Official Protocol Title:	An Open-Label, Single-Dose Study to Evaluate the Pharmacokinetics of MK-8527 in Participants with Moderate and Severe Renal Impairment
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Clinical Protocol

An Open-Label, Single-Dose Study to Evaluate the Pharmacokinetics of MK-8527 in Participants with Moderate and Severe Renal Impairment

Celerion Project No.: CA42394

Sponsor Project No.: MK-8527-008-00

US FDA IND No.: 165,532

Study Phase: Phase 1

Final Protocol Date: 11 December 2023

Good Clinical Practices (GCP) Statement

This study is to be performed in full compliance with the protocol, GCP, and applicable regulatory requirements. All required study documentation will be archived as required by regulatory authorities.

PROTOCOL REVISION HISTORY

Date/Name	Description
11Dec2023 by PPD	Final Protocol

PRINCIPAL INVESTIGATOR – SIGNATORY

An Open-Label, Single-Dose Study to Evaluate the Pharmacokinetics of MK-8527 in Participants with Moderate and Severe Renal Impairment

If the protocol is executed using the Veeva platform, the e-signature page will be found at the end of the PDF document.

Signature: Date: _____

Printed name:

Title:

Address:

SPONSOR AND SPONSOR'S REPRESENTATIVE – SIGNATORY

An Open-Label, Single-Dose Study to Evaluate the Pharmacokinetics of MK-8527 in Participants with Moderate and Severe Renal Impairment

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Merck Sharp & Dohme LLC (hereafter called the Sponsor or MSD)
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ABBREVIATIONS

Pharmacokinetic parameter abbreviations and definitions are found in Section 8.3.2 and Section 8.3.4 International units of measurement are not included in this list.

AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase
APaT	All Participants as Treated
AST	Aspartate aminotransferase
BMI	Body mass index
BSA	Body surface area
CFR	Code of Federal Regulations
CI	Confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
COVID-19	Coronavirus disease-2019
CRF	Case report form
CRU	Clinical research unit
CSR	Clinical study report
CV	Coefficient of variation
DMP	Data Management Plan
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECI	Event of clinical interest
eGFR	Estimated glomerular filtration rate
FBR	Future Biomedical Research
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GMR	Geometric mean ratio
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus

IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IND	Investigational New Drug
IRB	Institutional Review Board
IUD	Intrauterine device
ln	Natural logarithm
LSM	Least-squares mean
No.	Number
PBMC	Peripheral blood mononuclear cell
PI	Principal Investigator
PK	Pharmacokinetic(s)
PP	Per-Protocol
PrEP	Pre-exposure prophylaxis
QA	Quality Assurance
QTcF	Corrected value of the interval between the Q and T waves on the electrocardiogram tracing, corrected using Fridericia formula
RI	Renal impairment
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
TEAE	Treatment-emergent adverse event
TP	Triphosphate
ULN	Upper limit of normal
US	United States
USA	United States of America

1 PROTOCOL SUMMARY

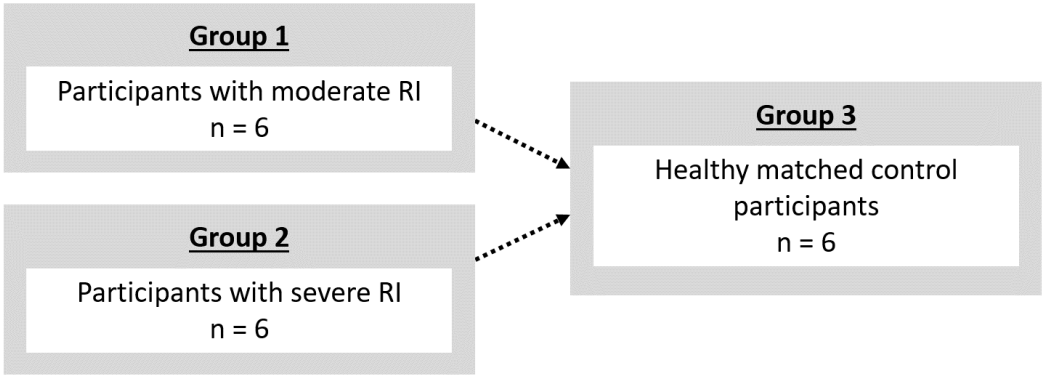
1.1 Protocol Synopsis

Protocol Title:	An Open-Label, Single-Dose Study to Evaluate the Pharmacokinetics of MK-8527 in Participants with Moderate and Severe Renal Impairment
Short Title:	MK-8527 Renal Impairment Study
Compound:	MK-8527
Study Phase:	Phase 1
Study Objectives:	**Primary objective:** • To evaluate the plasma pharmacokinetics (PK) of MK-8527 in participants with moderate and severe renal impairment (RI) compared to healthy matched control participants. **Estimation:** In participants with moderate and severe RI, plasma PK (e.g., AUC0-inf, Cmax) of MK-8527 following a single 6 mg dose of MK-8527 will be estimated and compared to those observed in healthy matched control participants. **Secondary objectives:** • To evaluate the safety and tolerability of MK-8527 in participants with moderate and severe RI. • To evaluate the intracellular PK of MK-8527 triphosphate (MK-8527-TP) in peripheral blood mononuclear cells (PBMCs) in participants with moderate and severe RI compared to healthy matched control participants. **Estimation:** In participants with moderate and severe RI, intracellular PK (e.g., AUC0-inf, Cmax) of MK-8527-TP in PBMCs following a single 6 mg dose of MK-8527 will be estimated and compared to those observed in healthy matched control participants.
Study Design:	This is a multi-site, open-label, single-dose study to evaluate the effect of moderate and severe RI on the PK, safety, and tolerability of MK-8527. Participants will receive a single oral dose of MK-8527 on Day 1. PK sampling will be performed predose and up to 168 hours postdose for plasma MK-8527 and predose and up to 672 hours

	postdose for PBMC MK-8527-TP. Urine will be collected predose and up to 48 hours postdose for MK-8527 PK. All participants who received the study drug (including participants who terminate the study early) will return to the clinical research unit (CRU) on Day 29 (±1 day) for follow-up procedures and to determine if any adverse event (AE) has occurred since the last study visit.
Study Duration:	The total planned study duration (from screening to follow-up) for each participant is approximately 8 weeks.
Number of Participants:	A total of approximately 18 adult male and female participants will be enrolled, with 6 participants with moderate RI, 6 participants with severe RI, and 6 healthy matched control participants. Healthy control participants will be enrolled after all moderate and severe RI participants have been dosed and will be matched by the mean age (± 15 years), mean body mass index (BMI; ± 3.5 kg/m^2), and sex (± 2) of participants with moderate and severe RI. At least 1 participant of each sex will be enrolled in each group.
Dosage, Dosage Form, Route, and Dose Regimen:	All participants will receive a single oral dose of 6 mg MK-8527 (1 x 1 mg capsule + 1 x 5 mg capsule) on Day 1.
Key Assessments:	**Pharmacokinetics:** The following PK parameters, as appropriate, will be calculated: MK-8527 in plasma: AUC0-last, AUC0-inf, Cmax, Tmax, t½, CL/F, and Vz/F. MK-8527-TP in PMBC: AUC0-last, AUC0-inf, Cmax, C168, C672, Tmax, and t½. MK-8527 in urine: Ae, CLr, and fe. **Safety:** Safety will be monitored through AEs, clinical laboratory tests, total lymphocytes and CD4+ T cell counts, vital signs, 12-lead electrocardiograms (ECGs), and physical examination. Treatment-emergent AEs (TEAEs) will be tabulated and summary statistics for the clinical laboratory tests, total lymphocytes and CD4+ T cell counts, vital signs, and 12-lead ECGs will be computed and provided, as deemed appropriate.

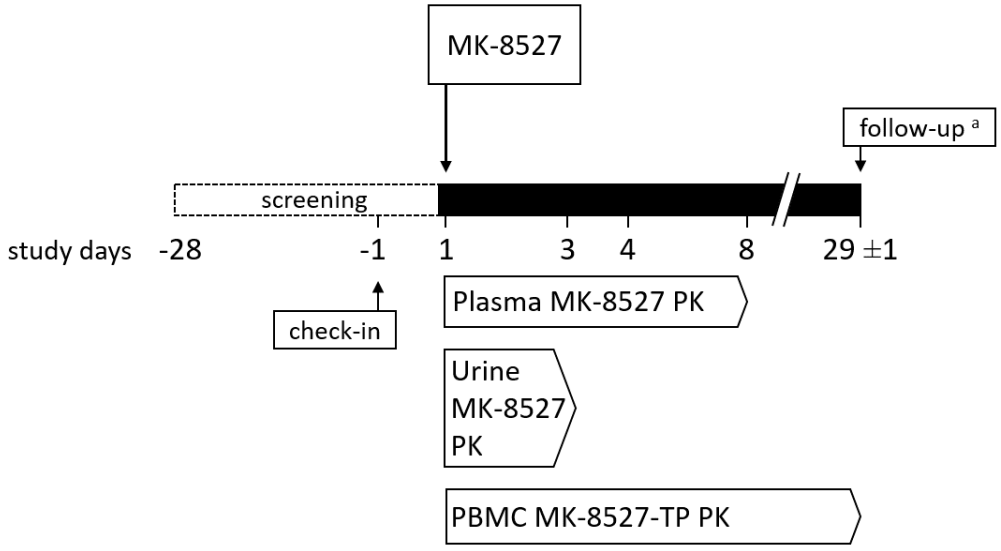
1.2 Study Schema

Figure 1: Overall Study Workflow



Abbreviations: n = sample size, RI = renal impairment.

Figure 2: Schematic of Study Design for Each Group



a: All participants who received the study drug (including participants who terminate the study early) will return to the CRU on Day 29 (±1 day) for follow-up procedures and to determine if any AE has occurred since the last study visit.

Abbreviations: AE = adverse event, CRU = clinical research unit, PK = pharmacokinetic(s).

