Official Protocol Title:	An Open-Label Trial to Evaluate the Pharmacokinetics of MK-3402 Following Administration of a Single IV Dose to Participants with Mild, Moderate, and Severe Renal Impairment and End-Stage Renal Disease
NCT number:	NCT04678505
Document Date:	30-Oct-2020

Title Page

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Protocol Title: An Open-Label Trial to Evaluate the Pharmacokinetics of MK-3402 Following Administration of a Single IV Dose to Participants with Mild, Moderate, and Severe Renal Impairment and End-Stage Renal Disease

Protocol Number: 004-00

Compound Number: MK-3402

Sponsor Name:

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

Legal Registered Address:

One Merck Drive

PO Box 100

Whitehouse Station, New Jersey, 08889-0100, USA

Regulatory Agency Identifying Number(s):

IND	148,130

Approval Date: 30 October 2020

Sponsor Signatory

Typed Name: Title:	Date

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

Investigator Signatory

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

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Original Protocol	30-OCT-2020	Not applicable

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: An Open-Label Trial to Evaluate the Pharmacokinetics of MK-3402 Following Administration of a Single IV Dose to Participants with Mild, Moderate, and Severe Renal Impairment and End-Stage Renal Disease

Short Title: Study of MK-3402 in Renal Impairment and End Stage Renal Disease

Acronym: NA

Hypotheses, Objectives, and Endpoints:

The study will be conducted in male and female (non-childbearing potential only) participants, 18 to 75 years of age with mild, moderate or severe renal impairment, end stage renal disease, or healthy adults.

[Will be populated by selections made in Section 3 Objectives and Endpoints]

Objectives	Endpoints
Primary	
• Objective: To compare the plasma PK (eg, AUC0-inf, Ceoi, Tmax, elimination terminal t1/2, CL, and Vd) of MK-3402 following a single IV dose in participants with varying degree of renal impairment (mild, moderate, severe, ESRD before HD, ESRD after HD) to those of healthy matched control participants. • Estimation: MK-3402 AUC0-inf following a single IV dose of MK-3402 administered to participants with varying degrees of real impairment (mild, moderate, severe, ESRD before HD, ESRD after HD) will be estimated and compared to MK-3402 AUC0-inf when administered to healthy matched control participants.	• Plasma MK-3402 AUC0-inf, Ceoi, Tmax, elimination terminal t1/2, CL, and Vd

Objectives	Endpoints
Secondary	
• Objective: To investigate the extent MK-3402 is removed by hemodialysis. • Estimation: The extent to which MK-3402 is removed by hemodialysis from the plasma (eg, $CL_{D,\ plasma}$) or the dialysate (eg, C_D, AE_D, AE_D (%dose), $CL_{D,\ dialysate}$) will be estimated.	• Plasma MK-3402, $CL_{D,\ plasma}$ or the dialysate (eg, C_D, AE_D, AE_D (%dose), $CL_{D,\ dialysate}$)
• Objective: To compare the urine PK (eg, Ae0-24, Fe, CLr) of MK-3402 following a single IV dose of MK-3402 to participants of varying degrees of renal impairment, where possible, to those of healthy matched control participants. • Estimation: MK-3402 Ae0-24, Fe, and CLr following a single IV dose of MK-3402 administered to participants with varying degrees of renal impairment, as appropriate, will be estimated and compared to those estimated in mean healthy matched control participants.	• Urine MK-3402 Ae0-24, F3, and CLr
• Objective: To evaluate the safety and tolerability of the administration of a single IV dose MK-3402 in participants with varying degrees of renal impairment.	• Adverse events, vital signs, 12-lead electrocardiograms, laboratory safety tests
Tertiary/Exploratory	
• Objective: To explore the relationship between estimated renal clearance (eGFR and CrCl) and PK (AUC0-inf and Ceoi) of MK-3402 using a model-based approach.	• eGFR and CrCl
• Objective: To explore the relationship between genetic variation and response to the treatment(s) administered, and mechanisms of disease. Variation across the human genome may be analyzed for association with clinical data collected in the study.	• Germline genetic variation and association to clinical data collected in this study.

Overall Design:

Study Phase	Phase 1
Primary Purpose	Treatment
Indication	Treatment of Bacterial Infection
Population	Healthy Participants, Participants with Mild, Moderate, or Severe Renal Impairment, Participants with End Stage Renal Disease
Study Type	Interventional
Intervention Model	Sequential This is a multi-site study.
Type of Control	No Treatment Control, Matched Healthy Participants
Study Blinding	Unblinded Open-label
Blinding Roles	No Blinding
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 6 months from the time the first participant (or their legally authorized representatitive) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Approximately 30 to 42 participants will be allocated/randomized.

Intervention Groups and Duration:

<table>
<tr><td>Intervention Groups</td><td>
<table>
<tr><th>Inter-vention Group Name</th><th>Drug</th><th>Dose Strength</th><th>Dose Frequency</th><th>Route of Adminis-tration</th><th>Treatment Period</th><th>Use</th></tr>
<tr><td>Panels A, B, C, and D</td><td>MK-3402</td><td>100 mg</td><td>Once</td><td>Intravenous</td><td>Single Dose</td><td>Experi mental</td></tr>
<tr><td>Panel E</td><td>MK-3402</td><td>100 mg</td><td>Twice</td><td>Intravenous</td><td>Single Dose, Periods 1 and 2</td><td>Experi mental</td></tr>
</table>
</td></tr>
<tr><td>Total Number of Intervention Groups/ Arms</td><td>5</td></tr>
<tr><td>Duration of Participation</td><td>Each participant will participate in the study for approximately 6 weeks (Panels A to D) or 7 weeks (Panel E) from the time the participant provides documented informed consent through the final contact.</td></tr>
</table>

Study Governance Committees:

Steering Committee	No
Executive Oversight Committee	No
Data Monitoring Committee	No
Clinical Adjudication Committee	No

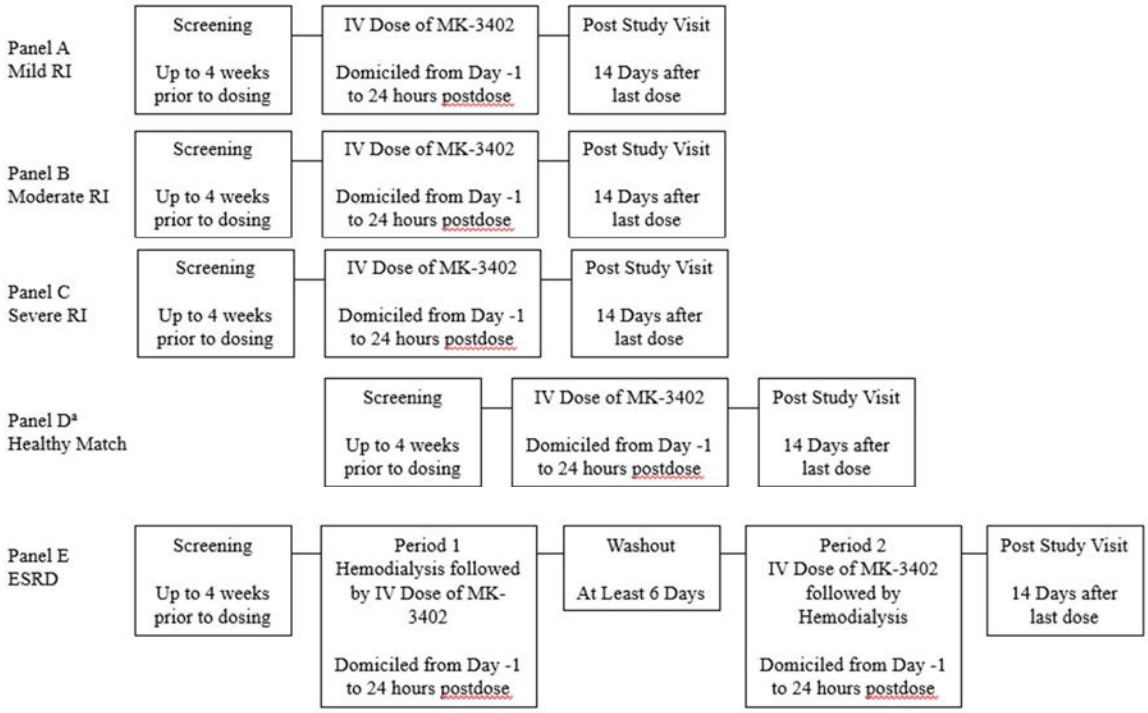
Study Accepts Healthy Volunteers: Yes

A list of abbreviations is in Appendix 11.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Study Design



ESRD=end stage renal disease; IV=intravenous; RI=renal impairment

[a] Panel D is to commence following the completion of enrollment of Panels A and B. Participants will be enrolled into Panel D as per the protocol specified matching criteria. The total number of participants in this Panel will be between 6 and 18.

