Official Protocol Title:	An Open-Label, Single-Dose Study to Evaluate the Pharmacokinetics of Islatravir (MK-8591) in Subjects with Severe Renal Impairment
NCT number:	NCT04303156
Document Date:	24-JUN-2020

Title Page

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

This protocol amendment is applicable only to Germany.

Protocol Number: 026-02

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:

One Merck Drive

P.O. Box 100

Whitehouse Station, New Jersey, 08889-0100, U.S.A.

Regulatory Agency Identifying Number(s):

IND	128, 595
EudraCT	2020-000153-27

Approval Date: 24 June 2020

Sponsor Signatory

Typed Name: Title:	Date

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

Investigator Signatory

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

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment -02	24-Jun-2020	Inclusion criteria were clarified to define 'good health' with respect to blood pressure limits and laboratory values for healthy and renally impaired participants (country specific, Germany only).
Amendment -01	19-May-2020	Exclusion criteria and ECG abnormality criteria to adjust the threshold value of QTc for all participants and adjust the upper limit of heart rate for healthy participants were modified. The eGFR threshold for healthy participants was also adjusted to align with the European guidance and the CKD-EPI equation will be used for all participants. Exclusion criteria was also added to ensure enrolled subjects are at low risk for HIV infection (country specific, US only).
Original Protocol	10-Feb-2020	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 02

Overall Rationale for the Amendments:

Inclusion criteria were clarified to define 'good health' with respect to blood pressure limits and laboratory values for healthy and renally impaired participants (country specific, Germany only).

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
Section 5.1.1 Inclusion Criteria for Healthy Participants, Section 5.1.2 Inclusion Criteria for Renally Impaired Participants	Clarify that the inclusion criteria apply to all healthy or renally impaired participants and additional inclusion criteria that apply to Germany only can be found in Appendix 7 Country Specific Requirements.	Country specific requirements have been added for Germany only.
Section 10.7 Country Specific Requirements	Define good health in inclusion # 1 and #2 for healthy participants as follows: With respect to blood pressure, "good health" is defined as systolic blood pressure not more than 139 mm Hg and the diastolic blood pressure not more than 89 mm Hg. With respect to specific laboratory results, "good health" is defined so that ALT, AST, and bilirubin values (except if consistent with Gilbert's disease) should not exceed the upper limit of normal (ULN); any other abnormal laboratory parameters must be considered not clinically significant.	Inclusion criteria was clarified to define 'good health' with respect to blood pressure limits and laboratory values for healthy and renally impaired participants (country specific, Germany only).

Section # and Name	Description of Change	Brief Rationale
	Define good health in inclusion # 1 and #2 for renally impaired participants as follows: With respect to blood pressure, “good health” is defined as systolic blood pressure not more than 160 mm Hg and diastolic blood pressure not more than 100 mm Hg. With respect to specific laboratory results, “good health” is defined so that only clinically significant lab abnormalities associated with renal disease are acceptable; any other abnormal laboratory parameters must be considered not clinically significant for inclusion.	

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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 Subjects with Severe Renal Impairment

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

Acronym: Not applicable

Hypotheses, Objectives, and Endpoints:

Hypotheses are aligned with objectives in the Objectives and Endpoints table.

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 subjects with severe renal impairment compared to healthy control subjects. Estimation: In subjects with severe renal 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 subjects.	- 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 subjects with severe renal 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 subjects with renal impairment compared to healthy control subjects.	- AUC0-∞, AUC0-last, Cmax, C24, C168, C672, Tmax, and apparent terminal t½ of ISL-TP in PBMC

Tertiary/Exploratory Objectives	Tertiary/Exploratory Endpoints
- To evaluate the plasma pharmacokinetics of the metabolite M4 (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 subjects with severe renal impairment compared to healthy control subjects.	- AUC0-∞, AUC0-last, Cmax, Tmax, apparent terminal t½, CL/F, and Vz/F of plasma M4
- To explore the relationship between genetic variation and response to the treatment administered. Variation across the human genome will be analyzed for association with clinical data collected in this study.	- Germline genetic variation

Overall Design:

Study Phase	Phase 1
Primary Purpose	Treatment
Indication	Treatment of HIV Infection
Population	Participants with Severe Renal Impairment and Healthy Participants
Study Type	Interventional
Intervention Model	Single Group This is a multi-site study.
Type of Control	Healthy matched control subjects
Study Blinding	Unblinded Open-label
Blinding Roles	No Blinding
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 5 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 randomized.

Intervention Groups and Duration:

<table>
<tr><td>Interven-tion Groups</td><td>
<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>Severe Renal 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>
</td></tr>
<tr><td>Total Number</td><td>2</td></tr>
<tr><td>Duration of Participation</td><td>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.</td></tr>
</table>

Study Governance Committees:

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

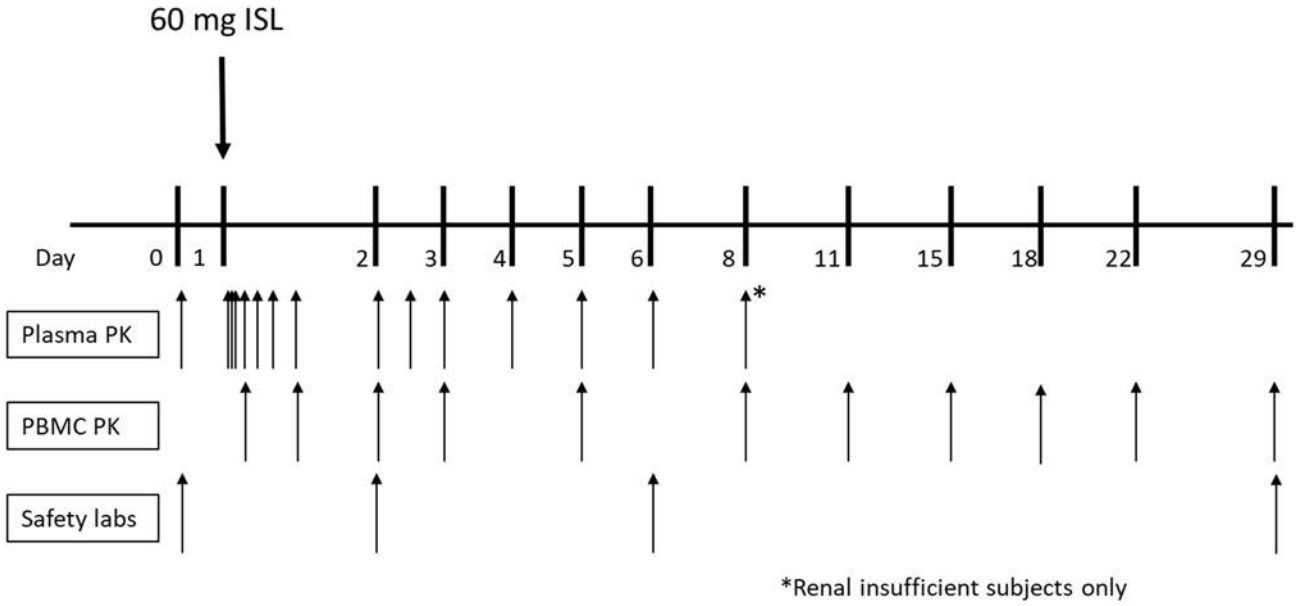
Study Accepts Healthy Volunteers: Yes

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		3	4	5	6	8	
Scheduled Hour	Screening	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	X																	
Prior/Concomitant Medication Review	X	X	X ----------X																
Assignment of Screening Number	X																		
Assignment of Treatment Number		X																	Site will follow local SOP for the timing of treatment allocation.
Domiciling		X----------X																	Refer to Section 8.1.11
MK-8591 (ISL) Administration			X																
Safety Procedures																			
Full physical examination (PE)	X	X[a]																	Symptom-driven PE may be performed at other times, at the Investigator's discretion.
Height	X																		
Weight	X																		
Vital Signs (heart rate, blood pressure)	X	X										X					X		Refer to Section 8.3.2
Respiratory Rate	X	X																	
Body Temperature	X	X																	

All Participants																			
			Intervention																Notes
Scheduled Day			1									2		3	4	5	6	8	
Scheduled Hour	Screening	Pre-dose	0	0.25	0.5	1	2	4	6	8	12	24	36	48	72	96	120	168	
12-lead ECG	X	X										X					X		Refer to Section 8.3.3
HIV, hepatitis B and C screen (per site SOP)	X																		
Serum/urine β-Human Chorionic Gonadotropin (β-hCG)	X	X																	Required for WOCBP. Serum or urine β-hCG at predose (per site SOP). Serum β-hCG required at Screening.
Serum Follicle Stimulating Hormone (FSH)	X																		For WONCBP.
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.
Hematology, urinalysis, and chemistry	X	X[a]										X					X		
AE/SAE review	X	X	X----------															X	
Pharmacokinetics/Biomarkers																			
Blood Collection for Plasma ISL in Severe Renal Impairment Group		X[a]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Blood collection for M4 metabolite in Severe Renal Impairment Group		X[a]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Blood for PBMC ISL-TP in Severe Renal Impairment Group		X[a]						X				X		X		X		X	
Blood Collection for Plasma ISL in Healthy Control Group		X[a]		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Blood collection for M4 metabolite in Healthy Control Group		X[a]		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Blood for PBMC ISL-TP in Healthy Control Group		X[a]						X				X		X		X		X	
Blood for Genetic Analysis[b]		X																	

All Participants																			
			Intervention																Notes
Scheduled Day			1									2		3	4	5	6	8	
Scheduled Hour	Screening	Pre-dose	0	0.25	0.5	1	2	4	6	8	12	24	36	48	72	96	120	168	

a. Pre-dose PE, urine drug screen, safety labs, and blood sample for plasma ISL/M4 metabolite/PBMC ISL-TP can be conducted 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. This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at the site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for future biomedical research if the participant signs the future biomedical research consent. If the planned genetic analysis is not approved, but future biomedical research is approved and consent is given, this sample will be collected for the purpose of future biomedical research.

*Please refer to Appendix 7 Country Specific Requirements for screening tests that are applicable to the US only.

	Intervention					Notes
Scheduled Day	11	15	18	22	Post-trial visit/Day 29 [c]	
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	
Pharmacokinetics						
Blood for PBMC ISL-TP PK in Severe Renal Impairment Group	X	X	X	X	X	
Blood for PBMC ISL-TP PK in Healthy Control Group	X	X	X	X	X	

c. Post-trial study procedures will be conducted on Day 29 of the study

*Please refer to Appendix 7 Country Specific Requirements for screening tests that are applicable to the US only.

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 who are at high risk of becoming infected. Currently, ISL is being evaluated in a Phase 2 trial at a dose of 0.75 mg QD (in combination with 100 mg doravirine, DOR; NCT03272347), 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

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

2.2 Background

Refer to the IB for detailed background information on 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 renal 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. Unlike conventional NRTIs, ISL acts via multiple mechanisms, leading to both immediate and delayed chain termination. The inactive parent is phosphorylated to the active ISL-TP in PBMCs and other cells. In in vitro studies in PBMCs, ISL-TP demonstrated antiviral activity, with an IC_{50} of 0.21 nM, while other NRTIs demonstrated IC_{50}s ranging from 10.1 to 144 nM. ISL demonstrates a favorable mutant selection profile compared to other NRTIs, selecting only for the M184V/I mutant, against which ISL is active but with a decrease in sensitivity of 7.3- to 9.5-fold.