1.3 Schedule of Activities

Study Procedures [a]		**Study Days**																				
Days →	**Scr** [b]	**-1**	**1**										**2**	**3**	**4**	**5**	**6**	**7**	**8**	**15 ±1**	**22 ±1**	**29 ±1**
Hours →		C-I [c]	0	0.25	0.5	1	1.5	2	4	6	8	12	24	48	72	96	120	144	168	336	504	672
Administrative Procedures																						
Informed Consent	X																					
Informed Consent for FBR	X																					
Inclusion/Exclusion Criteria	X	X	X [d]																			
Medical History	X																					
Participant ID Card																			X			
Safety Evaluations																						
Full Physical Examination	X	X																	X			X [e]
Height	X																					
Weight	X	X																				
Vital Signs (HR, BP, RR, and T)	X		X [f]																X			X [e]
12-Lead ECG	X		X [f]																X			X [e]
Hem, Chem [g], and UA	X	X																	X			X [e]
Pregnancy Test (♀ only) [h]	X	X																				
Serum FSH (PMP ♀ only)	X																					
Urine/Saliva Drug Screen	X	X																				
Urine/Breath Alcohol Screen	X	X																				
HIV/Hepatitis Screen	X																					
COVID-19 Screen		X																				
Blood for Immunophenotyping			X [d]											X					X			X [e]
AE Monitoring	X												X									
Concomitant Medication Monitoring	X												X									
Study Drug Dosing / PK / Biomarkers																						
Participant Assignment			X																			
MK-8527 Dosing			X																			
Blood for MK-8527 PK			X [d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X			
Blood for MK-8527-TP PK			X [d]						X			X	X	X		X	X	X	X	X	X	X
Urine for MK-8527 PK								X [i]														
Blood for Genetic Analysis			X [j]																			
Other Procedures																						
Confinement in the CRU [k]										X												
Visit and Return Visits	X																			X	X	X
Follow-up																						X [l]

a For details on procedures, refer to Section 8.

b Within 28 days prior to dosing.

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

d To be performed prior to dosing.

e To be performed on Day 29 (±1 day) or prior to early termination from the study.

f To be performed within 3 hours prior to dosing.

g Samples for serum chemistry will be obtained after a fast of at least 8 hours, however, in case of discontinuations or rechecks, participants may not have fasted for 8 hours prior to when the serum chemistry sample is taken.

h Serum pregnancy test(s) will be performed at screening. Serum or urine pregnancy tests will be performed at all other scheduled time points.

i Urine collection intervals are predose, 0-4 hours, 4-8 hours, 8-12 hours, 12-24 hours, and 24-48 hours postdose. Urine samples will be collected per schedule whenever possible, as some participants with RI may not be able to produce urine during each collection interval.

j To be obtained predose on Day 1, but may be collected at the next scheduled blood draw, if needed.

k As per site preference, participants may be confined longer at the discretion of the PI or designee, and/or confined for additional short periods throughout the study (e.g., to facilitate attendance at return visits).

l All participants who received the study drug (including participants who terminate the study early) will return to the CRU on Day 29 (±1 day) for follow-up procedures and to determine if any AE has occurred since the last study visit.

Abbreviations: ♀ = Females, AE = Adverse event(s), BP = Blood pressure, C-I = Check-in, Chem = Chemistry, COVID-19 = Coronavirus disease 2019, CRU = Clinical research unit, ECG = Electrocardiogram, FBR = Future biomedical research, FSH = Follicle-stimulating hormone, Hem = Hematology, HIV = Human immunodeficiency virus, HR = Heart rate, ID = Identification, PI = Principal Investigator, PK = Pharmacokinetics, PMP = Postmenopausal, RI = Renal impairment, RR = Respiratory rate, Scr = Screening, T = Temperature, UA = Urinalysis.

2 INTRODUCTION

2.1 MK-8527

Human immunodeficiency virus (HIV)-1 is the etiologic agent of acquired immunodeficiency syndrome (AIDS). While there are effective antiretroviral treatments for HIV-1, productive infection with HIV-1 results in the establishment of a life-long, persistent infection characterized by low level viremia even with therapy due to virus integration into the host. The estimated number of people living with HIV-1 worldwide was approximately 39 million in 2022 (UNAIDS, 2023). Although effective antiretroviral therapy halts disease progression, reduces mortality, and decreases the likelihood of HIV-1 transmission, the incidence of new infections is still high, with an estimated 1.3 million people newly infected in 2022. Access to reliable and highly effective pre-exposure prophylaxis (PrEP) is crucial to reduce the rate of new HIV-1 infections, and there is a clear need for new, effective means of preventing HIV-1 infection with PrEP. An oral PrEP regimen that can be taken once monthly is viewed widely as a promising long-acting option for HIV PrEP due to the ease of implementation. An oral monthly dosing regimen is anticipated to improve adherence, thereby offering the potential to be highly effective in the prevention of new HIV-1 infections.

MK-8527 is a novel potent deoxyadenosine analog being developed for HIV-1 PrEP. MK-8527 is converted intracellularly to the active triphosphate anabolite (MK-8527-TP) that is highly potent and has a long t½, enabling monthly dosing.

MK-8527 has been studied in 3 completed Phase 1 studies, 2 ongoing Phase 1 studies, and 1 ongoing Phase 2 study. The completed studies were MK-8527-001 (a single ascending dose study in healthy male participants), MK-8527-002 (a single-dose study in treatment naïve participants with HIV-1), and MK-8527-003 (a multiple ascending dose study in male and female participants of non-childbearing potential). MK-8527-004 is an ongoing Phase 1 study and is evaluating single doses at additional dose levels in treatment naïve participants with HIV-1. MK-8527-006 is a drug-drug interaction study between MK-8527 and the combination oral contraceptive levonorgestrel/ethinylestradiol. MK-8527-007 is a Phase 2 study to evaluate once monthly MK-8527 in participants at low risk for HIV-1 infection.

As of 15-Sep-2023, MK-8527 has been administered to a total of 101 study participants (70 healthy adults and 31 people living with HIV-1) and has generally been well tolerated following administration of single oral doses up to 200 mg and 3 weekly doses up to 40 mg. MK-8527 has also shown efficacy in reduction of viral load as monotherapy in treatment naïve HIV-1 infected individuals with single doses as low as 0.5 mg.

Following oral administration, MK-8527 was rapidly absorbed with a median Tmax of 0.5 to 1 hour. Plasma concentrations decreased in a biphasic manner with t½ of approximately 36 to 81 hours and exposures appeared to increase in an approximately dose-proportional manner. The active MK-8527-TP moiety reached intracellular Cmax at a median Tmax of 10 to 48 hours and the concentrations in PBMC declined with a t½ of approximately 94 to

291 hours across doses. MK-8527-TP exposures showed less than dose-proportional increases over the dose range studied.

In clinical studies, the most frequently reported AEs were headache and nasopharyngitis, with all MK-8527-related AEs being mild to moderate in intensity and resolved by the end of the study.

Refer to the Investigator's Brochure (IB) for detailed background information on MK-8527.

2.2 Rationale

2.2.1 Rationale for this Study and Study Design

There are large numbers of people using PrEP worldwide and it is expected that a substantial number of these individuals accumulate co-morbidities, including chronic medical conditions such as diabetes and hypertension that can lead to renal insufficiency. Preclinical and clinical studies indicate that renal excretion plays a prominent role in the elimination of MK-8527, with the balance eliminated primarily through glucuronidation. In MK-8527-001 and MK-8527-003 studies, urine samples were collected for PK assessment after single or multiple weekly doses of MK-8527. Urine fe (fraction excreted) in these studies ranged from 28% to 38%. As such, this study is being conducted to assess the impact of moderate and severe RI on the PK of MK-8527 and MK-8527-TP.

The PK study design selected for this study is in accordance with Food and Drug Administration (FDA) recommendations for PK studies in participants with impaired renal function (FDA, 2020). Healthy matched control participants with normal renal function will be enrolled in the study as controls to detect any clinically relevant PK differences between healthy control participants with normal renal function and participants with moderate and severe RI. Healthy participants will be matched to the combined mean age, mean BMI, and sex of participants with moderate and severe RI. In addition, at least 1 participant of each sex will be enrolled in each group (i.e., moderate RI, severe RI, and healthy control).

2.2.2 Rationale for the Dose Selection

The single dose of 6 mg MK-8527 selected for this study is expected to be safe and well tolerated for participants. Multiple doses of 6 mg MK-8527 given monthly are being studied in an ongoing Phase 2 study (MK-8527-007). PK of MK-8527 and MK-8527-TP is dose-proportional across doses ranging up to 100 mg and thus increases up to 2-fold in renally impaired participants would not be expected to exceed the exposures at the 12 mg top dose in the MK-8527-007 study.

2.2.3 Rationale for Endpoints

Plasma MK-8527 PK (AUC0-last, AUC0-inf, Cmax, Tmax, t½, CL/F, and Vz/F) is the primary endpoint as MK-8527 is renally excreted and will be the primary PK parameter that will be monitored in Phase 3 studies. Intracellular MK-8527-TP PK will be a secondary

endpoint as it is important to evaluate the impact of RI on the active metabolite MK-8527-TP levels.

2.3 Risks and/or Benefits to Participants

The dose of MK-8527 administered in this study is not expected to induce any potential risk to participants in this study, as it was generally well-tolerated in prior clinical studies.

Dose-dependent decreases in total lymphocyte and lymphocyte subset counts were observed in clinical studies with islatravir (MK-8591), another investigational nucleoside reverse transcriptase inhibitor agent, in development for HIV treatment by the Sponsor. CCI [redacted] It is expected that the risk of lymphocyte reductions is low at the levels of MK-8527-TP obtained following a 6 mg single dose of MK-8527, based on available nonclinical and clinical data. In the MK-8527 clinical studies to date, there have been no AEs associated with lymphocyte reductions, and mean lymphocyte counts were unchanged in both single and multiple ascending dose studies. As precautionary safety measures, however, lymphocyte parameters (e.g., total lymphocytes counts, CD4+ T cell counts) will be monitored in this study for any potential reductions.