1.3 Schedule of Activities

1.3.1 Panels A to D

Panels A to D																		
Study Period:	**Screening**			**Intervention (hours)**													**Post-study [a]**	**Notes**
	Screening	**Day -1**	**Pre-dose**	**0**	**0.5**	**0.75**	**1**	**1.5**	**2**	**4**	**6**	**8**	**10**	**12**	**24**	**48**		
Administrative Procedures																		
Informed Consent	X																	See Section 8.1.1
Informed Consent for FBR	X																	See Section 8.1.1
Participant ID Card	X																	See Section 8.1.3
Inclusion/Exclusion Criteria	X	X	X															See Sections 5.1 and 5.2
Medical History	X																	Includes any substance use (drugs, alcohol, tobacco, and caffeine).
Prior/Concomitant Medication Review	X----------																----------X	See Section 8.1.5
Assignment of Treatment/Allocation Number			X															See Section 8.1.7
Study Procedures																		
MK-3402 IV Administration				X	----X													Infusion of 100-mL solution over ~ 30 minutes (start t=0).
Standard Meals										X	----------	----------	----------	X				See Section 5.3.1
Domiciling		X----------													----------	X		See Section 8.1.11
Safety Procedures																		
Full physical examination	X		X														X	See Section 8.3.1
Height	X																	
Weight	X																X	BMI to be calculated only at screening.

Panels A to D																		
Study Period:	**Screening**			**Intervention (hours)**													**Post-study [a]**	**Notes**
	Screening	**Day -1**	**Pre-dose**	**0**	**0.5**	**0.75**	**1**	**1.5**	**2**	**4**	**6**	**8**	**10**	**12**	**24**	**48**		
Vital Signs (HR, BP, RR, body temperature)	X		X		X				X		X				X		X	See Section 8.3.2.
12-lead ECG	X		X		X				X						X			See Section 8.3.3.
1-minute ECG rhythm strip					X													See Section 8.3.3.
Serum FSH	X																	Postmenopausal women only. See Appendix 2 and 5.
HIV, hepatitis B and C screen	X																	Per site SOP.
Drug Screen	X	X																Drug screening is mandatory; any additional assessments are conducted per site SOP.
Hematology/Chemistry	X	X													X			See Appendix 2
Urinalysis	X	X													X			See Appendix 2
AE/SAE review	X----------																X	See Section 8.4
Pharmacokinetics																		
Blood for Plasma MK-3402			X		X	X	X	X	X	X	X	X	X	X	X	X		See Section 8.6.1.
Urine for MK-3402			X	X----------X---------X--------X------X														Collected: Predose (spot collection), 0-4 hrs, 4-8 hrs, 8-12 hrs and 12-24 hrs postdose. See Section 8.6.2.
Biomarkers																		
Blood for Genetic Analysis			X															Collect Predose from enrolled participants only. See Section 8.8.

Panels A to D																		
Study Period:	**Screening**			**Intervention (hours)**													**Post-study [a]**	**Notes**
	Screening	**Day -1**	**Pre-dose**	**0**	**0.5**	**0.75**	**1**	**1.5**	**2**	**4**	**6**	**8**	**10**	**12**	**24**	**48**		

AE=adverse event; BMI=body mass index; BP=blood pressure; DNA=deoxyribonucleic acid; ECG=electrocardiogram; FBR=future biomedical research; FSH=follicle stimulating hormone; HIV=human immunodeficiency virus; HR=heart rate; ID=identification; IV=intravenous; RR=respiratory rate; SAE=serious adverse event; SOP=standard operating procedure; VS=vital signs.

[a] The Poststudy visit will occur approximately 14 days following administration of last dose of study drug in the final period. Follow up for any clinical or laboratory AEs should occur by phone or in person if the Poststudy visit occurs before 14 days after the last dose of study drug.

1.3.2 Panel E Period 1

Panels E Period 1 (MK-3402 Administered Post Dialysis)																	
Study Period:	**Screening**			**Intervention (hours)**													**Notes**
	Screening	**Day-1**	**Pre-dose**	**0**	**0.5**	**0.75**	**1**	**1.5**	**2**	**4**	**6**	**8**	**10**	**12**	**24**	**48**	
Administrative Procedures																	
Informed Consent	X																See Section 8.1.1
Informed Consent for FBR	X																See Section 8.1.1
Participant ID Card	X																See Section 8.1.3
Inclusion/Exclusion Criteria	X	X	X														See Sections 5.1 and 5.2
Medical History	X																Includes any substance use (drugs, alcohol, tobacco, and caffeine).
Prior/Concomitant Medication Review	X----------X																See Section 8.1.5
Assignment of Treatment/Allocation Number			X														See Section 8.1.7
Study Procedures																	
MK-3402 IV Administration				X-------X													Infusion of 100-mL solution over ~ 30 minutes (start t=0) immediately following the end of HD.
Standard Meals							X----------X										See Section 5.3.1.
Domiciling		X----------X															See Section 8.1.11.
Safety Procedures																	
Full physical examination	X		X														See Section 8.3.1
Height	X																
Weight	X																BMI to be calculated only at screening
Vital Signs (HR, BP, RR, body temperature)	X		X		X				X		X				X		See Section 8.3.2.
12-lead ECG	X		X		X				X						X		See Section 8.3.3
1-minute ECG rhythm strip					X												See Section 8.3.3.

Panels E Period 1 (MK-3402 Administered Post Dialysis)																	
Study Period:	**Screening**			**Intervention (hours)**													**Notes**
	Screening	**Day-1**	**Pre-dose**	**0**	**0.5**	**0.75**	**1**	**1.5**	**2**	**4**	**6**	**8**	**10**	**12**	**24**	**48**	
Serum FSH	X																Postmenopausal women only. See Appendix 2 and 5.
HIV, hepatitis B and C screen	X																Per site SOP.
Drug Screen	X	X															Drug screening is mandatory; any additional assessments are conducted per site SOP.
Hematology/Chemistry	X	X													X		See Appendix 2
Urinalysis	X	X													X		See Appendix 2
AE/SAE review	X----------															X	See Section 8.4
Pharmacokinetics																	
Blood for Plasma MK-3402			X		X	X	X	X	X	X	X	X	X	X	X	X	See Section 8.6.1
Urine for MK-3402			X	X----------X----------X----------X-----X													Collected: Predose (spot collection), 0-4 hrs, 4-8 hrs, 8-12 hrs and 12-24 hrs postdose. See Section 8.6.2
Biomarkers																	
Blood for Genetic Analysis			X														Collect Predose from enrolled participants only. See Section 8.8.

AE=adverse event; BMI=body mass index; BP=blood pressure; DNA=deoxyribonucleic acid; ECG=electrocardiogram; FBR=future biomedical research; FSH=follicle stimulating hormone; HIV=human immunodeficiency virus; HR=heart rate; ID=identification; IV=intravenous; RR=respiratory rate; SAE=serious adverse event; SOP=standard operating procedure; VS=vital signs.

1.3.3 Panel E Period 2

Panels E Period 2 (MK-3402 Administered Pre-Dialysis)																				
Study Period:		**Intervention (hours)**																	**Post-study [a]**	**Notes**
	Pre-dose	**0**	**0.5**	**0.75**	**1**	**1.5**	**2**	**2.5**	**3**	**3.5**	**4**	**4.5**	**6**	**8**	**10**	**12**	**24**	**48**		
Administrative Procedures																				
Concomitant Medication Review	X----------X																			See Section 8.1.5
Study Procedures																				
MK-3402 IV Administration		X-----X																		Infusion of 100-mL solution over ~30 minutes (start t=0).
Standard Meals											X----------X									See Section 5.3.1
Domiciling	X----------X																			See Section 8.1.11
Safety Procedures																				
Full physical examination	X																		X	See Section 8.3.1
Weight																			X	BMI to be calculated only at screening.
Vital Signs (HR, BP, RR, body temperature)	X		X				X						X				X		X	See Section 8.3.2
12-lead ECG	X		X				X										X			See Section 8.3.3
1-minute ECG rhythm strip			X																	See Section 8.3.3.
Hematology/Chemistry	X																X			See Appendix 2
Urinalysis	X																X			See Appendix 2
Hemodialysis			X																	HD session will be initiated immediately following the 0.5-hr postdose blood draw, VS and ECG.
AE/SAE review	X----------X																			

Panels E Period 2 (MK-3402 Administered Pre-Dialysis)																				
Study Period:		**Intervention (hours)**																	**Post-study [a]**	**Notes**
	Pre-dose	**0**	**0.5**	**0.75**	**1**	**1.5**	**2**	**2.5**	**3**	**3.5**	**4**	**4.5**	**6**	**8**	**10**	**12**	**24**	**48**		
Pharmacokinetics																				
Blood for Plasma MK-3402	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		See Section 8.6.1. Blood samples collected during HD will be collected from both the pre-dialyzer and post-dialyzer blood lines.
Dialysate for MK-3402 PK	X				X	X	X	X	X	X	X	X								Dialysate samples will be taken every 30 minutes until dialysis is completed (30 minutes [predialysis], 1, 1.5, 2, 2.5, 3, 3.5, 4, and 4.5 hr) post the start of infusion. See Section 8.6.3.
Urine for MK-3402	X	X----------X----------X----------X																		Collected: Predose (spot collection), 0-4 hrs, 4-8 hrs, and 8-12 hrs postdose. See Section 8.6.2.

