN003) are 0.228 ln(hr*nmol/L), 0.356 ln(nmol/L), 0.414 ln(hr* pmol/10^6 Cells) and 0.518 ln(pmol/10^6 Cells), respectively. Assuming the same variability for 60-mg ISL, with 6 moderate hepatic impairment participants and 6 healthy participants, the half width of the 90% confidence intervals of geometric mean ratios (GMR)s for plasma ISL AUC0-∞ and Cmax, PBMC MK-8951-TP AUC0-∞ and Cmax on the log scale will be 0.239, 0.372, 0.443, and 0.542 respectively. The lower and upper 90% confidence limits for the true GMRs will be given by OBS/1.27 and OBS*1.27 for plasma ISL AUC0-∞, OBS/1.45, and OBS*1.45 for plasma ISL Cmax, OBS/1.54 and OBS*1.54 for AUC0-∞ ISL-TP in PBMC, OBS/1.72, and OBS*1.72 for Cmax ISL-TP in PBMC, where OBS is the observed least squares geometric mean.

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

Estimation: In participants with moderate hepatic impairment, plasma pharmacokinetics (AUC0-∞, Cmax) of ISL following a single 60 mg ISL dose will be estimated and compared to those observed in healthy mean matched control participants.

9.4 Analysis Endpoints

Primary Endpoints

The primary PK endpoints include plasma ISL AUC0-∞, AUC0-last, Cmax, Tmax, apparent terminal t½, CL/F, and Vz/F.

Secondary Endpoints

The secondary PK endpoints include AUC0-∞, AUC0-last, Cmax, C24, C168, C672, Tmax, and apparent terminal t½ of ISL-TP in PBMC. The secondary safety endpoints include adverse experiences, laboratory safety tests, ECGs, and VSs.

Exploratory Endpoints:

The exploratory endpoints include AUC0-∞, AUC0-last, Cmax, and Tmax of M4 in plasma. The exploratory endpoints also include Ae, CLr, and fe of ISL and M4 in urine.

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 (APaT): 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 (PP): The Per-Protocol Population consists of the subset of participants who comply with the protocol sufficiently to ensure that generated 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 prior to unblinding 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 procedure as aforementioned and have available data considered sufficient to exhibit the effect of treatment will be included in the Per-Protocol dataset. This population will be used for the PK analyses.