The elimination of ISL is anticipated to occur by both excretion of unchanged parent drug and metabolism via adenosine deaminase (ADA) to the major circulating ISL metabolite M4 (4'-ethynyl-2-fluoro-2'deoxyinosine). In rats, ISL was eliminated predominantly as M4, while in monkeys, elimination was balanced between M4 formation and renal excretion of unchanged parent drug. No metabolism of ISL was observed in human liver preparations but limited turnover of ISL, via direct glucuronidation, was observed in liver preparations from both rats and monkeys. Islatravir was metabolized in intestinal preparations across species to M4, the same as observed in vivo in rat and monkey.

M4 exhibits weak antiviral activity against WT HIV-1 (7000-8000-fold less potent than ISL parent). Metabolism via ADA is a non-cytochrome P450 (CYP) mediated pathway. Therefore, ISL is not anticipated to be a victim of drug interactions. Of note, ISL is also not likely to perpetrate drug interactions, as it is not an inducer or inhibitor of major CYP enzymes or of major hepatic and renal transporters.

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 is therefore not directly excreted or metabolized. ISL-TP has a significantly longer intracellular half-life than the parent drug; the intracellular half-life of the triphosphate anabolite was determined to be 25 and 50 hr, in rat and monkey, respectively. 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.

2.2.2 Preclinical and Clinical Studies

Potential systemic effects of ISL have been extensively evaluated in nonclinical safety studies as part of the oral program, 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 MK-8591 (ISL) IB. Overall, target organ/system toxicities identified in enterally administered ISL exploratory and/or GLP studies in rats and monkeys were considered not relevant at the anticipated human AUC exposure for a 60 mg dose of ISL based on the safety margins (≥182X) at the NOAELs over the intended clinical exposures compared to the dose. [redacted]

Orally administered ISL has been evaluated in 8 completed Phase 1 studies and is being evaluated in 1 ongoing Phase 1 study and 2 ongoing Phase 2 studies. Across the 9 Phase 1 studies, as of 30-Sep-2019, 192 adult participants (including 30 participants with HIV-1 infection) received a single dose (up to 400 mg orally) or multiple doses of ISL (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 T_{max} 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.

Urine samples were collected for the PK assessment of ISL and to evaluate urinary excretion of intact ISL in healthy subjects in three Phase I studies (P002, P003, P009). Following multiple-dose administration with increasing dose from 0.75 mg to 5 mg ISL QD (P009), GM Ae and fe of urine ISL increased with repeated administration within the 0.75 and 5 mg dose levels, whereas GM CLr values appeared similar. Urine fe (fraction excreted) levels ranged from 27-40% at steady state.

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 three ongoing studies involving oral ISL.

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 subjects were dosed in November 2019.

Protocol 015 (P015) is a multiple panel double-blind placebo-controlled trial in 64 healthy adult Japanese males, examining PK and general safety and tolerability of ISL up to 30 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 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 subjects on DOR/3TC/TDF throughout the study period. As of 30-Sep-2019, ISL has been administered to ~90 HIV-1 positive individuals for at least 48 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.

Five participants reported 7 SAEs, of which only one was considered drug-related. This was in a subject who received DOR/3TC/TDF (therefore not receiving ISL), who had a worsening of congenital long QT syndrome; this subject withdrew from the study and the event resolved. Two additional subjects discontinued study medication due to a drug-related AE. Both of these subjects initially received ISL (2.25 mg)/DOR/3TC; one subject discontinued because of diarrhea, nausea and vomiting, and the other discontinued due to Hepatitis B reactivation.

Of note, enrollment in P011 is open to PLWH with mild renal impairment (CrCL $\geq$50 mL/min). Five individuals receiving ISL had screening eGFRs ranging from 50-90 mL/min. In exploratory analysis of potential covariates on PK from P011, CrCL does not appear to be a significant covariate. Given the low number of participants with mild renal insufficiency in P011, no conclusions can be drawn yet regarding safety and tolerability in this population.

2.3 Benefit/Risk Assessment

Participants in this clinical study 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

Hypotheses are aligned with objectives in the Objectives and Endpoints table.

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 subjects with severe renal impairment compared to healthy control subjects. Estimation: In subjects with severe renal 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 subjects.	• AUC0-∞, AUC0-last, Cmax, Tmax, apparent terminal t½, CL/F, and Vz/F of plasma ISL

Objectives	Endpoints
Secondary	
• To evaluate the safety and tolerability of ISL in subjects with severe renal 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 subjects with renal impairment compared to healthy control subjects.	• 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, Tmax, apparent terminal t½, CL/F, and Vz/F) after a single oral dose of 60 mg ISL in subjects with severe renal impairment compared to healthy control subjects.	• AUC0-∞, AUC0-last, Cmax, Tmax, apparent terminal t½, CL/F, and Vz/F of plasma M4
• To explore the relationship between genetic variation and response to the treatment administered. Variation across the human genome will be analyzed for association with clinical data collected in this study.	• Germline genetic variation

4 STUDY DESIGN

4.1 Overall Design

This is an open-label, single-dose, multi-site study in subjects with severe renal impairment (N=6) and healthy mean matched controls (N=6). Once all subjects with severe renal impairment are enrolled, the healthy matched control subjects will be enrolled. Individual age and weight of healthy matched control subjects will be within the range ± 10 years and ± 10 kg of the mean age and weight of subjects with severe renal impairment. In addition, the numbers of males and females of the healthy subjects will be generally matched to the numbers of renal insufficient subjects within ± 1.

Assignment to a renal function group will be as follows:

Impairment Stage	N	eGFR (mL/min/1.73 m^2)[a]
Severe	6	< 30, not on dialysis[b]
Healthy	6	≥ 90

[a] eGFR based on the CKD-EPI equation. Baseline eGFR will be obtained twice (at least 72 hours apart as part of subject screening) and the mean of the two values will be used. The second baseline eGFR sample may be obtained at the time of check-in.

[b] Reasonable efforts will be made to enroll 1-2 subjects in the severe renal impairment group who have eGFR values of 10 - 20 mL/min/1.73 m^2.