The safety monitoring practices employed by this protocol (i.e., AEs, clinical laboratory tests, total lymphocytes and CD4+ T cell counts, vital signs, 12-lead ECG, and physical examination) are adequate to protect the participants' safety and are appropriate for this stage of development based on the existing safety and tolerability profile.

There will be no direct therapeutic benefit for study participants from receipt of study drug, as clinical studies are designed to provide information about the safety and properties of an investigational medicine. A potential indirect health benefit to the participants enrolled in this study is the free medical tests received at screening and during the study.

3 STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the plasma PK of MK-8527 in participants with moderate and severe RI compared to healthy matched control participants. **Estimation:** In participants with moderate and severe RI, plasma PK (e.g., AUC0-inf, Cmax) of MK-8527 following a single 6 mg dose of MK-8527 will be estimated and compared to those observed in healthy matched control participants.	• AUC0-last, AUC0-inf, Cmax, Tmax, t½, CL/F, and Vz/F for MK-8527 in plasma.
Secondary	
• To evaluate the safety and tolerability of MK-8527 in participants with moderate and severe RI.	• AEs and discontinuations due to AEs.
• To evaluate the intracellular PK of MK-8527-TP in PBMCs in participants with moderate and severe RI compared to healthy matched control participants. **Estimation:** In participants with moderate and severe RI, intracellular PK (e.g., AUC0-inf, Cmax) of MK-8527-TP in PBMCs following a single 6 mg dose of MK-8527 will be estimated and compared to those observed in healthy matched control participants.	• AUC0-last, AUC0-inf, Cmax, C168, C672, Tmax, and t½ for MK-8527-TP in PBMCs.

Objectives	Endpoints
Exploratory	
• To explore the relationship between genetic variation and response to the treatment(s) administered, and mechanisms of disease. Variation across the human genome may be analyzed for association with clinical data collected in the study.	• Germline genetic variation and association to clinical data collected in this study.
• To evaluate urinary excretion of intact MK-8527 in participants with moderate and severe RI compared to healthy matched control participants.	• Ae, CLr, and fe for MK-8527 in urine.

4 STUDY DESIGN

4.1 Description of Study Design

This is a multi-site, open-label, single-dose study to evaluate the effect of moderate and severe RI on the PK, safety, and tolerability of MK-8527.

A total of approximately 18 adult male and female participants will be enrolled, with 6 participants with moderate RI, 6 participants with severe RI, and 6 healthy matched control participants. Healthy control participants will be enrolled after all moderate and severe RI participants have been dosed and will be matched by the mean age (± 15 years), mean BMI (± 3.5 kg/m^2), and sex (± 2) of participants with moderate and severe RI. At least 1 participant of each sex will be enrolled in each group.

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

Participants will receive a single oral dose of MK-8527 on Day 1. PK sampling will be performed predose and up to 168 hours postdose for plasma MK-8527 and predose and up to 672 hours postdose for PBMC MK-8527-TP. Urine will be collected predose and up to 48 hours postdose for MK-8527 PK.

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

Discontinued participants may be replaced at the discretion of the Sponsor.

4.1.1 Confinement, Return Visits, and Follow-Up

Participants will be housed on Day -1, at the time indicated by the CRU, until completion of study procedures on Day 8. Participants will return for study procedures as indicated in the Schedule of Activities (Section 1.3).

As per site preference, participants may be confined longer at the discretion of the Principal Investigator (PI) or designee, and/or confined for additional short periods throughout the study (e.g., to facilitate attendance at return visits).

All participants who received the study drug (including participants who terminate the study early) will return to the CRU on Day 29 (±1 day) for follow-up procedures and to determine if any AE has occurred since the last study visit.

4.1.2 Study Duration

The total planned study duration (from screening to follow-up) for each participant is approximately 8 weeks.

4.2 Beginning and End of Study

The overall study begins when the first participant provides documented informed consent. The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up.

The end of study is defined as the date of the last scheduled procedure. If there is an unresolved AE, end date of concomitant medication, or an assessment date that is after the end of study, the date of study completion will be inclusive of that resolution/assessment date.

A participant is considered to have completed the study if the participant completed dosing, did not terminate the study early, and has completed the last scheduled procedure i.e., the follow-up visit shown in the Schedule of Activities (Section 1.3).

The 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 institutional review board(s) (IRB[s]) will be apprised of the maximum duration of the study beyond the last participant out and the justification for keeping the study open.

4.2.1 Clinical Criteria for Early Study Termination

There are no prespecified criteria for terminating the study early.

4.3 Study Design/Dosing/Procedures Modifications Permitted Within Protocol Parameter

This is a Phase 1 assessment of MK-8527 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 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 design may be permitted based on newly available data:

- Alteration of the dose, but it cannot exceed the one currently outlined in the protocol
- Addition of PK pause

- Instructions to take study drug with or without food or drink may also be modified based on newly available data
- Modification of the PK/pharmacodynamic sample processing and shipping details based on newly available data
- Modification of urine sample collection

The PK/pharmacodynamic sampling scheme currently outlined in the protocol may be modified during the study based on newly available PK/pharmacodynamic data (e.g., 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.

The total blood volume withdrawn from any single participant will not exceed the maximum allowable volume during his/her participation in the entire study (Table 3).

The timing of procedures for assessment of safety procedures (e.g., vital signs, ECG, safety laboratory tests, total lymphocytes and CD4+ T cell counts, 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 use 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 PI for retention. The letter may be forwarded to the IRB at the discretion of the PI.

If necessary, a participant must be discontinued for the reasons described in Section 7.

5 STUDY POPULATION

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

5.1 Inclusion Criteria

Participants must fulfill all of the following inclusion criteria to be eligible for participation in the study:

All Participants:

1. The participant is an adult, male or female, 18 to 75 years of age, inclusive, at screening.

2. Female and male participants must follow protocol-specified contraception guidance as described in Section 5.3.4.

3. The participant is a continuous non-smoker or moderate smoker (≤ 10 cigarettes per day or equivalent) for at least 3 months prior to dosing. Participant must agree to maintain the same smoking status (i.e., smoker or non-smoker) from screening and until after the last PK sample collection. Smokers must agree to smoke no more than 5 cigarettes (or equivalent) per day from check-in until after the last PK sample collection.

4. The participant has a BMI ≥ 18.0 and ≤ 40.0 kg/m^2 at screening.

5. The participant understands the study procedures in the informed consent form (ICF), and is willing and able to comply with the protocol.

6. The participant has provided documented informed consent for the study. The participant may also provide consent for Future Biomedical Research (FBR). However, the participant may participate in the study without participating in FBR.

Participants with Moderate and Severe RI (Groups 1 and 2):

7. With the exception of RI, the participant is sufficiently healthy for study participation based on medical history, physical examination, vital signs, and ECGs, as deemed by the PI or designee, including the following:

   - Heart rate is ≥ 40 bpm and ≤ 110 bpm at screening.
   - QTcF interval is ≤ 500 msec and has ECG findings considered normal or not clinically significant by the PI or designee at screening.

   Participants with stable, chronic medical or psychiatric conditions, including but not limited to hypertension, cardiac disease, hypercholesterolemia, non-insulin dependent diabetes mellitus, hyper- or hypothyroidism, gout, and chronic anxiety or depression may be included at the discretion of the PI or designee and the Sponsor.

8. With the exception of RI, the participant is sufficiently healthy for study participation based on clinical laboratory profiles at screening and check-in.

9. The participant has impaired renal function as determined by estimated glomerular filtration rate (eGFR) using the 2021 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation at screening, as follows:

   - Group 1 (moderate RI): eGFR 30 to 59 mL/min, inclusive.
   - Group 2 (severe RI): eGFR 15 to 29 mL/min, inclusive.

   The baseline eGFR will be obtained by taking the mean of two eGFR values obtained ≥ 72 hours apart during screening. The second baseline eGFR sample may be obtained at the time of check-in.

   2021 CKD-EPI Creatinine Equation:

   $eGFR = 142 \times \min(Scr/k,1)^{\alpha} \times \max(Scr/k,1)^{-1.200} \times 0.994^{age} \times 1.012$ [if female]

   where Scr is serum creatinine, k is 0.7 for females and 0.9 males, α is -0.241 for females and -0.302 for males, min indicates the minimum of Scr/k or 1, max indicates the maximum of Scr/k or 1.

   The eGFR for eligibility will use de-indexed values to correct for participant's body surface area (BSA). To convert indexed eGFR expressed as mL/min/1.73 m^2, the indexed eGFR value will be multiplied by participant's BSA and this value will be divided by 1.73 and expressed as mL/min. The DuBois formula will be used to calculate BSA:

   $BSA\ (m^2) = Weight\ (kg)^{0.425} \times Height\ (cm)^{0.725} \times 0.007184$

10. The participant has stable renal function as determined by historical measurements. Stable renal function is defined as ≤ 30% difference between two measurements of eGFR taken ≥ 72 hours apart during screening.

Healthy Control Participants (Group 3):

11. The participant must match the mean age (± 15 years) of participants with moderate and severe RI (Groups 1 and 2).

12. The participant must match the mean BMI (± 3.5 kg/m^2) of participants with moderate and severe RI (Groups 1 and 2).

13. The participant is medically healthy with no clinically significant medical history, physical examination, vital signs, and ECGs, as deemed by the PI or designee, at screening.

14. The participant is medically healthy with no clinically significant clinical laboratory profiles, as deemed by the PI or designee, at screening and check-in.

15. The participant has normal renal function with eGFR ≥ 90 mL/min, determined using the 2021 CKD-EPI creatinine equation at screening. Healthy participants who have an eGFR of 80 to 89 mL/min may be enrolled in the study at the discretion of the PI or designee.

    The baseline eGFR will be obtained by taking the mean of two eGFR values obtained ≥ 72 hours apart during screening. The second baseline eGFR sample may be obtained at the time of check-in.

    The eGFR for eligibility will use de-indexed values to correct for participant's BSA. To convert indexed eGFR expressed as mL/min/1.73 m^2, the indexed eGFR value will be multiplied by participant's BSA and this value will be divided by 1.73 and expressed as mL/min. The DuBois formula will be used to calculate BSA:

    $$BSA\ (m^2) = Weight\ (kg)^{0.425} \times Height\ (cm)^{0.725} \times 0.007184$$

5.2 Exclusion Criteria

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

All Participants:

1. The participant is mentally or legally incapacitated or has significant emotional problems at the time of screening or expected during the conduct of the study.