9.6 Statistical Methods

Separately for each of the following PK parameters, after a single dose administration of 60 mg ISL to participants with moderate hepatic impairment and healthy control participants, will be natural log-transformed and evaluated with a linear fixed effects model containing a fixed effect for population (participants with moderate hepatic impairment, and healthy control participants): individual values of plasma ISL AUC0-∞, AUC0-last, and Cmax; PBMC ISL-TP AUC0-∞, AUC0-last, Cmax, C24, C168, and C672; and plasma M4 AUC0-∞, AUC0-last, and Cmax. 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 type=UN;
  lsmeans population /cl alpha=0.05;
  estimate 'moderate/normal' population 1 -1/cl alpha=0.1;
run;
```

To address the primary estimation objective and compare participants with moderate hepatic impairment to participants with normal hepatic function, a two-sided 90% confidence interval for the true difference in means (moderate hepatic impairment – normal hepatic function) will be calculated for each PK parameter 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 (moderate hepatic impairment/normal hepatic function) for each PK parameter.

Figures showing individual PK values with GMs (95% CIs) by population, plotted on the natural log scale, will be provided for plasma ISL AUC0-∞, AUC0-last, and Cmax; PBMC ISL-TP AUC0-∞, AUC0-last, Cmax, C24, C168, and C672; and plasma M4 AUC0-∞, AUC0-last, and Cmax.

Individual values will be listed for each PK parameter including plasma ISL AUC0-∞, AUC0-last, Cmax, Tmax, apparent terminal t½, CL/F, and Vz/F, PBMC ISL-TP AUC0-∞, AUC0-last, Cmax, C24, C168, C672, Tmax, apparent terminal t½, plasma M4 AUC0-∞, AUC0-last, Cmax, Tmax , and Ae, CLr, and fe of ISL and M4 in urine 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(s^2) - 1), where s^2 is the observed variance on the natural log-scale).

The relationship between ISL pharmacokinetics and hepatic insufficiency will be examined in an exploratory manner via a scatter plot of PK values (ISL plasma AUC0-∞, AUC0-last and Cmax) versus the Child-Pugh score. Plots of PK values (ISL plasma AUC0-∞, AUC0-last and Cmax) and the baseline laboratory components of the Child-Pugh score (i.e., bilirubin, albumin levels, and prothrombin time) will be provided. Plots of PK parameter values (ISL plasma AUC0-∞, AUC0-last and Cmax) vs age and body weight will also be provided.

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

9.7 Interim Analyses

Not applicable.

9.8 Multiplicity

There is no pre-specified hypothesis; therefore, no multiplicity adjustment is needed.

9.9 Sample Size and Power Calculations

The between-subject standard deviations (on the natural log scale) for plasma ISL AUC0-∞ and Cmax, PBMC MK-8951-TP AUC0-∞ and Cmax after administration of ISL observed in a previous study (PN003) are 0.228 ln(hr*nmol/L), 0.356 ln(nmol/L), 0.414 ln(hr* pmol/10^6 Cells) and 0.518 ln(pmol/10^6 Cells), respectively. Assuming the same variability for 60-mg ISL, with 6 moderate hepatic impairment participants and 6 healthy participants, the half width of the 90% confidence intervals of geometric mean ratios (GMR)s for plasma ISL AUC0-∞ and Cmax, PBMC MK-8951-TP AUC0-∞ and Cmax on the log scale will be 0.239, 0.372, 0.443, and 0.542 respectively. The lower and upper 90% confidence limits for the true GMRs will be given by OBS/1.27 and OBS*1.27 for plasma ISL AUC0-∞, OBS/1.45, and OBS*1.45 for plasma ISL Cmax, OBS/1.54 and OBS*1.54 for AUC0-∞ ISL-TP in PBMC, OBS/1.72, and OBS*1.72 for Cmax ISL-TP in PBMC, where OBS is the observed least squares geometric mean.

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 6 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 6 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	Chloride	Phosphorous
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose (fasting)	Calcium	Alkaline phosphatase	Gamma glutamyl transpeptidase (GGT)
Coagulation	• PT/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)			

Laboratory Assessments	Parameters
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. • Serum or urine β human chorionic gonadotropin (β hCG) pregnancy test (as needed for WOCBP) • Serology (HIV-1 and HIV-2 antibodies in all participants, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody in healthy participants only • GC/CT (gonorrhea + chlamydia), Syphilis serologic, or Trichomonas testing may be done at screening per site SOP • HIV-1 and HIV-2 testing to be done at screening and at the Day 29 post-trial visit.
NOTES: Laboratory safety tests will be performed after at least an 8-hour fast. Pre-dose Day 1 laboratory procedures can be conducted up to 24 hours prior to study drug administration.	

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."

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) by recording the grade according to the NIH DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1. Any AE which changes DAIDS grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.
    - Grade 1 Mild event: Mild symptoms causing no or minimal interference with usual social and functional activities with intervention not indicated.
    - Grade 2 Moderate event: Moderate symptoms causing greater than minimal interference with usual social and functional activities with intervention indicated.
    - Grade 3 Severe event: Severe symptoms causing inability to perform usual social and functional activities with intervention or hospitalization indicated.
    - Grade 4 Potentially life-threatening event: Potentially life-threatening symptoms causing inability to perform basic self-care funtions with intervention indicated to prevent permanent impairment, persistent disability, or death.
    - Grade 5 Death: Deaths related to an AE.