On Day 1, subjects will receive a single oral dose of 60 mg (6 x 10 mg capsules) ISL, followed by PK sampling until 120 hours postdose (healthy control group) or 168 hours postdose (severe renal impairment group). There will be additional visits at hours 168, 240, 336, 408, 504, 672 postdose for the collection of PBMCs. Safety will be monitored throughout the study by repeated clinical and laboratory evaluations.

Because this is a Phase 1 assessment of ISL 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 8.10.6 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

As the HIV+ population ages, more persons living with HIV (PLWH) will accumulate co-morbidities, including chronic medical conditions such as diabetes and hypertension that can lead to renal insufficiency. Existing preclinical and clinical data suggest that renal excretion of unchanged parent is a major mode of elimination for ISL, and therefore it seems likely that individuals with renal insufficiency may have higher levels of ISL and perhaps ISL-TP as well. Given the wide dose ranges throughout development noted above (0.25-400 mg), along with favorable preclinical toxicity studies and an excellent clinical tolerability profile to date, a potential increase in ISL in renally insufficient subjects is not anticipated to be clinically meaningful.

In this trial, PK of ISL in subjects with severe renal insufficiency are being compared to the PK in generally healthy study participants. Confirmation of the expected elevation in ISL levels, along with adequate tolerability, in subjects with severe renal insufficiency would support not assessing subjects with mild and moderate renal insufficiency in this trial. Based on preclinical and clinical PK to date, it is expected that ISL parent levels will increase only modestly (5% for Cmax, ~50% for AUC) in subjects with severe renal insufficiency relative

to healthy study participants (see Table 1 for levels projected using population PK modeling), while ISL-TP levels will increase as well. For comparison, the NOAEL from preclinical chronic toxicity studies is 118 µM*hr (0-168hr), which provides a ~10x exposure margin to the levels expected in subjects with severe renal insufficiency. As noted, doses up to 400 mg (which leads to an AUC of 47.1 µM*hr, or a 4x exposure margin) have been generally well tolerated, and to date no dose-related AEs have been observed; thus, a modest increase in ISL levels is not likely to lead to clinically significant effects. In addition, any increase in ISL-TP is not expected to have an adverse effect on efficacy. Such relatively modest increases in ISL and ISL-TP in subjects with severe renal insufficiency would suggest that there would be an even more modest effect in subjects with mild or moderate renal insufficiency.

Table 1 Population PK Modeling Projections for ISL Levels After 60 mg.

Dose	**Cmax (µM)**	**AUC (µM*hr)**
60 mg x1	1.01	7.42 (0-inf)
60 mg (severe renal insufficiency)	1.06	11.19 (0-inf)

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

No efficacy endpoints will be evaluated.

4.2.1.2 Safety Endpoints

Multiple trials have evaluated oral ISL in human subjects, including a Phase 1 trial with single doses as high as 400 mg and Phase 2 trial in which subjects have received daily doses of up to 2.25 mg ISL for at least 48 weeks. To date, oral ISL appears generally well tolerated, and there have been no concerning safety signals from oral ISL administration. As such, standard safety monitoring of adverse events, 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, should be adequate to assess tolerability of ISL in this trial.

4.2.1.3 Pharmacokinetic Endpoints

The primary endpoints for this study will include the pharmacokinetic parameters of AUC0-∞, AUC0-last, Cmax, Tmax, apparent terminal t½, CL/F, and Vz/F of plasma ISL. The pharmacokinetic parameters AUC0-∞, AUC0-last, Cmax, C24, C168, C672, Tmax, and apparent terminal t½ of ISL-TP in PBMC will be included as secondary endpoints. These parameters correspond to the systemic PK of ISL and ISL-TP, respectively, following a single dose of ISL. Assessment of these PK parameters for both ISL and ISL-TP has been consistently performed throughout the entire Phase 1 clinical development program.

As ISL is subject to renal clearance, the plasma concentration may be higher in renally impaired subjects. Plasma PK parameters included in the primary endpoints will be evaluated

and compared between healthy and renally impaired subjects, using geometric mean ratio (GMR) and confidence interval (CI) to assess differences between the two groups.

In addition to assessing parent ISL levels, ISL-TP PK parameters will be evaluated as secondary endpoints in healthy and renally impaired subjects. This will allow a more complete understanding of ISL-TP levels in this population. 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 renally 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, PK parameters of M4, the major circulating metabolite of ISL, will be evaluated as exploratory endpoints in healthy study participants and in the renally impaired subjects. As with ISL-TP, there is no a priori reason to expect M4 levels to not continue to track at ~30-40% of ISL levels in plasma in healthy subjects. This assessment, however, will allow determination of M4 plasma concentrations in renally insufficient subjects.

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 future biomedical research 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 future biomedical research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that participants receive the correct dose of the correct drug/vaccine at the correct time. The details of future biomedical research 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. As noted above, doses of 60 mg and 120 mg are being evaluated in the Phase 2 general tolerability and PK trial. A dose of 60 mg is being considered for future 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 renal insufficiency are not likely to vary with dose. Based on the assessment of urine excretion to date, an increase of ~50% is expected in ISL plasma levels in subjects with severe renal insufficiency. 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. As shown below (Table 2), the expected effect of severe renal insufficiency after QD dosing would lead to increases in ISL levels similar in magnitude to those expected after single dose administration (Table 1).

Table 2 Population PK Modeling Projection of ISL Levels After 0.75 mg QD Dosing

Dose	Cmax (µM)	AUC (µM*hr)
0.75 mg QD (steady state)	0.013	0.094 (0-24hr)
0.75 mg QD (steady state, severe renal insufficiency)	0.017	0.146 (0-24hr)

As this is a Phase 1 assessment of ISL 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 8.10.6.

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 severe renal impairment between the ages of 18 and 75 (inclusive) and healthy matched controls will be enrolled in this study.