AE=adverse event; BMI= body mass index; BP=blood pressure; DNA=deoxyribonucleic acid; ECG=electrocardiogram; FBR=future biomedical research; FSH=follicle stimulating hormone; HD=hemodialysis; HIV=human immunodeficiency virus; HR=heart rate; ID=identification; IV=intravenous; RR=respiratory rate; SAE=serious adverse event; SOP=standard operating procedure; VS=vital signs.

[a] The Poststudy visit will occur approximately 14 days following administration of last dose of study drug in the final period. Follow up for any clinical or laboratory AEs should occur by phone or in person if the Poststudy visit occurs before 14 days after the last dose of study drug.

2 INTRODUCTION

2.1 Study Rationale

MK-3402 is being developed as a component of treatment regimens for bacterial infections. The primary pathway of elimination is via renal excretion. As such, this study is being conducted to assess the impact of various degrees of renal insufficiency on the PK of MK-3402.

2.2 Background

Refer to the IB/approved labeling for detailed background information on MK-3402.

2.2.1 Pharmaceutical and Therapeutic Background

MK-3402 is a potent and selective small molecule inhibitor of clinically important bacterial MBL enzymes, which hydrolyze the β-lactam ring and confer bacterial resistance to β-lactam antibiotics. It is a reversible, active-site directed inhibitor of many MBLs with high enzymatic inhibition potency. β-lactam antibiotics (penicillins, cephalosporins, carbapenems, and monobactams) are among the most frequently used antimicrobial agents in clinical practice. The unrelenting development of resistance in gram-negative bacteria, especially *Pseudomonas* and Enterobacteriaceae, to β-lactam antibiotics by the production of BLs poses a growing threat to the clinical utility of all β-lactam antibiotics. There are 4 major classes of BLs: Classes A, B, C, and D. Classes A, C, and D are serine-based enzymes. Class B are metallo-enzymes with active site zinc required for hydrolysis of the β-lactam ring. Infections caused by BL-producing gram-negative bacteria represent a critical unmet medical need due to their life-threatening nature and the lack of effective therapies. Therefore, there is an urgent need for new BLIs that can be combined with existing β-lactam antibiotics to protect against hydrolysis by one or more of the 4 classes (A, B, C and D) of BL enzymes.

MK-3402 is class-specific for MBL (Class B) and has no activity against Classes A, C, and D serine BLs, or intrinsic antibacterial activity. It demonstrates broad inhibition against various subtypes of Class B enzymes. MK-3402 is being developed to treat resistant gram-negative bacterial infections in combination with a β-lactam antibiotic. The use of a BLI to overcome β-lactam resistance in gram-negative organisms is a clinically-validated concept. β-lactam/BLI combinations that inhibit the Class A and Class C enzymes are in clinical use. There are no approved MBLIs, and thus treatment options for patients with MBL-expressing gram-negative bacterial infections are severely limited. Based on in vitro microbiology, animal infection models, and hollow fiber experiments, MK-3402 is expected to have broad clinical efficacy against MBL-producing *Pseudomonas* and Enterobacteriaceae when used in combination with antipseudomonal β-lactam antibiotics.

The PK of MK-3402 in rats and monkeys were characterized by low plasma CL, low Vd, and short t1/2. The observed low Vd was consistent with the low passive permeability of MK-3402 determined in vitro. In vitro, MK-3402 was low to moderately bound to plasma protein in rat, monkey and human and did not preferentially distribute into red blood cells. The reversible binding of MK-3402 to plasma proteins in rat, monkey, and human, and the

percentage unbound was 71.8%, 77.6%, and 67.5%, respectively. The compound did not exhibit concentration-dependent binding in human plasma over the concentration range of 1 to 10 µM. Urinary excretion of unchanged MK-3402 was the predominant route of elimination in rats and monkeys, based on in vivo metabolism and disposition studies conducted with [^{3}H]MK-3402. In humans, urinary excretion accounted for ~ 56% of the elimination of a single dose of MK-3402 (Section 2.2.3.1), and CLr was estimated to be 2.11 L/hour. MK-3402 has a low potential to cause DDIs as a perpetrator by inhibition or induction of CYPs or by inhibition of major transporters.

2.2.2 Preclinical Studies

Detailed information on preclinical studies with MK-3402 is provided in the IB. A summary of a recently-conducted one-month toxicity study is described below.

In a recent one-month study of the combination of MK-3402 with relebactam (REL, MK-7655), another Merck compound, abnormal ECG morphologic observations were noted in one out of ten monkeys treated at the high dose level. In the study, entitled *1-month Intravenous Infusion Combination Toxicity Study in Rhesus Monkeys with a 4-week Treatment-Free Recovery period* (TT#20-1000), MK-3402 and REL were administered in combination intravenously to rhesus monkeys once daily for approximately 1-month. MK-3402 was administered daily as a 2-hour intravenous infusion followed immediately by a 4-minute intravenous infusion of REL. The study design and dose levels are summarized in Table 1.

Table 1 Study Design for 1-Month Intravenous Infusion Combination Toxicity Study in Rhesus Monkeys with a 4-week Treatment Period (TT#20-1000)

Dose Group	**MK-3402 (mg/kg/day)**	**REL (mg/kg/day)**	**Number of Animals, n=total**
Control	0	0	3M/3F + (2M/2F, progressed to recovery) n=10
Low Dose	20	50	3M/3F (no recovery animals) n=6
High Dose	50	50	3M/3F + (2M/2F, progressed to recovery) n=10
M: males; F: females			

ECGs were collected in all animals during Pretest and SW4, and in recovery animals in SW9, within 15 minutes from the end of the intravenous infusion with REL. There were no abnormalities in ECG morphology during the Pretest ECG collection at any dose level. In SW4, one female monkey (Animal# 20-1007) out of 10 animals in the high dose combination group exhibited abnormal ECG morphologic observations including multiple, single instances of non-conducted P waves (P wave without an associated QRS complex), frequent unifocal EVBs occurring at a rate of approximately 6-15 ectopic beats/min, considered to be ventricular escape beats, and intermittent increases in R-R intervals. These findings are not

commonly seen in untreated rhesus monkeys under these study conditions. These observations were seen in two additional ECG recordings from Animal# 20-1007, repeated within 4 minutes from each other on the following day, collected within 15 minutes from completion of daily dosing. There were no changes in HR or in any of the other ECG intervals (PR, QRS, QT, QTc) in Animal# 20-1007 during Pretest or SW4. Animal# 20-1007 went to planned necropsy at the end of the dosing phase (SW4); therefore, no additional ECG collections were performed on this animal during the recovery phase.

There were no abnormalities in ECG morphology in animals at the low dose (20 mg/kg/day MK-3402 + 50 mg/kg/day REL) or in control animals. There were no changes in HR or in any ECG intervals evaluated (RR, PR, QRS, QT, QTc) during Pretest or SW4 in any other animal on study.

There were no treatment-related changes in clinical signs, body weight, food consumption, or anatomic pathology evaluations (including no changes in the histopathologic evaluation of the heart) in any of the study animals, including Animal# 20-1007.