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 nonhormonal 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.

13. References

1. National Cancer Institute [Internet]: Available from https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45618

2. International Council on Harmonisation [Internet]: E15: Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. Available from http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/definitions-for-genomic-biomarkers-pharmacogenomics-pharmacogenetics-genomic-data-and-sample-cod.html

3. Industry Pharmacogenomics Working Group [Internet]: Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

4. Industry Pharmacogenomics Working Group [Internet]: Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

10.7 Appendix 7: Country-specific Requirements

Not applicable

10.8 Appendix 8: Blood Volume Table

All Participants	Pre-study	Treatment Period	Post-study	Total Collections	mL Per Collection	Total mL/ Test
Laboratory Safety Tests (all participants; includes FSH if applicable, β-hCG if applicable, and HIV/Hepatitis screen)	2	2	1	5	17	85[b]
Blood for Genetic Analysis	0	1	0	1	8.5	8.5
Blood for PBMC ISL-TP	0	11	0	11	16	176
Blood for Plasma ISL	0	16	0	16	4	64
Blood for plasma M4	0	16	0	16	3	48
Total Blood Volume per Participant [a]				381.5 mL		

[a.] If additional pharmacokinetic/pharmacodynamic and/or safety analysis is necessary, additional blood (up to 50 mL) may be obtained. Note: never to exceed 50 mL.

[b] Total blood volume for laboratory safety tests (including screening tests) throughout the study but may be a lower volume based on site's SOP. Additionally, HIV-1 and HIV-2 and syphilis serologic tests will be done at screening. HIV-1 and HIV-2 tests will be done on Day 29. Hepatitis screen is for healthy participants only.

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

12-Lead Electrocardiogram Abnormality Criteria		
	Screen Failure Criteria	Potentially Significant Postrandomization Findings (clarification on action to take)
Other Intra-Ventricular Conduction Delay	QRS ≥130 ms	QRS ≥130 ms + Increase of ≥10 ms
QTc (B or F)		
Male	QTc ≥470 ms	QTc ≥500 ms or Increase of ≥60 ms From Baseline
Female	QTc ≥480 ms	QTc ≥500 ms or Increase of ≥60 ms From Baseline
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: Abbreviations

Abbreviation	Expanded Term
3TC	Lamivudine
ADA	adenosine deaminase
Ae	Amount excreted in urine
AE	adverse event
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase
AN	Allocation number
APaT	All participants as Treated
AR	adverse reaction
ART	Anti-retroviral therapy
ARV	Antiretroviral
AST	Aspartate aminotransferase
ATP	adenosine triphosphate
AUC	Area under the concentration-time curve
AUC0-24	Area Under the Curve from time 0 to 24 hours post dose
AUC0-inf	Area Under the Curve from time 0 to infinity
AUC0-last	Area Under the Curve from time 0 to last sampling time post dose
BDS	blood drug screen
β-hCG	β-human chorionic gonadotropin
BMI	body mass index
BP	blood pressure
C24	Concentration at 24 hours post dose
C168	Concentration at 168 hours post dose
C672	Concentration at 672 hours post dose
Cmax	Maximum concentration
CI	confidence interval
CLr	Renal clearance
CL/F	Apparent clearance after extravascular administration
CRF	Case Report Form
CRU	clinical research unit
CV	coefficient of variation
DAIDS	Division of AIDS
DDI	Drug-drug interaction
DILI	drug-induced liver injury
DOR	Doravirine
DP	Diphosphate
DTG	Dolutegravir
DNA	deoxyribonucleic acid
ECG	electrocardiogram

Abbreviation	Expanded Term
ECI	event of clinical interest
eCRF	electronic Case Report Form
eCTA	exploratory Clinical Trial Application
EDC	electronic data collection
EMA	European Medicines Agency
FBR	Future biomedical research
FDA	Food and Drug Administration
FDC	Fixed dose combination
fe	fraction of dose excreted in urine
FSH	follicle stimulating hormone
GC/CT	Gonorrhea/chlamydia
GCP	Good Clinical Practice
GCV	geometric coefficient of variation
GGT	Gamma glutamyl transpeptidase
GLP	good laboratory practice
GM	geometric mean
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IB	Investigator's Brochure
IC_{50}	50% inhibitory concentration
ICC	intraclass correlation
ICF	Informed Consent Form
ICH	International Council on Harmonization
IEC	Independent Ethics Committee
I/E	Inclusion/Exclusion
IMP	investigational medicinal product
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
LNG/EE	Levonorgestrel/ethinyl estradiol
ISL	Islatravir
ISL-DP	Islatravir- diphosphate
ISL-TP	Islatravir- triphosphate
MedDRA	Medical Dictionary for Regulatory Activities
M4	metabolite M4
MCV	Mean corpuscular volume
MCH	Mean corpuscular hemoglobin

Abbreviation	Expanded Term
NIMP	non-investigational medicinal product
NCS	not clinically significant
NOAEL	no observed adverse effect level
NOEL	No observed effect level
NRTI	Nucleoside reverse transcriptase inhibitor
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTTI	Nucleoside reverse transcriptase translocation inhibitor
PBC	Primary Biliary Cirrhosis
PBMC	Peripheral blood mononuclear cell
PK	pharmacokinetic
PP	Per-protocol
PrEP	Pre-exposure prophylaxis
QD	once-daily
QW	once-weekly
QM	Once-monthly
RBC	red blood cell
RR	Respiratory rate
SAC	Scientific Advisory Committee
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
SoA	schedule of activities
SOP	Standard operating procedure
STI	sexually transmitted infection
t1/2	Half-life
TDF	Tenofovir disoproxil fumarate
TK	toxicokinetic
T_{max}	time of maximum concentration
TP	Triphosphate
UDS	urine drug screen
VS	vital sign
Vz/F	Apparent volume of distribution during the terminal phase
WBC	white blood cell
WOCBP	woman/women of childbearing potential
WONCBP	woman/women of non-childbearing potential

11 REFERENCES

Not applicable.