The individual age and weight of the healthy subjects is aimed to be within the range ± 10 years and ± 10 kg of the mean age and weight of subjects with renal impairment. In addition, the numbers of males and females of the healthy subjects will be generally matched to the numbers of renal insufficient subjects within ± 1; i.e., if there are 3 males and 3 females in the renal insufficient group, every effort will be made to ensure a 3:3 ratio in the healthy subjects, 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. Additional inclusion criteria that apply to Germany only can be found in Appendix 7 Country Specific Requirements.

Type of Participant and Disease Characteristics

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

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 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.

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 $(m)^2$.

4. Have a baseline eGFR ≥ 90 mL/min/1.73 m2 based on eGFR equation from CKD-EPI at screening:

   The CKD-EPI equation is defined as follows:

   CKD-EPI Equation:

   $eGFR = 141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] × 1.159 [if African American]

   Baseline eGFR will be obtained twice (at least 72 hours apart as part of subject screening), and the mean of the two values will be used. The second baseline eGFR sample may be obtained at the time of check-in.

   Participants who have an eGFR of up to 10% below 90 mL/min/1.73m2 may be enrolled in the study at the discretion of the investigator.

Demographics

5. 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 study drug administration. 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

6. The participant 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 Renally Impaired Participants

The following inclusion criteria apply to all renally impaired participants. Additional inclusion criteria that apply to Germany only can be found in Appendix 7 Country Specific Requirements.

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

Type of Participant and Disease Characteristics

1. With the exception of renal 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, including but not limited to hypertension, hypercholesterolemia, non-insulin dependent diabetes mellitus, hyper- or hypothyroidism, gout, and chronic anxiety or depression may be included at the discretion of the investigator and the Sponsor. Appendix 9 provides a table of the 12-Lead Electrocardiogram Abnormality Criteria.

2. With the exception of renal 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.

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 $(m)^2$.

4. Have a baseline eGFR < 30 mL/min/1.73 m2 based on eGFR equation from CKD-EPI at screening.

   The CKD-EPI equation is defined as follows:

   CKD-EPI Equation:

   $eGFR = 141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] × 1.159 [if African American]

   Baseline eGFR will be obtained twice (at least 72 hours apart as part of subject screening), and the mean of the two values will be used. The second baseline eGFR sample may be obtained at the time of check-in.

   Reasonable efforts will be made to enroll an adequate number of subjects (1-2 subjects) in the severe renal impairment group who have eGFR values of 10 - 20 mL/min/1.73 m^2

Demographics

5. 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

6. The participant 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. Additional exclusion criteria that apply to the US only can be found in Appendix 7 Country Specific Requirements.

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 institutionalized or 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 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.

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

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

6. 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

7. 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

8. 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

9. Has a QTc interval >450 for males or >460 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

10. Is under the age of legal consent.

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

12. Consumes greater than 1 glass of alcoholic beverage or equivalent per day (12 g/d) for females and 2 glasses of alcoholic beverages or equivalent per day (24 g/d) for males (Note - 1 glass is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce]). Participants who consume more than the daily limit may be enrolled at the discretion of the investigator.

13. 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.

14. Is a regular user of cannabis or any illicit drugs or has a history of drug (including alcohol) abuse within approximately 2 years. Participants must have a negative drug screen prior to randomization.

15. 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.

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

17. 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 Renally Impaired Participants

The following exclusion criteria apply to all renally impaired participants. Additional exclusion criteria that apply to the US only can be found in Appendix 7 Country Specific Requirements.

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

Medical Conditions

1. Has a history or presence of renal artery stenosis.

2. Has had a renal transplant or nephrectomy.

3. Has rapidly fluctuating renal function as determined by historical measurements. Rapidly fluctuating renal function is defined as > 30% difference between two measurements of eGFR taken at least 72 hour apart as part of subject screening.

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

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

6. 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).

7. 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.

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

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

10. 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

11. Is taking medications to treat chronic medical conditions and/or conditions associated with renal disease and has not been on a stable regimen 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 subjects in whom a medication regimen has been adjusted within the three-month window, at the discretion of the Investigator and following consultation with the Sponsor. See Section 5.1.2 for allowed medical conditions, and Section 6.5 for allowed medications.

Prior/Concurrent Clinical Study Experience

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

Diagnostic Assessments

13. Has a QTc interval >450 for males or >460 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

14. Is under the age of legal consent.

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

16. Consumes greater than 1 glass of alcoholic beverage or equivalent per day (12 g/d) for females and 2 glasses of alcoholic beverages or equivalent per day (24 g/d) for males (Note - 1 glass is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce]). Participants who consume more than the daily limit may be enrolled at the discretion of the investigator.

17. 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.

18. Is a regular user of cannabis, any illicit drugs or has a history of drug (including alcohol) abuse within approximately 3 months. Participants must have a negative UDS prior to randomization. Participants with severe renal impairment will be allowed for inclusion with a positive UDS for opiates if they have an active prescription from a licensed health care provider.

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

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

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

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

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 4 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 1 glass of alcoholic beverage or equivalent per day (12 g/d) for females and 2 glasses of alcoholic beverages or equivalent per day (24 g/d) for males (Note - 1 glass is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce]). .

5.3.2.3 Smoking 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 severe renal 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 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.

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 supplies. 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 3.

Table 3 Study Interventions

Arm Name	Arm Type	Inter-vention Name	Type	Dose Formu-lation	Unit Dose Strength(s)	Dosage Level(s)	Route of Adminis-tration	Regimen/ Treatment Period	Use	IMP/ NIMP	Sourcing
Severe Renal Impair-ment Group	Experi-mental	MK-8591 (ISL)	Drug	Capsule	10 mg	60 mg	Oral	Single Dose on Day 1	Experi-mental	IMP	Provided by the Sponsor
Healthy Control Group	Experi-mental	MK-8591 (ISL)	Drug	Capsule	10 mg	60 mg	Oral	Single Dose on Day 1	Experi-mental	IMP	Provided by the Sponsor
Definition Investigational Medicinal Product (IMP) and Non-Investigational Medicinal Product (NIMP) is based on guidance issued by the European Commission. Regional and/or Country differences of the definition of IMP/NIMP may exist. In these circumstances, local legislation is followed.											