2. The participant has a history or presence of alcohol or drug abuse (except for cannabis) within the past 2 years prior to dosing.

3. The participant has a history or presence of hypersensitivity or idiosyncratic reaction to the study drug or related compounds.

4. The participant has a history of cancer (malignancy). Participants with adequately treated disease deemed as "cured," or who, in the opinion of the PI or designee, are highly unlikely to sustain a recurrence for the duration of the study may be enrolled at the discretion of the PI or designee.

5. The participant is a female participant with a positive pregnancy test at screening or at check-in or who is lactating.

6. The participant has a positive drug result at screening or check-in, unless the positive drug screen is due to prescription drug use that is approved by the PI or designee and Sponsor.

7. The participant has a positive alcohol result at screening or check-in.

8. The participant consumes greater than 3 servings of alcoholic beverages (1 serving is approximately equivalent to: beer [354 mL/12 oz], wine [118 mL/4 oz], or distilled spirits [29.5 mL/1 oz]) per day. Participants who consume 4 servings of alcoholic beverages per day may be enrolled at the discretion of the PI or designee.

9. The participant 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.

10. The participant has positive results for HIV, hepatitis B surface antigen (HBsAg), or hepatitis C virus (HCV) at screening.

11. The participant has a positive coronavirus disease 2019 (COVID-19) result at check-in.

12. The participant is unable to refrain from or anticipates the use of any drugs (except for permitted medication as detailed in Section 6.7), including prescription and non-prescription medications, herbal remedies, or vitamin supplements, as indicated in Section 6.7.

13. The participant has been on a diet incompatible with the on-study diet, in the opinion of the PI or designee, within the 30 days prior to dosing.

14. The participant has had major surgery and/or donated or lost significant volume of blood within 56 days prior to dosing.

15. The participant has donated plasma within 7 days prior to dosing.

16. The participant has been in another clinical study within 30 days or within 5 half-lives (if known), prior to dosing, whichever is longer. The 30-day window will be derived from the date of the last blood collection or dosing, whichever is later, in the previous study to Day 1 of the current study.

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

Participants with Moderate and Severe RI (Groups 1 and 2):

18. With the exception of RI, the participant has a history or presence of clinically significant medical or psychiatric condition or disease, any illness that, in the opinion of the PI or designee, might confound the results of the study or poses an additional risk to the participant by their participation in the study.

19. The participant has had a failed renal transplant or has had a nephrectomy.

20. The participant has end stage renal disease requiring dialysis.

21. The participant has any significant arrhythmia or conduction abnormality (including but not specific to atrioventricular block [second degree or higher], Wolff-Parkinson-White syndrome [unless curative radio ablation therapy]), which, in the opinion of the PI and Sponsor, could interfere with the safety for the individual participant.

22. The participant has non-sustained or sustained ventricular tachycardia (> 2 consecutive ventricular ectopic beats at a rate of > 1.7/second).

Healthy Control Participants (Group 3):

23. The participant has a history or presence of clinically significant medical or psychiatric condition or disease, or any illness that, in the opinion of the PI or designee, might confound the results of the study or poses an additional risk to the participant by their participation in the study.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

5.3.1.1 Meals

Water (except water provided with dosing) will be restricted 1 hour prior to and 1 hour after dosing, but will be allowed ad libitum at all other times. Other fluids may be given as part of meals and snacks but will be restricted at all other times throughout the confinement period.

Participants will be required to fast overnight for at least 10 hours prior to dosing and will continue to fast for at least 4 hours postdose.

Each meal and/or snacks served at the CRU will be standardized and of similar caloric content and composition and will be taken at approximately the same time on each day.

When confined, standard meals and snacks will be provided at appropriate times, except when participants are required to fast. When confined in the CRU, participants will be required to fast from all food and drink except water between meals and snacks.

5.3.1.2 Dietary Restrictions

The consumption of foods and beverages containing grapefruit and/or Seville orange will be prohibited from 14 days prior to dosing and until completion of study procedures on Day 8.

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

Participants will refrain to use the following:

- Xanthines/Caffeine-containing foods or beverages: 24 hours prior to dosing and until completion of study procedures on Day 8 (small amounts of caffeine derived from normal foodstuffs e.g., 250 mL/8 oz/1 cup decaffeinated coffee or other decaffeinated beverage, per day, with the exception of espresso; 45 g/1.5 oz chocolate bar, per day, would not be considered a deviation to this restriction).
- Alcohol-containing foods or beverages: 48 hours prior to dosing and until completion of study procedures on Day 8, and 24 hours prior to each subsequent visit on Days 15 (±1 day), 22 (±1 day), and 29 (±1 day).

- Tobacco/nicotine containing products: Participant must agree to maintain the same smoking status (i.e., smoker or non-smoker) from screening and until after the last PK sample collection. Depending on the CRU rules and regulations, participants may be prohibited from smoking during their confinement or during portions of their confinement.

5.3.3 Activity Restrictions

Participants will remain ambulatory or seated upright for the first 4 hours postdose, except when they are supine or semi-reclined for study procedures.

Should AEs occur at any time, participants may be placed in an appropriate position or will be permitted to lie down on their right side.

Specific measures will be taken to prevent the participant from missing a urine collection by strictly controlling and providing access to designated restrooms only. Participants will be asked to void prior to entering the shower.

Participants will be instructed to refrain from strenuous physical activity which could cause muscle aches or injury, including contact sports at any time from screening until the last blood sample collection.

Participants will be cautioned against activities requiring mental alertness, judgment and physical coordination such as driving, operating machinery, or power equipment for a period of 24 hours postdose.

5.3.4 Contraception Requirements

5.3.4.1 Definitions

Females of childbearing potential are defined as all females physiologically capable of becoming pregnant.

Females of non-childbearing potential are defined as follows:

- Females who have undergone one of the following sterilization procedures at least 6 months prior to dosing/the dosing administered to the male partner:
  - Hysteroscopic sterilization.
  - Bilateral tubal ligation or bilateral salpingectomy.
  - Hysterectomy.
  - Bilateral oophorectomy

  or

- Females who are postmenopausal with amenorrhea for at least 1 year prior to the dosing/the dosing administered to the male partner and have follicle-stimulating hormone (FSH) serum levels consistent with postmenopausal status at screening.

5.3.4.2 Guidance for Female Participants

Female participants of non-childbearing potential are not required to use any contraception methods.

Female participants of childbearing potential must agree to one of the following methods of contraception:

- Sexually inactive for at least 28 days prior to dosing.
- Non-hormonal releasing intrauterine device (IUD) or hormonal contraceptives (e.g., oral, IUD, vaginal ring, transdermal patch, depot, implantable, etc.) for at least 3 months prior to dosing.
- Surgical sterilization of the partner (vasectomy for 4 months minimum prior to dosing).
- Physical barrier method (e.g., condom, diaphragm) with spermicide for at least 14 days prior to dosing.

A female participant who claims to be sexually inactive, but becomes sexually active during the course of the study must agree to use a physical barrier method (e.g., condom, diaphragm) with spermicide from the time of the start of sexual activity and until at least 28 days after dosing.

In addition, female participants of childbearing potential will be advised to remain sexually inactive or to keep the same birth control method for at least 28 days after dosing.

Female participant must agree not to donate ova from dosing until at least 28 days after dosing.

5.3.4.3 Guidance for Male Participants

If capable of producing sperm, the male participant must agree to the following from dosing until at least 28 days after dosing of study drug:

- Refrains from donating sperm.

  PLUS either:

- Abstains from penile-vaginal intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agrees to remain abstinent.

  OR

- Uses contraception as detailed below unless confirmed to be azoospermic (vasectomized for at least 4 months prior to dosing or secondary to medical cause, documented from the

site personnel's review of the participant's medical records, medical examination, or medical history interview) as detailed below:

- Uses a penile/external condom when having penile-vaginal intercourse with a female partner of childbearing potential who is not currently pregnant and should also be advised of the benefit for that partner to use an additional method of contraception, as a condom may break or leak.

  Note: Participants capable of producing ejaculate whose partner is pregnant or breastfeeding must agree to use a penile/external condom during each episode of sexual activity in which the partner is at risk of drug exposure via ejaculate.

- Contraceptive use by participants capable of producing sperm should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study drugs are more stringent than the requirements above, the local label requirements are to be followed.

6 STUDY TREATMENTS AND CONCOMITANT THERAPY

6.1 Description of Study Treatments

The study drug to be used in this study is outlined in Table 1.

Study drug assignments are described in Section 6.3.1.

Table 1: Study Drugs

Group Name	Treatment Type	Study Drug Name	Study Drug Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period	Use	IMP/ NIMP/ AxMP	Sourcing
Moderate RI (Group 1)	Experimental	MK-8527	Drug	Capsule	1 mg 5 mg	6 mg	Oral	Single dose, Day 1	Test product	IMP	Sponsor
Severe RI (Group 2)											
Healthy Control (Group 3)											

Abbreviations: IMP = investigational medicinal product, NIMP/AxMP = non-investigational/auxiliary medicinal product.

The study drug will be administered orally with approximately 240 mL of water.

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

The pharmacy at the CRU will provide the dose in individual unit dose containers for each participant.

The exact clock time of dosing will be recorded.

6.2 Drug Supplies, Storage, and Accountability

The Sponsor will supply sufficient quantities of MK-8527 to allow completion of this study. The lot numbers and expiration dates (where available) of the study drugs supplied will be recorded in the clinical study report (CSR).

All study drugs must be stored in a secure, temperature controlled, and monitored area in accordance with the study drugs storage requirements, with access limited to the PI and designated CRU personnel.

Records will be made of the receipt and dispensing of the study drugs supplied. At the conclusion of the study, any unused study drug will be retained by Celerion, returned to the Sponsor or designee, or destroyed, as per Sponsor instructions.

6.3 Study Dose Modification

Refer to Section 4.3.