Plasma drug concentrations in control and treated animals were determined on Study Day 1 and in SW4. MK-3402 and MK-7655 exposures for Animal# 20-1007 were similar to other animals in the high-dose group. There were no substantial differences by sex in exposures or evidence of accumulation when comparing exposures on Study Day 1 to SW4. At the NOEL dose (20 mg/kg/day MK-3402 + 50 mg/kg/day REL), MK-3402 $AUC_{0\text{-}24hr}$ was 253 µM.hr and C_{max} 76 µM. At the high dose (50 mg/kg/day MK-3402 + 50 mg/kg/day REL), MK-3402 $AUC_{0\text{-}24hr}$ was 633 µM.hr and C_{max} 184 µM.

To note, the exposure of MK-3402 and REL observed in this study were comparable to the expected values in monkeys based on existing data where the animals were dosed with each compound alone. No treatment-related ECG-findings have been observed in nonclinical studies in rhesus monkeys at significantly higher doses for either MK-3402 alone (exposures in monkeys up to 550 mg/kg/day: $AUC_{0\text{-}24hr}$= 7210 µM.hr and C_{max}=1940 µM. These previously-conducted studies are described in the MK-3402 IB.

Overall, the cause of the abnormal ECG morphologic observation in the high-dose female monkey in the 1-month Intravenous Infusion Combination Toxicity Study in Rhesus Monkeys with a 4-week Treatment-Free Recovery Period, is currently unknown. Because the ECG morphologic observations were seen in a single animal that received the combination of MK-3402/REL at high dose, and no abnormal ECG morphologic changes were seen at significantly higher plasma exposures with either MK-3402 or REL when dosed alone, the Sponsor considers this observation to be of uncertain relationship to administration of the combination of MK-3402/REL.

2.2.3 Ongoing Clinical Studies

2.2.3.1 Single Ascending Dose Study (P001)

MK-3402 is currently being evaluated in the ongoing first-in-human single-ascending dose study, MK-3402-001. The study is clinically complete. A total of 17 healthy participants received MK-3402 or placebo administered IV over 30 minutes as single doses up to 600 mg and as 2 doses of up to 550 mg, administered 6 hours apart. MK-3402 was generally well tolerated. There have been no SAEs and no AEs leading to discontinuation. All AEs have been either mild or moderate in intensity. The most frequently reported drug related AEs in participants receiving study drug (MK-3402 or placebo; preliminary safety data remain blinded) have been headache and nausea [Table 2]. One participant reported a single mild episode of palpitations lasting 15 minutes, occurring 12 days after the final dose of study drug (MK-3402 or placebo as a divided dose of 1100 mg); this was considered not drug-related by the investigator. No clinically meaningful trends have been observed for changes in clinical laboratory values, VS, or ECGs as a function of dose or treatment. On blinded review of ECGs through the post-study visit, no clinically significant changes from baseline have been reported for rate, rhythm, morphology, and calculated intervals (PR, QRS, and QTcF).

Following single IV doses of 25 to 600 mg and 900 to 1100 mg as split doses, MK-3402 plasma concentrations declined in a biphasic manner. Exposure (AUC0-inf and Cmax) increases were approximately dose-proportional. Across the range of doses (25 to 1100 mg) CL was ~ 4 L/hour, Vd was ~ 25 L, and t1/2 was ~ 4 hours [Table 3]. Following a single IV dose of 200 mg and 400-mg MK-3402, approximately 60% of the dose was eliminated unchanged in the urine over 24 hours.

Table 2 Participants With Adverse Events (Incidence > 0% in One or More Treatment Groups) in P001

	Panel A Period 1 MK-3402 25 mg or PBO		Panel B Period 1 MK-3402 50 mg or PBO		Panel A Period 2 MK-3402 100 mg or PBO		Panel B Period 2 MK-3402 200 mg or PBO		Panel A Period 3 MK-3402 400 mg or PBO	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	8		8		8		7		8	
with one or more adverse events	2	(25.0)	5	(62.5)	4	(50.0)	3	(42.9)	5	(62.5)
with no adverse events	6	(75.0)	3	(37.5)	4	(50.0)	4	(57.1)	3	(37.5)
Cardiac disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Palpitations	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Eye disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(12.5)**
Photopsia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(12.5)
Gastrointestinal disorders	**1**	**(12.5)**	**1**	**(12.5)**	**0**	**(0.0)**	**1**	**(14.3)**	**1**	**(12.5)**
Abdominal discomfort	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Diarrhoea	1	(12.5)	1	(12.5)	0	(0.0)	0	(0.0)	0	(0.0)
Nausea	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(12.5)
Oral pain	0	(0.0)	0	(0.0)	0	(0.0)	1	(14.3)	0	(0.0)
Toothache	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Vomiting	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
General disorders and administration site conditions	**1**	**(12.5)**	**1**	**(12.5)**	**2**	**(25.0)**	**0**	**(0.0)**	**1**	**(12.5)**
Catheter site pain	1	(12.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Chest discomfort	1	(12.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Exercise tolerance decreased	0	(0.0)	0	(0.0)	1	(12.5)	0	(0.0)	1	(12.5)
Fatigue	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Influenza like illness	0	(0.0)	1	(12.5)	0	(0.0)	0	(0.0)	0	(0.0)
Malaise	0	(0.0)	0	(0.0)	1	(12.5)	0	(0.0)	0	(0.0)
Pyrexia	0	(0.0)	1	(12.5)	0	(0.0)	0	(0.0)	0	(0.0)
Infections and infestations	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Erysipelas	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

Table 2 Participants With Adverse Events (Incidence > 0% in One or More Treatment Groups) in P001 (Continued)

	Panel B Period 3 MK-3402 600 mg or PBO		Panel A Period 4 MK-3402 900 mg or PBO		Panel B Period 4 MK-3402 1100 mg or PBO		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	8		8		8		17	
with one or more adverse events	3	(37.5)	3	(37.5)	6	(75.0)	15	(88.2)
with no adverse events	5	(62.5)	5	(62.5)	2	(25.0)	2	(11.8)
Cardiac disorders	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(12.5)**	**1**	**(5.9)**
Palpitations	0	(0.0)	0	(0.0)	1	(12.5)	1	(5.9)
Eye disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(5.9)**
Photopsia	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.9)
Gastrointestinal disorders	**2**	**(25.0)**	**0**	**(0.0)**	**4**	**(50.0)**	**7**	**(41.2)**
Abdominal discomfort	0	(0.0)	0	(0.0)	1	(12.5)	1	(5.9)
Diarrhoea	0	(0.0)	0	(0.0)	0	(0.0)	2	(11.8)
Nausea	2	(25.0)	0	(0.0)	2	(25.0)	4	(23.5)
Oral pain	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.9)
Toothache	0	(0.0)	0	(0.0)	1	(12.5)	1	(5.9)
Vomiting	1	(12.5)	0	(0.0)	0	(0.0)	1	(5.9)
General disorders and administration site conditions	**0**	**(0.0)**	**1**	**(12.5)**	**1**	**(12.5)**	**4**	**(23.5)**
Catheter site pain	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.9)
Chest discomfort	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.9)
Exercise tolerance decreased	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.9)
Fatigue	0	(0.0)	1	(12.5)	1	(12.5)	2	(11.8)
Influenza like illness	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.9)
Malaise	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.9)
Pyrexia	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.9)
Infections and infestations	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(12.5)**	**1**	**(5.9)**
Erysipelas	0	(0.0)	0	(0.0)	1	(12.5)	1	(5.9)

Table 2 Participants With Adverse Events (Incidence > 0% in One or More Treatment Groups) in P001 (Continued)

	Panel A Period 1 MK-3402 25 mg or PBO		Panel B Period 1 MK-3402 50 mg or PBO		Panel A Period 2 MK-3402 100 mg or PBO		Panel B Period 2 MK-3402 200 mg or PBO		Panel A Period 3 MK-3402 400 mg or PBO	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Injury, poisoning and procedural complications	**0**	**(0.0)**	**2**	**(25.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Hand fracture	0	(0.0)	1	(12.5)	0	(0.0)	0	(0.0)	0	(0.0)
Skin wound	0	(0.0)	1	(12.5)	0	(0.0)	0	(0.0)	0	(0.0)
Investigations	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(25.0)**	**0**	**(0.0)**	**1**	**(12.5)**
Heart rate increased	0	(0.0)	0	(0.0)	1	(12.5)	0	(0.0)	0	(0.0)
SARS-CoV-2 test positive	0	(0.0)	0	(0.0)	1	(12.5)	0	(0.0)	0	(0.0)
White blood cell count decreased	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(12.5)
Metabolism and nutrition disorders	**0**	**(0.0)**	**1**	**(12.5)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Decreased appetite	0	(0.0)	1	(12.5)	0	(0.0)	0	(0.0)	0	(0.0)
Musculoskeletal and connective tissue disorders	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(12.5)**	**0**	**(0.0)**	**1**	**(12.5)**
Back pain	0	(0.0)	0	(0.0)	1	(12.5)	0	(0.0)	0	(0.0)
Musculoskeletal pain	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(12.5)
Neck pain	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Nervous system disorders	**0**	**(0.0)**	**2**	**(25.0)**	**0**	**(0.0)**	**2**	**(28.6)**	**1**	**(12.5)**
Dizziness	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Dizziness postural	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(12.5)
Dysgeusia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Headache	0	(0.0)	2	(25.0)	0	(0.0)	2	(28.6)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	**0**	**(0.0)**	**1**	**(12.5)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(12.5)**
Nasal congestion	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(12.5)
Oropharyngeal pain	0	(0.0)	1	(12.5)	0	(0.0)	0	(0.0)	0	(0.0)
Skin and subcutaneous tissue disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**