All supplies indicated in Table 3 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

Subjects will be assigned an allocation number (AN) for a single open-label treatment using the allocation schedule shown in Table 4.

Table 4 Allocation of Subjects to Treatment

Impairment Stage	N	Treatment
Severe	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 identification 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, he/she may be included in the study if the investigator can rationalize that the specific use of a prior medication is not clinically relevant within the context of the study.

Concurrent use of any prescription or nonprescription medication, or concurrent vaccination, during the ongoing study (ie, 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.

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

For Participants with Severe Renal Impairment:

Participants who are taking medications to treat general medical conditions and/or conditions associated with renal 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. Subjects 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. Examples of types of medications 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
- Synthroid
- Colchicine, allopurinol
- Selective serotonin uptake inhibitors (SSRIs), tricyclic antidepressants
- Proton pump inhibitors

Any medication (including over-the-counter) that would significantly alter eGFR, which, 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 first 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 a Serious Adverse Event 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 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 296.5 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 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 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 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.

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.

Any participant who is screened multiple times will retain the original screening number assigned at the initial screening visit. Specific details on the screening/rescreening visit requirements are provided in Section 8.10.1.

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 allocation. 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. 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.

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 120 hours post dose for healthy matched controls and 120 hours post dose for participants with severe renal 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 full physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) as per institutional standard per SoA. 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 14 days after study drug administration, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

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

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

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

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 study drug, 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 5.

Table 5 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	Reporting Time Period: Consent to Randomization/ Allocation	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:
Nonserious Adverse Event (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
Serious Adverse Event (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: - due to intervention - causes exclusion	Report all	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event
Event of Clinical Interest (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - potential drug-induced liver injury (DILI) - require regulatory reporting	Not required	Within 24 hours of learning of event
Event of Clinical Interest (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
Overdose	Report if: - receiving placebo run-in or other run-in medication	Report all	Not required	Within 24 hours of learning of 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 nonserious and SAEs 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 samples collected will be assayed for evaluation of PK 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 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.

8.7 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 participant signs the future biomedical research consent. If the planned genetic analysis is not approved, but future biomedical research is approved and consent is given, 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 3 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 randomization if there are Day -1 procedures planned per protocol.

8.10.2 Treatment Period

Refer to the Schedule of Activities (Section 1.3).

8.10.3 Discontinued Participants Continuing to be Monitored in the Study

At any point if a participant discontinues from treatment but continues to be monitored in the study, all of 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 6.

Table 6 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 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).

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

Pharmacokinetics: Separately for each PK parameter and analyte, individual values of plasma ISL AUC0-∞, AUC0-last, Cmax, CL/F, and Vz/F, PBMC ISL-TP AUC0-∞, AUC0-last, Cmax, C24, C168, C672, plasma M4 AUC0-∞, AUC0-last, Cmax, CL/F, and Vz/F after a single dose administration of 60 mg ISL to subjects with severe renal impairment and healthy subjects will be natural log-transformed and evaluated with a linear fixed effects model containing a categorical effect for population (subjects with severe renal impairment, healthy subjects). 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%) confidence intervals for the least squares means for each population will be constructed on the natural log scale and will reference the t-distribution. Exponentiating the least-squares means and their corresponding 95% confidence limits 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 subjects with severe renal impairment to subjects with normal renal function, a two-sided 90% confidence interval for the true difference in means (subjects with severe renal impairment – healthy subjects) 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 (subjects with severe renal impairment/healthy subjects) for each PK parameter.

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, 0.356, 0.414 and 0.518, respectively. Assuming the same variability for 60-mg ISL, with 6 severe renal impairment subjects and 6 healthy subjects, 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 subjects with severe renal 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 subjects.

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, Tmax, apparent terminal t½, CL/F, and Vz/F of M4 in plasma. The exploratory endpoints also include genetic variation and response to the treatment administered.

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 Subjects as Treated (ASaT): The All Subjects 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