6.3.1 Stopping Rules

The following stopping rules will be used 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. To continue the study (on joint agreement with the Sponsor and PI), a substantial amendment will be submitted for approval.

1. An individual participant reports an SAE considered related to the study drug by the PI.
2. Two (2) or more participants report Severe Nonserious AEs considered related to the study drug by the PI.

6.4 Participant Assignment and Randomization

All participants will receive a single oral dose of 6 mg MK-8527 (1 x 1 mg capsule + 1 x 5 mg capsule) on Day 1.

Each participant will be assigned a unique identification number upon screening. Participants who complete the study screening assessments and meet all the eligibility criteria will be assigned a unique identification number, different from the screening number, and will receive the study drug.

No randomization will be performed in this study. All participants will receive the study drug.

6.4.1 Participant Identification Card

Prior to first discharge from the CRU, participants who received any portion of study drug will be given a participant identification card identifying them as participants in a research study. The card will contain the identification number and CRU contact information (including direct telephone numbers) to be used in the event of an emergency.

6.5 Blinding

This is an open-label study.

6.6 Study Treatment Compliance

A qualified designee will be responsible for monitoring the administration of the timed oral dose. Once a participant has finished the dosing water, the qualified designee will use a flashlight and a tongue depressor to check the participant's mouth to ensure that the participant has swallowed the study drug. Participants' hands will also be verified to ensure that the study drug was ingested.

6.7 Concomitant Therapy

Participants with Moderate and Severe RI (Groups 1 and 2):

In general, the use of any concomitant medication/therapy required to treat the current disease of a participant may be permitted following consultation with the Sponsor (except when specifically prohibited).

Participants who are taking medications to treat manifestations of renal disease or medications needed to treat stable diseases (e.g., angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists, beta-blockers, diuretics, metformin, insulin, thiazolidinediones, sulfonylureas, dipeptidyl peptidase-4 inhibitors, alpha-glucosidase inhibitors, sodium-glucose cotransporter 2 inhibitors, statins) that are common in patients with RI will be allowed to participate in the study at the discretion of the PI or designee and following consultation with the Sponsor. Participants must be on a stable dose (steady dose, drug, and regimen) for at least 14 days before MK-8527 dosing (at least 28 days prior to MK-8527 dosing for diuretic treatment, and at least 3 months prior to MK-8527 dosing for thyroid hormone replacement medication) and able to withhold the use of their maintenance medication until at least 4 hours after MK-8527 dosing.

Phosphate binders containing aluminum, calcium, or lanthanum salts; iron supplements or other metal cations; H2-receptor antagonists (except cimetidine); or multivitamins containing iron or zinc must be withheld at least 8 hours before MK-8527 dosing and at least 4 hours postdose. Any medication (including over-the-counter) that would significantly alter eGFR, which, by the determination of the PI or designee, might interfere with the study (e.g., cimetidine) must be discontinued at least 2 weeks prior to MK-8527 dosing and throughout the study.

Changes to medication that require frequent dose adjustments, such as insulin, furosemide (Lasix), spironolactone (Aldactone), or analgesic, may be made at least 14 days prior to MK-8527 dosing and may be considered if medically necessary thereafter, at the discretion of the PI and following consultation with the Sponsor.

If a participant is prescribed prohibited medication, upon discussion between the Sponsor and the PI, the PI may substitute the previously prescribed medication to an allowed one for the purpose of this study.

Healthy Control Participants (Group 3):

Any drugs, including prescription and non-prescription medications (with the exception of oral contraception, hormone replacement therapy, and thyroid hormone replacement medication), vitamins, or herbal and dietary supplements, are prohibited beginning 14 days prior to MK-8527 dosing and until after the last PK sample collection. However, healthy participants who are on stable medication for at least 30 days prior to MK-8527 dosing may be enrolled upon approval by the PI or designee and the Sponsor.

Certain medications may be deemed acceptable at the discretion of the PI and following consultation with the Sponsor, but participants must be on a stable regimen for at least 28 days prior to MK-8527 dosing. If a participant is prescribed prohibited medication, upon discussion between the Sponsor and the PI, the PI may substitute the previously prescribed medication to an allowed one for the purpose of this study.

All Participants:

Birth control methods are allowed as described in Section 5.3.4.2.

Hormone replacement therapy and thyroid hormone replacement medication will be allowed, if the participant has been on the same stable dose for at least 3 months prior to dosing.

After dosing, acetaminophen (up to 2 g per 24-hour period) may be administered at the discretion of the PI or designee. Administration of other concomitant medication will be permitted for the treatment of AEs, only when deemed necessary and when agreed by the PI and Sponsor, unless appropriate medical care necessitates that therapy should begin before the PI and Sponsor can be consulted.

COVID-19 and flu vaccines may be allowed if administered at least 72 hours before dosing or at least 48 hours after dosing.

If deviations occur, the PI or designee in consultation with the Sponsor, if needed, will decide on a case-by-case basis whether the participant may continue participation in the study.

All medications taken by participants beginning 2 weeks prior to screening and during the course of the study will be recorded.

7 DISCONTINUATION OF STUDY DRUG AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Drug

Not applicable.

7.2 Participant Withdrawal from the Study

Participants are free to withdraw from the study at any time for any reason. If a participant withdraws from the study, they will no longer receive study drug or be followed at scheduled protocol visits.

In addition, participants may be withdrawn from the study by the PI or designee or the Sponsor for the following reasons but not limited to:

- AEs.
- Pregnancy.
- Difficulties in blood collection.
- Positive drug or alcohol test.
- Enrollment into the study is inappropriate.
- Non-compliance.
- Protocol violation.
- Study terminated by Sponsor.

The PI or designee must notify the Sponsor when a participant has discontinued or withdrawn from the study. If a participant discontinues or withdraws prior to study completion, efforts should be made to perform all procedures scheduled for early termination as outlined in the Schedule of Activities (Section 1.3), as well as specific details regarding withdrawal from FBR, are outlined in Section 7.2.1.

7.2.1 Withdrawal From Future Biomedical Research

Participants may withdraw their consent for FBR. Participants may withdraw consent at any time by contacting the PI or designee. If medical records for the study are still available, the PI or designee will contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.com). Subsequently, the participant's consent for FBR will be withdrawn. A letter will be sent from the Sponsor to the PI confirming the withdrawal. It is the responsibility of the PI or designee to inform the participant of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed before 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.

If the medical records for the study are no longer available (e.g., if the PI is no longer required by regulatory authorities to retain the 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.

7.3 Lost to Follow-up

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

- The CRU 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 PI or designee must make every effort to regain contact with the participant at each missed visit (e.g., 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

The Schedule of Activities (Section 1.3) summarizes the clinical procedures to be performed at each visit. Individual clinical procedures will be carried out as per CRU standard operating procedures and are described briefly below. Additional evaluations/testing may be deemed necessary by the PI or designee and/or the Sponsor for reasons related to participant safety.

For this study, the blood collection for MK-8527 is the critical parameter and needs to be collected as close to the exact time point as possible. All other procedures should be completed as close to the prescribed/scheduled time as possible, but can be performed prior or after the prescribed/scheduled time.

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

8.1 Screening Assessments and Procedures

Within 28 days prior to dosing, medical history and demographic data, including name, sex, age, race, ethnicity, body weight (kg), height (cm), BMI (kg/m^2), and history of tobacco use (including number of cigarettes smoked per day) will be recorded. At screening, each participant will be assessed by collection of clinical laboratory tests, vital sign measurements (heart rate, blood pressure, temperature, and respiratory rate), 12-lead ECG, and a physical examination.

Participants who do not qualify based on a reversible condition or mild intercurrent illness may be re-evaluated after further testing/examination or re-screened after the condition is resolved. Screening tests may be repeated per the PI's discretion and upon approval of the Sponsor. In the event that participation of a participant in the study is delayed and some or all screening procedures had been performed outside the prescribed screening window, outdated screening procedures will be repeated. Inclusion and categorization laboratory assessments that are deemed inconsistent with the usual stage of RI may be repeated at the discretion of the PI.

For eligibility purposes, abnormal laboratory test results may be repeated at the discretion of the PI if an abnormal result is observed at the initial reading.

8.1.1 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. The data from participants who fail at screening will not be reported in the case report forms (CRFs).

8.2 Safety Assessments and Procedures

8.2.1 Physical Examination

A full physical examination will be performed as outlined in the Schedule of Activities (Section 1.3). Additional physical examinations may be performed at other times, if deemed necessary by the PI or designee.

8.2.2 Vital Signs

Single measurements of body temperature, respiratory rate, blood pressure, and heart rate will be measured as outlined in the Schedule of Activities (Section 1.3). Additional vital signs may be taken at any other times, if deemed necessary by the PI or designee.

Blood pressure and heart rate measurements will be performed with participants in a seated position for 5 minutes, except when they are supine or semi-reclined because of study procedures and/or AEs (e.g. nausea, dizziness) or if deemed necessary by the PI or designee.

The same method must be used for all body temperature measurements for each individual participant and should be the same for all participants.

Vital signs will be measured within 3 hours prior to Day 1 dosing. When scheduled postdose, vital signs will be performed within ± 2 hours (for ≤ 168 hours postdose) and within ± 1 day (for > 168 hours and ≤ 672 hours postdose) of the scheduled time point.

8.2.3 Electrocardiograms

Single 12-lead ECGs will be performed will be performed within an approximately 5-minute time window as outlined in the Schedule of Activities (Section 1.3). Additional ECGs may be taken at any other times, if deemed necessary by the PI or designee.

ECGs will be performed with participants in a supine position for 5 minutes. All ECG tracings will be reviewed by the PI or designee.

ECGs will be measured within 3 hours prior to Day 1 dosing. When scheduled postdose, ECGs will be performed within ± 2 hours (for ≤ 168 hours postdose) and within ± 1 day (for > 168 hours and ≤ 672 hours postdose) of the scheduled time point.

8.2.4 Clinical Laboratory Assessments

All tests listed below will be performed as outlined in the Schedule of Activities (Section 1.3). In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the PI or designee.