Table 2 Participants With Adverse Events (Incidence > 0% in One or More Treatment Groups) in P001 (Continued)

	Panel B Period 3 MK-3402 600 mg or PBO		Panel A Period 4 MK-3402 900 mg or PBO		Panel B Period 4 MK-3402 1100 mg or PBO		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Injury, poisoning and procedural complications	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(11.8)**
Hand fracture	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.9)
Skin wound	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.9)
Investigations	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**3**	**(17.6)**
Heart rate increased	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.9)
SARS-CoV-2 test positive	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.9)
White blood cell count decreased	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.9)
Metabolism and nutrition disorders	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(12.5)**	**2**	**(11.8)**
Decreased appetite	0	(0.0)	0	(0.0)	1	(12.5)	2	(11.8)
Musculoskeletal and connective tissue disorders	**1**	**(12.5)**	**1**	**(12.5)**	**0**	**(0.0)**	**3**	**(17.6)**
Back pain	0	(0.0)	1	(12.5)	0	(0.0)	1	(5.9)
Musculoskeletal pain	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.9)
Neck pain	1	(12.5)	0	(0.0)	0	(0.0)	1	(5.9)
Nervous system disorders	**2**	**(25.0)**	**1**	**(12.5)**	**5**	**(62.5)**	**7**	**(41.2)**
Dizziness	0	(0.0)	1	(12.5)	0	(0.0)	1	(5.9)
Dizziness postural	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.9)
Dysgeusia	0	(0.0)	0	(0.0)	1	(12.5)	1	(5.9)
Headache	2	(25.0)	0	(0.0)	4	(50.0)	5	(29.4)
Respiratory, thoracic and mediastinal disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(11.8)**
Nasal congestion	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.9)
Oropharyngeal pain	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.9)
Skin and subcutaneous tissue disorders	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(12.5)**	**1**	**(5.9)**

Table 2 Participants With Adverse Events (Incidence > 0% in One or More Treatment Groups) in P001 (Continued)

	Panel A Period 1 MK-3402 25 mg or PBO		Panel B Period 1 MK-3402 50 mg or PBO		Panel A Period 2 MK-3402 100 mg or PBO		Panel B Period 2 MK-3402 200 mg or PBO		Panel A Period 3 MK-3402 400 mg or PBO	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Skin and subcutaneous tissue disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Skin irritation	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Vascular disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Hot flush	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

Table 2 Participants With Adverse Events (Incidence > 0% in One or More Treatment Groups) in P001 (Continued)

	Panel B Period 3 MK-3402 600 mg or PBO		Panel A Period 4 MK-3402 900 mg or PBO		Panel B Period 4 MK-3402 1100 mg or PBO		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Skin and subcutaneous tissue disorders	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(12.5)**	**1**	**(5.9)**
Skin irritation	0	(0.0)	0	(0.0)	1	(12.5)	1	(5.9)
Vascular disorders	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(12.5)**	**1**	**(5.9)**
Hot flush	0	(0.0)	0	(0.0)	1	(12.5)	1	(5.9)
Every participant is counted a single time for each applicable row and column.								

Source: [P001V01MK3402: adam-adsl; adae]

Table 3 Summary Geometric Mean (% GCV) Pharmacokinetic Parameter Values of MK-3402 in Plasma Following Single Intravenous Infusions (25, 50, 100, 200, 400, and 600 mg) and Two Intravenous Infusions (450 and 550 mg, given 6 hr apart; total dose of 900 and 1100 mg, respectively) of MK-3402 to Healthy Adult Participants. Infusions given over 30 minutes, (P001)

Geometric Mean (%GCV)												
Period	**Panel**	**Dose (mg)**	**Cmax (µmol/L)**	**Ceoi (µmol/L)**	**Tmax[b] (hr)**	**AUC0-inf (hr*µmol/L)**	**AUC0-last (hr*µmol/L)**	**AUC0-24 (hr*µmol/L)**	**t1/2 (hr)**	**CL (L/hr)**	**Vd (L)**
1	A	25	4.05 (7.1)	4.00 (6.9)	0.50 (0.50 - 0.75)	14.0 (9.1)	13.3 (10.7)	14.0 (9.2)	3.96 (19.7)	3.81 (9.1)	21.8 (21.7)
	B	50	7.00 (24.0)	6.79 (22.4)	0.50 (0.50 - 0.75)	23.9 (16.9)	23.5 (17.2)	23.5 (17.2)	4.32 (9.8)	4.46 (16.9)	27.8 (23.3)
2	A	100	14.8 (10.3)	14.8 (10.5)	0.50 (0.50 - 0.75)	50.9 (7.0)	50.1 (6.9)	50.1 (6.9)	4.47 (5.3)	4.18 (7.0)	27.0 (7.5)
	B	200	35.0 (12.2)	35.0 (12.2)	0.50 (0.50 – 0.50)	116 (13.3)	114 (12.7)	114 (12.7)	4.40 (11.5)	3.67 (13.3)	23.3 (9.2)
3	A	400	60.3 (8.3)	58.9 (11.3)	0.63 (0.50 – 0.75)	223 (8.5)	219 (8.3)	219 (8.3)	4.57 (3.4)	3.82 (8.5)	25.2 (6.5)
	B	600	93.7 (12.7)	93.0 (13.6)	0.50 (0.50 - 0.75)	340 (12.4)	334 (11.8)	334 (11.8)	4.47 (11.1)	3.76 (12.4)	24.3 (10.4)
4	A	900	79.6 (9.4)	67.8[a] (22.7)	6.50 (6.50 - 6.50)	537 (5.8)	531 (5.9)	522 (6.1)	4.46 (4.1)	3.57 (5.8)	22.9 (5.8)
	B	1100	98.4 (15.4)	90.6[a] (16.9)	6.50 (6.50 - 6.50)	655 (12.3)	649 (12.1)	638 (12.0)	4.17 (13.8)	3.57 (12.3)	21.5 (12.1)

Approximately N=6 per panel.

[a] Concentration at the end of first infusion
[b] Median (Min – Max)

2.2.3.2 Multiple Ascending Dose Study (P002)

MK-3402 is presently being evaluated in the current study, a randomized, placebo-controlled, double-blind multiple ascending dose study in healthy adult participants (healthy men and healthy WONCBP). This clinical study is designed to assess the safety, tolerability, and PK of MK-3402 in participants receiving multiple rising IV doses of MK-3402 or placebo from 100 to 400 mg q8hr for 8 days or 15 days. Each panel consists of 8 healthy adult participants who receive MK-3402 (n=6) or placebo (n=2) in a randomized, blinded fashion. As of 08-Oct-2020, dosing of 100 mg for 8 days and 200 mg for 15 days in the first two panels are complete.

There have been no SAEs and no AEs leading to discontinuation. All AEs have been mild, except for 1 moderate headache at the 100 mg MK-3402/placebo dose level. The most frequently reported AEs are infusion-site reactions (including extravasation, pain, paresthesia, and swelling), headache, and toothache. A summary of preliminary adverse events in Panels A and B is shown in Table 4 below.