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

Pharmacokinetics: Separately for each PK parameter and analyte, individual values of plasma ISL AUC0-∞, AUC0-last, Cmax, CL/F, and Vz/F, PBMC ISL-TP AUC0-∞, AUC0-last, Cmax, C24, C168, C672, plasma M4 AUC0-∞, AUC0-last, Cmax, CL/F, and Vz/F after a single dose administration of 60 mg ISL to subjects with severe renal impairment and healthy subjects will be natural log-transformed and evaluated with a linear fixed effects model containing a categorical effect for population (subjects with severe renal impairment, healthy subjects). 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%) confidence intervals for the least squares means for each population will be constructed on the natural log scale and will reference the t-distribution. Exponentiating the least-squares means and their corresponding 95% confidence limits 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;
run;
```

To address the primary estimation objective and compare subjects with severe renal impairment to subjects with normal renal function, a two-sided 90% confidence interval for the true difference in means (subjects with severe renal impairment – healthy subjects) 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 (subjects with severe renal impairment/healthy subjects) for each PK parameter.

Individual values will be listed for each PK parameter (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, and apparent terminal t½, plasma M4 AUC0--∞, AUC0-last, Cmax, Tmax, apparent terminal t½, CL/F, and Vz/F) by population, and the following (non-model-based) descriptive statistics will be provided: N (number of subjects with non-missing data), arithmetic mean, standard deviation, arithmetic percent CV (calculated as 100 x standard deviation/arithmetic mean), median, minimum, maximum, geometric mean, and geometric percent CV (calculated as 100 x sqrt(exp(s^2) - 1), where s^2 is the observed variance on the natural log-scale).

Figures showing individual PK values with GMs (95% CIs) by population, plotted on the natural log scale, will be provided for ISL plasma AUC0-∞, AUC0-last and Cmax. Individual subject PK values will also be plotted against BSA normalized eGFR and against BSA un-normalized eGFR, using different symbols to identify subjects from each population. For this analysis, eGFR will be calculated as the mean of the two values determined at screening. Plots of PK parameters versus CLcr using the C-G equation will also be provided. Additionally, plots of PK parameter values vs age and body mass index (BMI) may be provided.

Summary Statistics using BSA un-normalized eGFR The subjects will be re-categorized into different renal categories based on their BSA un-normalized eGFR and non -model based summary statistics by population will be provided for plasma ISL AUC0-∞, AUC0-last, Cmax, CL/F, and Vz/F, PBMC ISL-TP AUC0-∞, AUC0-last, Cmax, C24, C168, C672, plasma M4 AUC0-∞, AUC0-last, Cmax, CL/F, and Vz/F.

Analysis using CLcr (C-G equation): The subjects will be re-categorized into different renal categories based on their CLcr obtained from C-G equation and non-model based summary statistics by population will be provided for plasma ISL AUC0-∞, AUC0-last, Cmax, CL/F, and Vz/F, PBMC ISL-TP AUC0-∞, AUC0-last, Cmax, C24, C168, C672, plasma M4 AUC0-∞, AUC0-last, Cmax, CL/F, and Vz/F.

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

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 severe renal impairment subjects and 6 healthy subjects, 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 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. 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 fraud,

scientific/research misconduct or serious GCP-non-compliance is suspected, the issues are investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees 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. 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 7 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 7 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	
	Magnesium			
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, [bilirubin, urobilinogen, nitrite, leukocyte esterase] by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• Follicle-stimulating hormone (as needed in women of nonchildbearing potential only) • Serum or urine alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines). Alcohol breath test for alcohol screen is permitted. • Serum or urine β human chorionic gonadotropin (β hCG) pregnancy test (as needed for WOCBP) • Serology [(HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody)] *Please refer to Appendix 7 Country Specific Requirements for screening tests that are applicable to the US only.			
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, or protocol specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

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

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

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

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

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

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

- Any new cancer or progression of existing cancer.

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

- Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened.

- Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.2 Definition of SAE

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

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

a. **Results in death**

b. **Is life-threatening**

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

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

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

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

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.

- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

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

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

f. **Other important medical events**

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

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

10.3.3 Additional Events Reported

Additional events that require reporting

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

- Is a cancer
- Is associated with an overdose

10.3.4 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.

- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.

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

Assessment of intensity/toxicity

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

- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) 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: Device Events, Adverse Device Events, and Medical Device Incidents: Definitions, Collection, and Documentation

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 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.
Acceptable Contraceptive Methods *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 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 participant' 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 gender, 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

10.7.1 Country-specific Requirements - Germany

The following specifies "good health" with respect to the inclusion criteria.

Section 5.1.1 Inclusion Criteria for Healthy Participants

Inclusion criterion #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"

In this Inclusion Criterion, with respect to blood pressure, "good health" is defined as systolic blood pressure not more than 139 mm Hg and the diastolic blood pressure not more than 89 mm Hg.

Inclusion criterion #2:

"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."

In this Inclusion Criterion, with respect to specific laboratory results, "good health" is defined so that ALT, AST, and bilirubin values (except if consistent with Gilbert's disease) should not exceed the upper limit of normal (ULN); any other abnormal laboratory parameters must be considered not clinically significant.

Section 5.1.2 Inclusion Criteria for Renally Impaired Participants

Inclusion criterion #1:

"With the exception of renal 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, including but not limited to hypertension, hypercholesterolemia, non-insulin dependent diabetes mellitus, hyper- or hypothyroidism, gout, and chronic anxiety or depression may be included at the discretion of the investigator and the Sponsor. Appendix 9 provides a table of the 12-Lead Electrocardiogram Abnormality Criteria."

In this Inclusion Criterion, with respect to blood pressure, "good health" is defined as systolic blood pressure not more than 160 mm Hg and diastolic blood pressure not more than 100 mm Hg.

Inclusion criterion #2:

"With the exception of renal 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."

In this Inclusion Criterion, with respect to specific laboratory results, "good health" is defined so that only clinically significant lab abnormalities associated with renal disease are acceptable; any other abnormal laboratory parameters must be considered not clinically significant for inclusion.

10.7.2 Country-specific Requirements – US

Section 1.3 Schedule of Activities

The following safety procedures are applicable to the United States (US) only. Please refer to Section 1.3 Schedule Activities for other safety procedures required for all participants.

Participants in the US only																		
			Intervention															Notes
Scheduled Day			1								2		3	4	5	6	8	
Scheduled Hour	Screening	Pre-dose	0	0.25	0.5	1	2	4	6	8	12	24	36	48	72	96	120	168	
Safety Procedures																			
HIV, hepatitis B and C screen. HIV-2 included for the US only	X																		
GC/CT (gonorrhea + chlamydia) screen – US only	X																		Per site SOP
Syphilis serologic screening – US only	X																		Per site SOP
Trichomonas testing – US only	X																		If available, per site SOP

	Intervention					Notes
Scheduled Day	11	15	18	22	Post-trial visit/Day 29 [c]	
Scheduled Hour	240	336	408	504	672	
Safety Procedures						
HIV Screen (including HIV-2) – US only					X	
c. Post-trial study procedures will be conducted on Day 29 of the study.						

Section 5.2 Exclusion Criteria

The following exclusion criteria apply to healthy and renally impaired participants in the US only. Please refer to Section 5.2 Exclusion Criteria for other exclusion criteria required for all participants.

1. 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.

Section 10.2 Clinical Laboratory Tests

The following Clinical Laboratory Tests are applicable to the US only. Please refer to Appendix 2 Clinical Laboratory Tests for other screening tests required for all participants.

Other Screening Tests	• HIV-2 included in HIV screen at screening and HIV screen (HIV-1/HIV-2) on Day 29 – US only • Syphilis serologic testing - US only • GC/CT testing per site SOP - US only • Trichomonas testing, if available, per site SOP – US only

10.8 Appendix 8: Blood Volume Table

All Participants	Pre-study	Treatment Periods	Post-study	Total Collections	mL Per Collection	Total mL/ Test
Laboratory Safety Tests (all subjects; includes FSH if applicable, β-hCG if applicable, and HIV/Hepatitis screen)	2	2	1	5	17	85[c]
Blood for Genetic Analysis	1	0	0	1	8.5	8.5
Blood for PBMC ISL-TP	0	11	0	11	16	176
Blood for Plasma ISL	1	14-15[b]	0	15-16	4	60 – 64
Blood for plasma M4	1	14-15[b]	0	15-16	3	45-48
Total Blood Volume per participant:						374.5 to 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] During the treatment period, 15 blood collections for plasma ISL and M4 in healthy control group and 16 blood collections for plasma ISL and M4 in severe renal impaired group.

c. 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 screen will include HIV-2 in the US only, syphilis serologic testing will be conducted in the US only, and an HIV screen will be conducted on Day 29 in the US only. Please refer to Appendix 7 Country Specific Requirements.

10.9 Appendix 9: 12-Lead Electrocardiogram Abnormality Criteria

12-Lead Electrocardiogram Abnormality Criteria		
	Screen Failure Criteria	Potentially Significant Post-randomization Findings (clarification on action to take)
RHYTHM		
Sinus Tachycardia	>110 bpm for renally impaired participants >90 bpm for healthy participants	HR >110 bpm for renally impaired participants and >90 bpm for healthy participants AND HR increase of ≥25 bpm from baseline
Sinus Bradycardia	<50 bpm	HR <50 bpm and HR decrease of ≥5 bpm from baseline
Sinus Pause/Arrest	>2.0 seconds	>2.0 seconds
Atrial Premature Complex	> 1 beat	≥ 3 beats
Ventricular Premature Complex	All	≥ 3 beats
Ectopic Atrial Rhythm	None	None
Junctional Rhythm	Junctional Rhythm with HR <40 bpm	Junctional Rhythm with HR <40 bpm
Idioventricular Rhythm	All	All
Atrial Fibrillation	All	All
Atrial Flutter	All	All
Supraventricular Tachycardia	All	All
Ventricular Tachycardia	All	All
AXIS		
Left Axis Deviation	RBBB With Left Anterior Hemiblock (LAHB)	New Onset LAHB
Right Axis Deviation	RBBB With Left Posterior Hemiblock (LPHB)	New Onset LPHB
CONDUCTION		
1st Degree AV Block	PR ≥230 ms	PR ≥ 230 ms + Increase of >15 ms; or PR Increase of >25%
2nd Degree AV Block	Mobitz Type II	Mobitz Type II
3rd Degree AV Block	All	All
LBBB	All	All
RBBB	RBBB With LAHB/LPHB as Defined Above	New Onset RBBB (Not Including Rate-related)
Incomplete Right BBB (ICRBBB) (QRS <120 ms)	No Exclusion	Nothing
Short PR/ Preexcitation Syndrome	Delta Wave + PR <120 ms	Delta Wave + PR <120 ms
Other Intra-Ventricular Conduction Delay	QRS ≥130 ms	QRS ≥130 ms + Increase of ≥10 ms
QTc F		
Male	QTc ≥450 ms	QTc ≥500 ms or Increase of ≥60 ms From Baseline
Female	QTc ≥460 ms	QTc ≥500 ms or Increase of ≥60 ms From Baseline

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

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

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

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

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

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

    1. The participant may be excluded from the study;

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

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

    OR

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

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

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

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

10.11 Appendix 11: Abbreviations

Abbreviation	Expanded Term
3TC	Lamivudine
AE	adverse event
APaT	All-Participants-as-Treated
AR	adverse reaction
ART	anti-retroviral therapy
ATP	adenosine triphosphate
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase
ART	Anti-retroviral therapy
ARV	Antiretroviral
AST	Aspartate aminotransferase
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
Bx	biopsy
C24	Concentration at 24 hours post dose
C168	Concentration at 168 hours post dose
C672	Concentration at 672 hours post dose
Cmax	Maximum concentration
CCC	concordance correlation
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL	clearance
CL/F	Apparent clearance after extravascular administration
CrCl	creatinine clearance
CRF	Case Report Form
CRU	clinical research unit
CV	coefficient of variation
DAIDS	Division of AIDS
DILI	drug-induced liver injury
DOR	Doravirine
DP	Diphosphate
DTG	Dolutegravir
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
eCTA	exploratory Clinical Trial Application
EDC	electronic data collection
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
FBR	Future biomedical research
FDA	Food and Drug Administration
FDC	Fixed dose combination
FSH	follicle stimulating hormone

Abbreviation	Expanded Term
FTC	Emtricitabine
GCP	Good Clinical Practice
GCV	geometric coefficient of variation
GLP	good laboratory practice
GM	geometric mean
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B 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
IRB	Institutional Review Board
LNG/EE	Levonorgestrel/ethinyl estradiol
MedDRA	Medical Dictionary for Regulatory Activities
M4	metabolite M4
MCV	Mean corpuscular volume
MCH	Mean corpuscular hemoglobin
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
PBMC	Peripheral blood mononuclear cell
PK	pharmacokinetic
PP	Per-protocol
PrEP	Pre-exposure prophylaxis
QD	once-daily
QW	once-weekly
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
t1/2	Half-life
TDF	Tenofovir disoproxil fumarate
TK	toxicokinetic
T_{max}	time of maximum concentration

Abbreviation	Expanded Term
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.