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

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

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

Additional Tests
- HIV test
- HBsAg
- HCV
- Urine/saliva drug screen
  - Opiates
  - Opioids
  - Amphetamines
  - Cocaine
  - Barbiturates
  - Benzodiazepines
- Urine/breath alcohol screen
- COVID-19 screen
- Serum/urine pregnancy test (for females only)
- Serum FSH (for postmenopausal females only)

* Serum chemistry tests will be performed after at least an 8-hour fast; however, in case of discontinuations or rechecks, participants may not have fasted for 8 hours prior to when the serum chemistry sample is taken.

** At screening, eGFR will be calculated.

*** If urinalysis is abnormal for protein, blood, nitrite and/or leukocyte esterase, a microscopic examination (for red blood cells, white blood cells, bacteria, casts, and epithelial cells) will be performed.

8.2.5 Immunophenotyping

For all participants, blood samples for immunophenotyping (total lymphocyte counts and CD4+ T cell counts) will be collected at scheduled time points as delineated in the Schedule of Activities (Section 1.3).

Instructions for blood sampling, collection, processing, and sample shipment will be provided separately.

8.2.6 Adverse Events and Serious Adverse Events

8.2.6.1 Definition of Adverse Event

An AE means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE will be considered treatment-emergent if the onset date and time is at the time of or after study drug administration.

A suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. Reasonable possibility means there is evidence to suggest a causal relationship between the drug and the AE.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Note: For purposes of AE definition, study drug includes any pharmaceutical product, biological product, vaccine, diagnostic agent, medical device, combination product, or protocol-specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in treatment), 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 (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the PI or designee.
- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study drug 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 as determined by the PI or designee.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concomitant medication as determined by the PI or designee.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology “accidental or intentional overdose without adverse effect.”

Events NOT meeting the AE definition

- Medical or surgical procedure (e.g., 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 preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgical procedure(s) planned prior to informed consent to treat a preexisting condition that has not worsened.

8.2.6.2 Definition of Serious Adverse Event

A serious adverse event (SAE) is any AE or suspected adverse reaction that in the view of either the PI or designee or Sponsor, results in any of the following outcomes: Death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Life-threatening is defined as an AE or suspected adverse reaction that in the view of the PI or designee or Sponsor, its occurrence places the patient or participant at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

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 preexisting condition that has not worsened is not an SAE.) A preexisting condition is a clinical condition that is diagnosed prior to the use of a Sponsor product and is documented in the participant's medical history.

Unexpected is defined as an AE or suspected adverse reaction that is not listed in the IB or is not listed at the specificity or severity that has been observed; or is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

8.2.6.3 Monitoring

Participants will be monitored for adverse reactions to the study drug and/or procedures from the time of signing the ICF until the follow-up visit. Prior to release, participants will be asked how they are feeling. At each subsequent visit, participants will be queried with an open-ended question such as: 'How have you been feeling since your last visit?'

AEs (whether serious or non-serious) and clinically significant abnormal laboratory test value(s) will be evaluated by the PI or designee and treated and/or followed up until the symptoms or value(s) return to normal, or acceptable levels, as judged by the PI or designee.

Treatment of SAEs will be performed by a licensed health care professional, either at Celerion or at a nearby hospital emergency room where appropriate medical test(s) and/or examination(s) will be performed to document resolution of event(s). Outcome may be classified as fatal, not recovered/not resolved, recovered/resolved, recovered/resolved with sequelae, or recovering/resolving.

8.2.6.4 Reporting

All AEs that occur during this clinical study will be recorded. All clinically significant abnormal laboratory results should be reported as AEs.

AEs, SAEs, and other reportable safety events that occur after the participant provides documented informed consent, but before dosing, must be reported by the PI or designee under any of the following circumstances:

- If the participant is receiving placebo run-in or other run-in treatment.
- If the event causes the participant to be excluded from the study.
- If it is the result of a protocol-specified treatment, including but not limited to washout or discontinuation of usual therapy, diet, placebo, or a procedure.

From the time of dosing through approximately 28 days after cessation of study drug, all AEs, SAEs, and other reportable safety events must be reported by the PI.

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

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

Exception: A positive pregnancy test at the time of initial screening is not a reportable event unless the participant has received the study drug.

Assessment of causality

- Did the study drug cause the AE?
- The determination of the likelihood that the study drug caused the AE will be provided by a PI who is a qualified physician. The PI'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 PI 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 study drug and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the study drug caused the AE:**
    - **Exposure**: Is there evidence that the participant was actually exposed to the study drug 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 study drug? 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 study drug 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 study drug; (3) the study is a single-dose drug study; or (4) study drug(s) is/are only used 1 time.)
    - **Rechallenge**: Was the participant re-exposed to the study drug 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) study drug(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 STUDY DRUG, OR IF RE-EXPOSURE TO THE STUDY DRUG 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.

- **Consistency with study drug profile**: Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the study drug or drug class pharmacology or toxicology?
- The assessment of relationship will be reported on the CRFs/worksheets by a PI who is a qualified physician according to their 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 study drug relationship).
    - Yes, there is a reasonable possibility of study drug relationship:
        - There is evidence of exposure to the study drug. The temporal sequence of the AE onset relative to the administration of the study drug is reasonable. The AE is more likely explained by the study drug than by another cause.
    - No, there is not a reasonable possibility of study drug relationship:
        - Participant did not receive the study drug OR temporal sequence of the AE onset relative to administration of the study drug is not reasonable OR the AE is more likely explained by another cause than the study drug. (Also entered for a participant with overdose without an associated AE.)
- The PI must review and provide an assessment of causality for each AE/SAE and document this in the medical notes.
- There may be situations in which an SAE has occurred and the PI has minimal information to include in the initial report to the Sponsor. However, it is very important that the PI always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The PI may change their 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.

Assessment of intensity/toxicity

Each sign or symptom reported will be graded on a 3-point severity scale (mild, moderate, or severe), and the date of onset, time of onset, and outcome of each event will be noted.

The following definitions will be used for rating the severity of AEs:

Mild	The AE is easily tolerated and does not interfere with daily activity.
Moderate	The AE interferes with daily activity, but the participant is still able to function. Medical intervention may be considered.
Severe	The AE is incapacitating and requires medical intervention.

8.2.6.5 Reporting for SAEs

If any AEs are serious, as defined by the FDA Code of Federal Regulations (CFR), Chapter 21, special procedures will be followed. All SAEs will be reported to the Sponsor via fax or e-mail within 24 hours of becoming aware of the event, whether or not the serious events are deemed drug-related. This will be followed by the SAE Report within 24 hours. All serious event reporting will adhere to 21 CFR 312.32 for Investigational New Drugs (IND) and to the Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE, dated December 2012. The IRB will be notified of the Alert Reports as per FDA regulations.

If an SAE occurs to a participant on this study, contact the Sponsor personnel listed in the Additional Key Contacts for the Study section.

8.2.7 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 International Council for Harmonisation (ICH) definition, are reportable to the Sponsor.

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

8.2.8 Events of Clinical Interest

Selected serious and non-serious AEs are also known as events of clinical interest (ECIs) and must be reported to the Sponsor.

ECIs for this study include:

1. An overdose of study drug, as defined in Section 8.2.9.
2. Potential drug-induced liver injury events defined as an elevated AST or ALT laboratory value that is greater than or equal to 3x the upper limit of normal (ULN) and an elevated total bilirubin laboratory value that is greater than or equal to 2x the ULN and, at the same time, an alkaline phosphatase laboratory value that is less than 2x the ULN, as

determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based on available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The 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.

8.2.9 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 PI or the reporting physician to decide whether a dose is to be considered an overdose, in consultation with the Sponsor.

Refer to the IB for specific treatment of overdose. Decisions regarding dose interruptions or modifications will be made by the PI or designee in consultation with the Sponsor Clinical Director based on the clinical evaluation of the participant.

8.3 Pharmacokinetic Assessments

8.3.1 Blood Sampling and Processing

For all participants, blood samples for the determination of MK-8527 and MK-8527-TP will be collected at scheduled time points as delineated in the Schedule of Activities (Section 1.3).

Instructions for blood sampling, collection, processing, and sample shipment will be provided separately.

The allowed window for PK blood sampling is indicated in Table 2.

Table 2: Window for PK Blood Sample Collection

Nominal Time	Allowed Window
Predose	Within 30 minutes prior to dosing
> 0 to < 1 hour	≤ ± 5 minutes
1 to < 2 hours	≤ ± 10 minutes
2 to < 24 hours	≤ ± 15 minutes
24 to < 48 hours	≤ ± 1 hour
48 to ≤ 168 hours	≤ ± 4 hours
> 168 to < 672 hours	≤ ± 24 hours
≥ 672 hours	≤ ± 48 hours

8.3.2 Plasma and PBMC Pharmacokinetic Parameters

The following PK parameters for plasma MK-8527 and PBMC MK-8527-TP will be calculated, as appropriate:

AUC0-last:	Area under the concentration versus time curve from 0 to the time of the last quantifiable (above lower limit of quantitation) sample
AUC0-inf:	Area under the concentration versus time curve from 0 to infinity after single dosing
AUC%extrap:	Percent of AUC0-inf extrapolated
CL/F:	Apparent clearance (plasma MK-8527 only)
Cmax:	Maximum observed drug concentration after the administration of a given dose
C168:	Drug concentration at Hour 168 (PBMC MK-8527-TP only)
C672:	Drug concentration at Hour 672 (PBMC MK-8527-TP only)
Tmax:	Time to maximum observed drug concentration
λz:	Lambda z, Apparent terminal elimination rate constant
t½:	Apparent terminal half-life
Vz/F:	Apparent volume of distribution during terminal phase (plasma MK-8527 only)

No value for λz, AUC0-inf, AUC%extrap, CL/F, Vz/F, or t½ will be reported for cases that do not exhibit a terminal log-linear phase in the concentration-time profile.

PK parameters will not be calculated for participants with less than 3 consecutive postdose time points with quantifiable concentrations.