Table 4 Preliminary Summary of Number of Participants Reporting Adverse Events for Panels A and B in Protocol 002

	MK-3402 or placebo[a,b]	
	Panel A	**Panel B**
Adverse Events	**100 mg[c]**	**200 mg [d]**
alanine aminotransferase increased		1
blood potassium increased		1
Catheter site pain	1	1
catheter site infection	1	
Catheter site irritation	1	
Catheter site paresthesia	1	
catheter site phlebitis		1
Contact allergy to chlorhexidine	1	
dysphagia		1
fatigue		1
Headache	3	1
Infusion site extravasation	1	
Infusion site pain	1	1
infusion site paresthesia		1
infusion site swelling		1
Insomnia	1	
loose stools	1	
Muscle strain		1
myalgia		1
Nausea	1	1
Orthostatic dizziness	1	

	MK-3402 or placebo[a,b]	
	Panel A	**Panel B**
Adverse Events	**100 mg[c]**	**200 mg [d]**
paresthesia	1	
pelvic girdle pain		1
phlebitis	1	
shoulder pain		1
tooth ache		2

[a] Data for this trial are still blinded; all adverse events regardless of causality are listed.
[b] N=8 participants per dose (6 active: 2 placebo)
[c] Dosing every 8 hours for 1 week.
[d] Dosing every 8 hours for 2 weeks.

No clinically meaningful dose-related trends have been observed for changes in clinical laboratory values, VS, or ECGs. Transient elevations in ALT (up to 2.8 X ULN) were observed in 4 participants; in 2 of these cases, AST was also transiently elevated (up to 1.6 X ULN). Clinically significant increases in heart rate upon standing were seen in one participant at the 100 mg MK-3402/placebo dose level (occurring 1 hour following the first dose on Day 1) and in another participant at the 200 mg MK-3402/placebo dose level (occurring 4 hours following the final dose on Day 15). On blinded review of ECGs from Panels A and B through the post-study visit, no clinically significant changes from baseline have been reported for rate, rhythm, morphology, and calculated intervals (PR, QRS, and QTcF).

Following multiple doses of MK-3402 q8 hr of 100 mg and 200 mg, MK-3402 plasma concentrations declined in a biphasic manner. Exposure (AUC0-8 and Ceoi) increases were approximately dose-proportional. The estimated CL was ~ 4 L/hour and Vd was ~ 21 L, which were comparable to values observed in P001. The accumulation ratio is approximately 1.2 for q8h dosing for MK-3402. Preliminary PK data are shown in Table 5.

Table 5 Summary Geometric Mean (% GCV) Pharmacokinetic Parameter Values of MK-3402 in Plasma Following Intravenous Infusion of Multiple Ascending Dose of 100 and 200 mg MK-3402 Every 8 Hours to Healthy Adult Participants. Infusions Given Over 30 Minutes, P002

Geometric Mean (%GCV)												
Panel	**Dose (mg)**	**Day**	**Cmax (µmol/L)**	**Tmax[a] (hr)**	**Ceoi (µmol/L)**	**AUC0-8 (hr*µmol/L)**	**AUC0-24 (hr*µmol/L)**	**CLss[d] (L/hr)**	**Vss[d] (L)**	**Accumulation Ratio (AR)**		
										Cmax	**AUC0-8**	**Ceoi**
A[b]	100	1	15.4 (12.9)	0.5 (0.5 – 0.5)	15.4 (12.9)	42.2 (11.3)	--	--	--	--	--	--
		8	18.6 (14.3)	0.5 (0.5 – 0.5)	18.6 (14.3)	54.6 (9.0)	163.8 (9.0)	3.90 (9.0)	20.6 (12.2)	1.21 (8.1)	1.29 (10.5)	1.21 (8.1)
B[c]	200	1	33 (16.5)	0.5 (0.5 – 0.5)	33 (16.5)	86.9 (14.2)	--	--	--	--	--	--
		15	36 (13.6)	0.5 (0.5 – 0.5)	36 (13.6)	110 (15.3)	330 (15.3)	3.88 (15.3)	20.8 (12.9)	1.09 (12.3)	1.26 (6.5)	1.09 (12.3)

Approximately N=6 per panel.
[a]Median (Min – Max)
[b] A dose of 100 mg MK-3402 administered q8 hr on Days 1-8; on Day 8 only one dose was administered (in the morning)
[c] A dose of 200 mg MK-3402 administered q8 hr on Days 1-15; on Day 15 only one dose was administered (in the morning)
[d] CLss and Vss are calculated based on steady state AUC0-8

2.3 Benefit/Risk Assessment

Participants in this clinical study will not receive direct benefit from treatment as this clinical study is designed to provide information about the safety and profile of an investigational medicine.

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

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

The study will be conducted in male and female (non-childbearing potential only) participants, 18 to 75 years of age with mild, moderate or severe renal impairment, end stage renal disease, or healthy adults.

Objectives	Endpoints
Primary	
• Objective: To compare the plasma PK (eg, AUC0-inf, Ceoi, Tmax, elimination terminal t1/2, CL, and Vd) of MK-3402 following a single IV dose in participants with varying degrees of renal impairment (mild, moderate, severe, ESRD before HD, ESRD after HD) to those of healthy matched control participants. • Estimation: MK-3402 AUC0-inf following a single IV dose of MK-3402 administered to participants with varying degrees of real impairment (mild, moderate, severe, ESRD before HD, ESRD after HD) will be estimated and compared to MK-3402 AUC0-inf when administered to healthy matched control participants.	• Plasma MK-3402 AUC0-inf, Ceoi, Tmax, elimination terminal t1/2, CL, and Vd
Secondary	
• Objective: To investigate the extent MK-3402 is removed by hemodialysis. • Estimation: The extent to which MK-3402 is removed by hemodialysis from the plasma (eg, $CL_{D,\ plasma}$) or the dialysate (eg, C_D, AE_D, AE_D (%dose), $CL_{D,\ dialysate}$) will be estimated.	• Plasma MK-3402, $CL_{D,\ plasma}$ or the dialysate (eg, C_D, AE_D, AE_D (%dose), $CL_{D,\ dialysate}$)

Objectives	Endpoints
• Objective: To compare the urine PK (eg, Ae0-24, Fe, CLr) of MK-3402 following a single IV dose of MK-3402 to participants of varying degrees of renal impairment, where possible, to those of healthy matched control participants. • Estimation: MK-3402 Ae0-24, Fe, and CLr following a single IV dose of MK-3402 administered to participants with varying degrees of renal impairment, as appropriate, will be estimated and compared to those estimated in mean healthy matched control participants.	• Urine MK-3402 Ae0-24, F3, and CLr
• Objective: To evaluate the safety and tolerability of the administration of a single IV dose MK-3402 in participants with varying degrees of renal impairment.	• Adverse events, vital signs, 12-lead electrocardiograms, laboratory safety tests
Tertiary/Exploratory	
• Objective: To explore the relationship between estimated renal clearance (eGFR and CrCl) and PK (AUC0-inf and Ceoi) of MK-3402 using a model-based approach.	• eGFR and CrCl
• Objective: To explore the relationship between genetic variation and response to the treatment(s) administered, and mechanisms of disease. Variation across the human genome may be analyzed for association with clinical data collected in the study.	• Germline genetic variation and association to clinical data collected in this study.

4 STUDY DESIGN

4.1 Overall Design

This is an open-label, single-dose study in participants with RI and healthy matched control participants. Panel A to C will include participants with mild, moderate, and severe RI, Panel D will include healthy control participants, and Panel E will include participants with ESRD undergoing HD.

Screening of participants will occur within 28 days prior to the first dose. Up to 32 adult, male and female (non-childbearing potential only) participants with RI, and at least 6 (up to 18) age- and BMI-matched healthy control adult male and female participants will be enrolled.

Study assignment to a renal function group will be as follows in Table 6.

Table 6 Renal Function Panels

Panel	Renal Function	N	eGFR mL/min/1.73 m^{2a}
A	Mild	6	60≤ eGFR <90
B	Moderate	6	30≤ eGFR <60[b]
C	Severe	6	15≤ eGFR <30 not on dialysis
D	Healthy Matched Control	≥6 (up to 18)	eGFR ≥90
E	ESRD requiring HD	6	Requiring HD

eGFR=estimated glomerular filtration rate; ESRD= end stage renal disease; HD= hemodialysis; MDRD=Modification of Diet in Renal Disease.

[a] eGFR based on MDRD equation at screening. Panels A, B, and C will have baseline eGFR will be obtained by taking the mean of the eGFR obtained from screening and from historical values within a 3-month period prior to screening. If no historical measurement is available, a second baseline eGFR sample will be taken during the screening period (≥72 hours apart) and the mean of the 2 values will be used for group assignment; the second baseline eGFR sample may be obtained at the time of check-in.

[b] Reasonable efforts will be made to enroll at least 2 participants with eGFR values of 30 to 40 mL/min/1.73 m^2.

Participants with mild (Panel A), moderate (Panel B), and severe (Panel C) RI and those with ESRD on HD (Panel E) shall be enrolled in parallel, and each panel shall enroll a minimum of 2 participants of each sex.