8.3.3 Urine Sampling and Processing

Urine for PK assessments will be collected at the specified intervals delineated in the Schedule of Activities (Section 1.3). Urine samples will be collected per schedule whenever possible, as some participants with RI may not be able to produce urine during each collection interval.

Prior to the predose sample, each participant will be instructed as to urine collection methods. All urine during an interval is to be collected.

On Day 1, a spot collection will be obtained prior to dosing for the predose sample. Participants will be asked again to empty their bladder within approximately 15 minutes prior to dosing, and no urine will be collected at this time unless it is needed for the predose sample. Only one predose urine sample will be collected on Day 1.

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

Urine will be refrigerated during the collection intervals. At the end of each interval, urine will be pooled and thoroughly mixed. Total urine volume will be weighed and recorded.

Instructions for urine sampling, collection, processing, and sample shipment will be provided separately.

8.3.4 Urine Pharmacokinetic Parameters

The following PK parameters for urine MK-8527 will be calculated, as appropriate:

Ae:	Amount of unchanged drug excreted in urine (cumulative or during a collection interval)
CLr:	Renal clearance calculated as Ae(t'-t")/AUC(t'-t") where t'-t" is the longest interval of time during which Ae and AUC are both obtained
fe:	Fraction (in percentage) of dose excreted in urine

8.3.5 Long Term Storage and Use

Any residual plasma, PBMC, and/or urine from the PK samples will be stored by the Sponsor or bioanalytical facility for up to 15 years after dosing and may be used for future analyses (e.g., PK assessment). Tubes will be identified with a barcode using an appropriate label. No diseases/conditions, deoxyribonucleic acid (DNA), or ribonucleic acid (RNA) will be the focus of these analyses. The analyses will only focus on analytes/biomarkers. Samples will not be submitted to a public database. The Sponsor and contract research organizations involved in the clinical conduct, bioanalytical analyses and PK and statistical analyses of the

data will have access to the samples and/or the data that resulted from the analysis, if performed. By signing the ICF, participants agree to the possible future analysis of these samples. Any additional research on these samples unspecified by this protocol will require approval from the participants.

8.3.6 Analytical Method

Samples from all participants will be assayed even if the participants do not complete the study.

Samples will be analyzed for plasma MK-8527, PBMC MK-8527-TP, and urine MK-8527 using validated bioanalytical methods.

If indicated, these samples may also be measured and/or pooled for assay in an exploratory manner for metabolites and/or additional pharmacodynamic markers.

8.4 Planned Exploratory Biomarker Research

8.4.1 Biomarkers

8.4.1.1 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 allow, a sample will be collected for DNA analysis from consenting participants.

DNA samples may be used for research related to the study drug(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 drug(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 multistudy assessment of genetic factors involved in the response to understand study disease or related conditions.

8.4.1.1.1 Planned Genetic Analysis Sample Collection

The planned genetic analysis sample should be collected 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 does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for FBR if the participant provides

documented informed consent for FBR. If the planned genetic analysis is not approved, but FBR is approved, this sample will be collected for the purpose of FBR.

The planned genetic analysis sample should be obtained predose on Day 1, but may be collected at the next scheduled blood draw, if needed. Sample collection, storage, and shipment instructions for planned genetic analysis samples will be in the operations/laboratory manual.

8.4.2 Future Biomedical Research

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

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for FBR is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure participants receive the correct dose of the correct drug/vaccine at the correct time. The details of FBR research are presented in Appendix 1.

8.4.2.1 Future Biomedical Research Sample Collection

All sample collections for study-specific assessments shown in the Schedule of Activities (Section 1.3) are described within the main informed consent.

If the participant has provided documented informed consent for FBR, leftover samples will be used for FBR. The following specimens will be included for FBR:

- Leftover samples listed in Section 8.4.1

8.5 Blood Volume Drawn for Study Assessments

Table 3: Blood Volume during the Study

Sample Type	Number of Time Points	Approximate Volume per Time Point * (mL)	Approximate Sample Volume Over Course of Study (mL)
Screening laboratory safety tests (including hematology, serum chemistry, and serology), FSH (for postmenopausal female participants only), and serum pregnancy (for female participants only)	1	12.5	12.5
Blood for planned genetic analysis	1	8.5	8.5
On-study hematology and serum chemistry (this includes serum pregnancy for female participants only when scheduled at the same time)	3	12.5	37.5
Blood for immunophenotyping	4	10	40
Blood for plasma MK-8527	16	3	48
Blood for PBMC MK-8527	12	16	192
		Total Blood Volume (mL)→	338.5 **

* A smaller or larger collection tube size may be used if the present collection tube size is not available.

** If additional blood is needed for safety or PK analysis, additional blood may be collected (up to a maximum of 500 mL for the study).

9 STATISTICAL CONSIDERATIONS

Data will be handled and processed according to Celerion Standard Operating Procedures, which are written based on the principles of GCP.

9.1 Sample Size Determination

The between-participant standard deviations (on the natural log [ln] scale) for plasma MK-8527 AUC0-inf and Cmax, and for PBMC MK-8527-TP AUC0-inf and Cmax after administration of MK-8527 observed in a previous study (MK-8527-003) are 0.253 ln(h*nmol/L), 0.313 ln(nmol/L), 0.213 ln(h*pmol/10^6 cells) and 0.262 ln(pmol/10^6 cells), respectively. Assuming the same variability for 6 mg MK-8527, with 6 severe RI participants, 6 moderate RI participants, and 6 healthy participants, the half-width of the 90% confidence intervals (CIs) of geometric mean ratios (GMRs) for plasma MK-8527 AUC0-inf and Cmax, and for PBMC MK-8527-TP AUC0-inf and Cmax on the log scale will be 0.196, 0.242, 0.165, and 0.203 respectively. The lower and upper 90% confidence limits for the true GMRs will be given by OBS/1.21 and OBS*1.21 for plasma MK-8527 AUC0-inf, OBS/1.27, and OBS*1.27 for plasma MK-8527 Cmax, OBS/1.18 and OBS*1.18 for AUC0-inf MK-8527-TP in PBMC, OBS/1.22, and OBS*1.22 for Cmax MK-8527-TP in PBMC, where OBS is the observed least squares geometric mean ratio.

9.2 Population for Analyses

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

All Participants as Treated (APaT): The APaT Population consists of all participants who received the study drug. This population will be used for assessments of safety and tolerability.

Per-Protocol (PP): The PP 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 study drug, availability of measurements and absence of important protocol deviations. Important protocol deviations will be identified to the extent possible prior to database lock. 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 PP dataset. This population will be used for the PK analyses.

9.3 Statistical Analyses

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP). The SAP will be prepared by Celerion and agreed upon with the Sponsor. This document may modify the plans outlined in

the protocol; however, any major modifications of the primary endpoints definition and/or its analysis will also be reflected in a protocol amendment. Additional statistical analyses other than those described in this section may be performed if deemed appropriate.

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 Medicine Department of the Sponsor.

If, after the study has begun, changes are made to the statistical analysis 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.

9.3.1 Pharmacokinetic Analyses

9.3.1.1 Descriptive Statistics

The plasma and urine MK-8527 and PBMC MK-8527-TP concentrations and the PK parameters listed in Section 8.3.2 and Section 8.3.4 will be summarized using the appropriate descriptive statistics which will be fully outlined in the SAP.

9.3.1.2 Renal Function Categorization

For study eligibility and primary analysis, participants will be categorized using de-indexed eGFR values (with eGFR expressed as mL/min) calculated at screening.

For additional analyses, participants will also be re-categorized into renal function groups using indexed eGFR values from the 2021 CKD-EPI creatinine equation (with eGFR expressed as mL/min/1.73 m^2), calculated from values collected at screening.

Summary Statistics using De-indexed eGFR

The participants will be categorized into different renal categories based on their de-indexed eGFR. Non-model based summary statistics by population will be provided for plasma MK-8527 AUC0-last, AUC0-inf, Cmax, Tmax, t½, CL/F, and Vz/F, and for PBMC MK-8527 AUC0-last, AUC0-inf, Cmax, C168, C672, Tmax, and t½.

Summary Statistics using the 2021 CKD-EPI Creatinine Equation

The participants will be re-categorized into different renal categories based on their indexed eGFR calculated using the 2021 CKD-EPI creatinine equation. Non-model based summary statistics by population will be provided for plasma MK-8527 AUC0-last, AUC0-inf, Cmax, Tmax, t½, CL/F, and Vz/F, and for PBMC MK-8527-TP AUC0-last, AUC0-inf, Cmax, C168, C672, Tmax, and t½.

9.3.1.3 Statistical Analyses for Plasma MK-8527 and PBMC MK-8527-TP

Separately for each PK parameter, individual values of plasma MK-8527 AUC0-last, AUC0-inf, and Cmax, of PBMC MK-8527-TP AUC0-last, AUC0-inf, Cmax, C168, and C672, after a single-dose administration of MK-8527 to participants with severe and moderate RI and to healthy control participants will be ln-transformed and evaluated with a linear fixed effects model containing a categorical effect for population (participants with severe RI, with moderate RI, and healthy control participants). An unstructured covariance matrix will be used to allow for unequal population variances via the REPEATED and GROUP statement in SAS PROC MIXED. Kenward and Roger's method will be used to calculate the denominator degrees of freedom for the fixed effect (DDFM=KR). Ninety-five percent (95%) CIs for the least-squares means (LSM) for each population will be constructed on the ln scale and will reference the t-distribution. Exponentiating the LSM and their corresponding 95% confidence limits will yield estimates for the population geometric means and CIs 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 and secondary estimation objectives and compare participants with severe RI or moderate RI to healthy control participants with normal renal function, a two-sided 90% CI for the true difference in means (participants with severe RI – healthy control participants) and true difference in means (participants with moderate RI – healthy control participants) 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% CI for the true ratio of geometric means (participants with severe RI/healthy control participants) and (participants with moderate RI/healthy control participants) for each PK parameter.

Individual values will be listed for each PK parameter (plasma MK-8527 AUC0-last, AUC0-inf, Cmax, Tmax, t½, CL/F, and Vz/F; PBMC MK-8527-TP AUC0-last, AUC0-inf, Cmax, C168, C672, Tmax, and t½) by population, and the following (non-model-based) descriptive statistics will be provided: n (number of participants with non-missing data), arithmetic mean, standard deviation, arithmetic percent coefficient of variation (CV; calculated as 100 x standard deviation/arithmetic mean), median, minimum, maximum, geometric mean, and geometric percent CV (calculated as 100 x sqrt(exp(s^2) - 1), where s^2 is the observed variance on the ln scale).

Figures showing individual PK values with geometric means (95% CIs) by population, plotted on the ln scale, will be provided for plasma MK-8527 AUC0-last, AUC0-inf, and Cmax, and for PBMC MK-8527-TP AUC0-last, AUC0-inf, Cmax, C168, and C672.

Individual participant PK values will also be plotted against indexed eGFR using each individual's BSA, using different symbols to identify participants from each population. For this analysis, eGFR will be calculated as the mean of the two values determined at screening.

Additionally, plots of PK parameter values versus age, BMI, and/or sex may be provided.

Statistical modelling of the relationship between renal function (based on de-indexed eGFR) and PK parameters using linear (and non-linear as appropriate) regression analysis of eGFR versus AUC and Cmax (total and unbound) may be performed.

9.3.1.4 Statistical Analysis for Urine MK-8527

The amount of MK-8527 excreted in the urine collection interval from the time of dosing through 48 hours (Ae0-48) will be determined from the urine concentration and volume data. The fraction, fe, of MK-8527 excreted in urine expressed as a % MK-8527 administered dose will be determined. CLr of MK-8527 will be calculated from the urine Ae and plasma AUC available for the same time period (e.g., Ae0-48 and AUC0-48). Urinary drug clearance for each urine collection interval will be calculated for each group (with de-indexed eGFR expressed as mL/min). A descriptive summary of MK-8527 urine collection may be provided.

9.3.1.5 Multiplicity

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

9.3.2 Safety Analyses

AEs will be coded using the most current version of Medical Dictionary for Regulatory Activities available at Celerion and summarized by group for the number of participants reporting the TEAE and the number of TEAEs reported. A by-participant AE data listing including verbatim term, coded term, treatment, severity, action, and relationship to treatment will be provided.

Safety data including clinical laboratory results, immunophenotyping results, vital sign assessments, and 12-lead ECGs will be summarized by time point of collection.

Quantitative safety data as well as the change from baseline, when appropriate, will be summarized using the appropriate descriptive statistics.

Concomitant medications will be listed by participant and coded using the most current version of World Health Organization Drug Dictionary available at Celerion.

Medical history will be listed by participant.

9.3.3 Interim Analysis

Not applicable.

10 STUDY ADMINISTRATION

10.1 Ethics

10.1.1 Institutional Review Board

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

10.1.2 Ethical Conduct of the Study

This research will be carried out in accordance with the protocol, US Code of Federal Regulations, 21 CFR Parts 50, 56, and 312, the ethical principles set forth in the Declaration of Helsinki, GCP, and the ICH harmonized tripartite guideline regarding GCP (E6[R2] Good Clinical Practice: Integrated Addendum to E6 [R1], November 2016).

10.1.3 Participant Informed Consent

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

10.1.3.1 General Informed Consent

Informed consent given by the participant must be documented on a consent form. The form must include the study protocol number, study protocol title, dated signature, and agreement of the participant and of the person conducting the consent discussion.

A copy of the signed and dated ICF will be given to the participant before participating in the study, or FBR.

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

Specifics about the study and the study population are to be included in the study informed consent form.

Informed consent will adhere to IRB requirements, applicable laws and regulations, and Sponsor requirements.

10.1.3.2 Consent and Collection of Specimens for Future Biomedical Research

The PI or designee will explain the FBR consent to the participant, answer all of his/her questions, and obtain documented informed consent before performing any procedure related to FBR.

A copy of the signed and dated informed consent will be given to the participant before performing any procedure related to FBR.

10.1.4 Confidentiality

All clinical sites and vendors will have signed confidentiality agreements with Celerion. By signing this protocol, the PI and CRU staff will regard all information provided by the Sponsor and all information obtained during the course of the study as confidential.

The clinical site and Celerion must guarantee the privacy of the participants taking part in the study. Participants will be identified throughout documentation and evaluation by a unique participant study number. Throughout the study, a participant's source data will only be linked to the Sponsor's clinical study database or documentation via a unique identification number. If participant name appears on any study document, it must be redacted before the copy of the documents is supplied to the Sponsor. Any information concerning the participants (clinical notes, identification numbers, etc.) must be kept on file by the PI or designee who will ensure that it is revealed only to the Sponsor, IRB, or regulatory authorities for the purposes of trial monitoring, auditing or official inspections. As required, in the case of an event where medical expenses are the responsibility of the Sponsor, personal information i.e., full name, social security details etc. may be released to the Sponsor. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information in strictest confidence and in accordance with local data protection laws.

10.2 Study Termination

The CRU(s) reserves the right to terminate the study in the interest of participant welfare.

The Sponsor reserves the right to suspend or terminate the study at any time.

10.3 Data Management

Data management activities will be detailed in the Data Management Plan (DMP). Each vendor involved with this study will adhere to Good Documentation Practices and their standard operating procedures covering their respective activities relevant to participation in this study, as applicable. The PI or designee will ensure that all data related to the conduct of this study is attributable, legible, contemporaneous, original, accurate, enduring, and readily accessible.

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

The Clinical Study Report will be audited by the QA department and the QA audit certificate will be included in the Clinical Study Report.

10.3.1 Data Entry and Verification

Data will be transcribed from original sources by the PI or designee into the CRF. Data received from external sources, as applicable, will be integrated into the Clinical Data Interchange Standards Consortium study data tabulation model datasets.

10.3.2 Data Validation

After the data have been entered, various edit checks (including manual review of listings) will be performed to ensure the accuracy, integrity and validation of the database against the CRF as described in the DMP.

Inconsistencies that arise from these edit checks will be resolved with the PI or designee.

10.3.3 Database Lock

Upon study completion, after data entry is complete, the data has been pronounced clean, and the PI has reviewed and provided approval via signature, the database will be locked and final write access will be removed.

The Sponsor will be required to provide database lock approval.

Any changes to the data following database lock will be documented and approved by the Sponsor prior to unlocking the database to make changes to the data.

The final transfer of all study data to the Sponsor will be in SAS format with supporting documentation as described in the DMP.

10.4 Direct Access to Source Data/Documents

All CRUs and vendors will ensure that the Sponsor, IRB and inspection by domestic and foreign regulatory authorities will have direct access to all study-related sites, source data/documents, and reports for the purpose of monitoring and auditing (ICH[E6][R2] 5.1.2 & 6.10). In the event that other study-related monitoring should be done by other parties, they will be required to sign a confidentiality agreement prior to any monitoring and auditing.

10.5 Reporting of the Study

10.5.1 Case Report Forms

A CRF is completed for each dosed participant whether or not the participant has completed the study. The PI will assure complete and accurate entries on the forms. Each CRF will be reviewed and signed by the PI. The final signed CRFs will be archived electronically at the end of study in a document repository system. Final CRFs will be provided to the Sponsor in the format and transfer method as decided between Celerion and the Sponsor which will be documented in the DMP.

10.5.2 Record Keeping

Records and documents, including participants' documented informed consent, pertaining to the conduct of this study must be retained by the PI 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.

It is the responsibility of the Sponsor to inform the PI/Institution as to when these documents no longer need to be retained.

10.5.3 Report Format

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

10.6 Publication Policy

All unpublished information given to Celerion and/or the CRU by the Sponsor shall not be published or disclosed to a third party without the prior written consent of the Sponsor.

The data generated by this study are considered confidential information and the property of the Sponsor. This confidential information may be published only in collaboration with participating personnel from the Sponsor or upon Sponsor's written consent to publish the article.

11 REFERENCES

Food and Drug Administration: Center for Drug Evaluation and Research (CDER). Guidance for Industry. Pharmacokinetics in Patients with Impaired Renal Function - Study Design, Data Analysis, and Impact on Dosing. Draft Guidance. Sep 2020.

Global HIV & AIDS statistics - Fact sheet. UNAIDS. https://www.unaids.org/en/resources/fact-sheet. Published 2023. Accessed 26Oct2023.

12 APPENDICES

12.1 Appendix 1: 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 [3, 4]

The specimens consented and/or collected in this study as outlined in Section 8.4.1 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 [3, 4]

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 (i.e., DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all participants at a study visit by the PI or designee. Informed consent for FBR should be presented to the participants on the visit designated in the Schedule of Activities (Section 1.3). 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 FBR will be performed as outlined in the Schedule of Activities (Section 1.3). In general, if additional blood specimens are being collected for FBR, 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 [3, 4]

In order to optimize the research that can be conducted with FBR specimens, it is critical to link participants' clinical information with future test results. In fact, little or no research can be conducted without connecting the clinical study data to the specimen. The clinical data allow specific analyses to be conducted. Knowing participant characteristics like sex, age, medical history, and intervention outcomes are critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for FBR, 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 FBR 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 [3, 4]

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses using the future biomedical research specimens may be performed by the Sponsor, or an additional third party (e.g., a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and

confidentiality requirements. Any contracted third party analyses will conform to the specific scope of analysis outlined in FBR protocol and consent. FBR specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research [3, 4]

Participants may withdraw their consent for FBR and ask that their biospecimens not be used for FBR. Participants may withdraw consent at any time by contacting the PI. If medical records for the study are still available, the PI 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 study use only. If specimens were collected from study participants specifically for FBR, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the PI confirming withdrawal and/or destruction, if applicable. It is the responsibility of the PI 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 before 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.

If the medical records for the study are no longer available (e.g., if the PI is no longer required by regulatory authorities to retain the 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

FBR specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the 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 [3, 4]

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 [3, 4]

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 [3, 4]

Every effort will be made to recruit all participants diagnosed and treated on Sponsor clinical studies for FBR.

11. Risks Versus Benefits of Future Biomedical Research [3, 4]

For FBR, risks to the participant have been minimized and are described in the FBR 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 FBR 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/