Panel D will be made up of at least 6 and up to 18 healthy participants. There should be a minimum of 2 participants of each sex in each panel. Participants in Panel D will have a mean age (± 15 years) and BMI (± 10%) of participants with the mild, moderate, severe RI, and participants with ESRD panels (Panels A, B, C, and E) shall be enrolled as follows:

Enrollment in Panel D will commence following the completion of enrolment of Panels A and B. Six healthy control participant will be matched to the mean age (± 15 years) and the mean BMI (± 10%) of the participants in Panels A and B combined.

The data from the already enrolled healthy participants who satisfy the mean age and BMI matching criteria of the RI participants in Panels C and E will be used. However, if any of the healthy participants do not meet the matching criteria described above, additional healthy participants will be enrolled to result in a total of 12 healthy participants who match the mean

age (± 15 years) and the mean BMI (± 10%) of Panel C and E, to be assessed independently. The sex of the additional healthy participant(s) will be selected to ensure that there is a minimum of 2 participants of each sex in the group of participants within Panel D who match with Panels C and E.

The PK comparisons between each RI panel (Panels A, B, C, and E) and healthy controls will include only the control participants who meet the matching criteria for the respective RI panel.

In all Panels, MK-3402 will be administered IV over approximately 30 minutes.

Participants in Panels A, B, C, and D will receive a single IV dose of MK-3402. Plasma samples will be taken at prespecified time points up to 48 hours (Panels A, B, C and D) and urine samples will be taken at prespecified time points up to 24 hours postdose, where possible, for PK assessment of MK-3402.

Participants in Panel E will receive a single IV dose of MK-3402 on 2 separate occasions. In Period 1, participants will receive a single IV dose of MK-3402 immediately following completion of their normally scheduled HD, followed by 48-hours plasma and 24-hours urine sampling, where possible, for PK assessment of MK-3402.

In Period 2, participants will receive a single IV dose of MK-3402 approximately 30 minutes prior to their normally scheduled HD followed by 48-hours plasma and 12-hours urine sampling, where possible, for PK assessment of MK-3402. During this dialysis session, additional plasma and dialysate samples will be taken for MK-3402 analysis.

There will be a washout period of at least 6 days between MK-3402 dosing in Periods 1 and 2 of Panel E.

Because this is a Phase 1 assessment of MK-3402 in humans, the PK, pharmacodynamic, and safety profiles of the compound are still being elucidated. This protocol is therefore written with flexibility to accommodate the inherent dynamic nature of Phase 1 clinical studies. Refer to Section 8.10.6 for examples of modifications permitted within the protocol parameters.

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

4.2 Scientific Rationale for Study Design

MK-3402 is likely to be used in patients with various degrees of RI, as a proportion of patients with serious gram-negative infections have baseline RI, and also patients can develop acute renal failure in the setting of gram-negative sepsis. The primary purpose of this trial is to understand the effect of RI on the pharmacokinetics of MK-3402 in order to guide dosing recommendations in these patients.

CLr is expected to be the major elimination pathway for MK-3402. Parameter estimates were obtained from an interim PK analysis, indicating that ~ 60% of MK-3402 is excreted in the urine following a single IV dose. The potential effect of RI on single-dose PK will be a reduction in clearance, thereby increasing the terminal t1/2 and AUC. A change in the Cmax following a single dose is not anticipated. However, these predictions do not take into consideration of the potential contribution from non-renal elimination (e.g. hepatic elimination), which might involve in the elimination of MK-3402. It is noted that the potential for RI to affect the non-renal clearance of compounds like MK-3402 cannot be ruled out.

Due to the projected impact of RI on MK-3402 PK, a PK study design was selected that will enable the estimation of effect across the spectrum of RI, in order to inform dose adjustments which may be needed in each of mild, moderate, and severe RI, as well as the establishment of recommendations for dosing with respect to HD.

Plasma protein binding is often altered in patients with impaired renal function and is assessed in some instances in renal insufficiency trials. However, this study will not assess plasma protein binding due to the low to moderate protein binding seen in vitro and that binding is not concentration dependent in the clinically relevant concentration range.

MK-3402 will be administered in a fasted state. It is recognized that food will likely have minimal impact on the PK of an IV administered drug. However, food may have systemic effects, in particular on drug metabolizing enzymes. As such, study drug will be administered in the fasted state in order to reduce variability.

Given the limited developmental and reproductive toxicity data available for MK-3402, enrollment shall be restricted to adult males and females of nonchildbearing potential who meet the study's eligibility criteria. Healthy participants and participants with RI, but not patients with acute bacterial infection (the target patient population), will be enrolled to allow the assessment of PK, safety, and tolerability of MK-3402; these assessments may be confounded in the presence of active infection.

4.2.1 Rationale for Endpoints

4.2.1.1 Pharmacokinetic Endpoints

Pharmacokinetic parameters selected for evaluation in this study will effectively inform the pharmacokinetic profile of MK-3402 and include the following: AUC0-inf, Ceoi, Tmax, terminal elimination t1/2, CL, Vd, Ae0-24 hr, Fe, and CLr.

4.2.1.2 Safety Endpoints

Preclinical and clinical assessments to date have not identified any safety signals of concern. As such, standard safety monitoring will be implemented consisting of physical examinations, VS assessments, ECG evaluations, adverse event assessments, and blood/urine laboratory assessments. Due to preclinical ECG safety findings in one rhesus monkey, 1 minute cardiac monitoring is implemented at Cmax for additional assessment.

4.2.1.3 Planned Exploratory Biomarker Research

4.2.1.3.1 Planned Genetic Analysis

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

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

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

4.2.1.4 Future Biomedical Research

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

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for FBR is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure participants receive the correct dose of the correct drug/vaccine at the correct time. The details of FBR are presented in Appendix 6.

4.2.2 Rationale for Control

Healthy participants with normal renal function, matched by mean age, mean BMI, and sex, will serve as the control group. Comparison of data from participants with renal impairment to data from healthy participants will effectively inform the differences of safety and PK between the 2 groups.

4.3 Justification for Dose

To determine the PK parameter that is most relevant to efficacy, in vitro hollow fiber studies that incorporated β-lactamase (IMP, VIM, and NDM)-producing, imipenem-resistant *P. aeruginosa* and Enterobacterales strains were conducted to evaluate the bacterial log reduction in relation to PK data from the hollow fiber studies. PK/PD analysis of hollow fiber

data showed that the PK/PD driver was determined as the unbound AUC0-24hr over the MIC (*f*AUC/MIC), where the MIC is the MIC of the strain for the antibacterial agent in the presence of REL and MK-3402; the *f*AUC/MIC PK/PD target is 2.3 when co-administered with cefepime for 1-log kill and 3.3 for 2-log kill. The *f*AUC/MIC PK/PD target is 3.9 when coadministered with imipenem for 1-log kill and 4.5 for 2-log kill. Assuming 50% lung penetration in human, the plasma PK/PD target is 9 when coadministered with imipenem for HABP/VABP.

The PK/PD target for MK-3402 in combination with cefepime and REL was estimated in a mouse thigh infection model using cefepime-resistant *P. aeruginosa*. The PK/PD target for MK-3402 in combination with IMI and REL is being evaluated in a mouse lung infection model using imipenem-resistant *P. aeruginosa*. Based on a preliminary analysis of the mouse thigh model data, the PK/PD driver was confirmed to be *f*AUC/MIC with the magnitude of approximately 2 to achieve 1-log kill when administered with cefepime and REL with a human-simulated regimen.

The preliminary Monte Carlo simulations using human PK data from the initial Phase 1 study and the available PK/PD data (hollow fiber and mouse thigh infection model) identify that a MK-3402 dose of ≥ 75 mg every 6 hours is expected to achieve >90% target attainment at PK/PD target of *f*AUC/MIC=3 in combination with cefepime and *f*AUC/MIC=9 in combination with imipenem. Considering the potential changes of PK target, 100 mg was selected as the dose of MK-3402 in this study.

MK-3402 was observed to be eliminated predominantly through renal elimination (~ 60%) and participants with renal insufficiency are projected to attain higher exposures relative to participants with normal renal function due to decreased CLr. It is assumed that there is generally a linear relationship between eGFR and CLr which will impact the terminal t1/2 and AUC, as shown in the table below. Projections have been based on the preliminary PK analysis of the single ascending dose study. Of note, it is difficult to provide accurate estimates for ESRD, due to the severity of the illness. One assumption made when estimating the parameter values is that Vd does not change with decease of renal function. Clinical safety data are available up to 600 mg delivered as a single dose and 1100 mg delivered as a divided dose which have been generally well tolerated with AUC0-inf of 655 µM•hr at the 1100-mg dose. These doses are projected to provide a greater than 6.7x exposure margin for the 100-mg proposed dose in ESRD (not on dialysis) patients and a 12.9x exposure margin in healthy participants.

Regarding the 1-month MK-3402/REL combination toxicity study (as discussed above), at the NOEL dose (20 mg/kg/day MK-3402 + 50 mg/kg/day REL), the exposures and safety margins to 100 mg dose of MK-3402 to be administered in the current study (P004; projected for ESRD participants not on dialysis) are $AUC_{0\text{-}24hr}$= 253 µM.hr (2.6X) and C_{max}= 76 µM (5.1X) [Table 7].

Table 7 MK-3402 Systemic Exposure Multiples Between Monkeys in the 1-Month Combination Toxicity Study with REL (TT#20-1000) and Projected Human Exposure at 100 mg in P004

1-month IV Combination Tox Study in Monkeys	AUC µM.hr	Exposure Multiple[a]	Cmax µM	Exposure Multiple[a]
Control				
MK-3402 Placebo	0		0	
Low Dose (LD)				
MK-3402 20 mg/kg/day	253	2.6X	76	5.1X
High Dose (HD)				
MK-3402 50 mg/kg/day	633	6.5X	184	12.4X
a. Exposure margins are calculated to the projected exposure at the maximum protocol-specified dose of MK-3402 (100 mg, 30 min IV infusion, $AUC_{0\text{-}inf}$ of 98 µM.hr, C_{max} 14.8 µM) in ESRD participants not on dialysis. Plasma protein binding is similar between species, with similar % unbound for MK-3402 (78% in monkeys and 68% in humans).				

No treatment-related ECG-findings have been observed in nonclinical studies in rhesus monkeys at significantly higher doses for MK-3402 alone (exposures in monkeys up to 550 mg/kg/day: $AUC_{0\text{-}24hr}$= 7210 µM.hr, 74X and C_{max}=1940 µM, 131X relative to the projected exposure at 100 mg).

Single dose PK are anticipated to be predictive of multiple dose PK; accumulation is expected to be modest, with an accumulation ratio of ~ 1.3 in healthy participants. As this is a Phase 1 assessment of MK-3402 in humans, and the PK, pharmacodynamic and safety profiles of the compound are still being evaluated, modifications to the dose or dosing regimen may be required to achieve the scientific goals of the study objectives and/or to ensure appropriate safety monitoring of the study participants. Details of allowed modifications are provided in Section 8.10.6.

Subgroup	eGFR (mL/min)	CL (L/hr)	AUC0-inf (µM•hr)	Half-life (hr)
Normal	>90	4.18	50.9	4.47
Mild	60-89	3.17	67.1	5.89
Moderate	30-59	2.57	82.8	7.27
Severe	15-29	2.42	87.9	7.72
ESRD (not on dialysis)	<15	2.17	98.0	8.61
All parameter estimates are based on interim model results.				

4.3.1 Rationale for Dose Interval

For Panels A to D, a single dose of MK-3402 will be administered. For Panel E, participants will be administered 2 separate doses of MK-3402, one prior to HD and one after HD which will occur after a washout interval of 6 days. The t1/2 of MK-3402 is estimated to be ~ 4 hours in participants with normal renal function. It is unknown the extent to which HD clears MK-3402; however, based on a compound with a similar pathway of elimination, increases on the order of 3-fold have been observed. In addition, HD removed ~ 50% of the drug. As such, the proposed washout interval of 6 days along with HD should provide a sufficient interval of time for appropriate PK assessment in Period 2 without carryover.

For each of the Panels, participants will be administered trial drug as scheduled per the clinical study unit. There are no requirements regarding the interval between dosing of participants. As noted above, MK-3402 has been clinically evaluated up to 600 mg administered as single doses and up to 1100 mg as a divided dose. There were no safety signals of concern identified. There will be frequent, careful assessments of AEs throughout the postdose period. This recommendation is in keeping with the projected safety profile and the ability of the Phase 1 unit to monitor each participant closely.

4.4 Beginning and End-of-Study Definition

The overall study begins when the first participant (or their legally authorized representative) 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 (ie, the participant is unable to be contacted by the investigator).

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

4.4.1 Clinical Criteria for Early Study Termination

There are no prespecified criterial for terminating the trial early.

5 STUDY POPULATION

Male/female participants with mild, moderate, or severe renal impairment, end stage renal disease, or healthy matched adults between the ages of 18 and 75 years (inclusive) will be enrolled in this study.

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

5.1 Inclusion Criteria

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

Type of Participant and Disease Characteristics

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

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

Demographics

3. Has a BMI ≥18 kg/m^2 and ≤40 kg/m^2. See Section 8.3.1 for criteria on rounding to the nearest whole number. BMI = weight (kg)/height $(m)^2$.

   Panel D: BMI must be within ± 10% of the mean BMI of participants within the RI panel(s) to which the participant is matched.

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

   Panel D: Age must be within ± 15 years of the mean age of participants within the RI panel(s) to which the participant is matched.

Male Participants

5. Male participants are eligible to participate if they agree to the following during the intervention period and for at least 90 days after the last dose of study intervention:

- Refrain from donating sperm

  PLUS either:

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent

OR

- Must agree to use contraception unless confirmed to be azoospermic (vasectomized or secondary to medical cause [Appendix 5]) as detailed below:

  - Agree to use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant. Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile-vaginal penetration.

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

Female Participants

6. A female participant is eligible to participate if:

   - She is a WONCBP, as defined in Appendix 5.

Informed Consent

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

Additional Categories

8. **Panel A:** Has a baseline eGFR ≥60 and <90 mL/min/1.73 m^2 based on the MDRD equation.

9. **Panel B**: Has a baseline eGFR ≥30 and <60 mL/min/1.73 m^2 based on the MDRD equation. Reasonable efforts will be made to enroll at least 2 participants with eGFR values between 30 and 45 mL/min/1.73 m^2.

10. **Panel C:** Has a baseline eGFR ≥15 and <30 mL/min/1.73 m^2 based on the MDRD equation.

11. **Panels A, B and C:** Has had no clinically significant change in renal status at least 1 month prior to dosing and is not currently receiving or has not previously been on hemodialysis.

12. **Panel D:** Has an eGFR ≥90 mL/min/1.73 m^2 based on the MDRD equation.

13. **Panel E:** Has ESRD and maintained on a stable regimen of at least three times per week HD for at least 3 months prior to first dosing.

MDRD Equation:

eGFR (mL/min/1.73 m^2) =
175 x (serum creatinine)$^{-1.154}$ x (age)$^{-0.203}$ x (0.742 [if female]) x (1.212 [if Black or African American])

Panels, A, B and C: Baseline eGFR will be obtained by taking the mean of the eGFR obtained from screening and from historical values within a 3-month period prior to screening. If no historical measurement is available, a second baseline eGFR sample will be taken during the screening period (≥72 hours apart) and the mean of the 2 values will be used for group assignment; the second baseline eGFR sample may be obtained at the time of check-in.

5.2 Exclusion Criteria

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

Medical Conditions

1. **Panels A, B, C and E:** Has a history of any clinically significant concomitant disease or condition (including treatment for such conditions) or diseases whose current condition is considered clinically unstable that, in the opinion of the investigator, could either interfere with the study drug, compromise interpretation of study data, or pose an unacceptable risk to the patient.

2. **Panel D:** Has a history of clinically significant endocrine, GI, cardiovascular, hematological, hepatic, immunological, renal, respiratory, genitourinary, or major neurological (including stroke and chronic seizures) abnormalities or diseases. Participants with a remote history of uncomplicated medical events (eg, uncomplicated kidney stones, as defined as spontaneous passage and no recurrence in the last 5 years, or childhood asthma) may be enrolled in the study at the discretion of the investigator.

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

4. Has a history of cancer (malignancy).

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

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

6. Is positive for HBsAg, hepatitis C antibodies or HIV.

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

Prior/Concomitant Therapy

8. **Panels A, B, C and E:** Is unable to refrain from or anticipates the use of any medication, including prescription and nonprescription drugs or herbal remedies as indicated in Section 6.5 for the prohibited time period.

9. **Panel D:** Is unable to refrain from or anticipates the use of any medication, including prescription and nonprescription drugs or herbal remedies beginning approximately 2 weeks (or 5 half-lives) prior to administration of the initial dose of study drug, throughout the study (including washout intervals between treatment periods), until the poststudy visit. There may be certain medications that are permitted (see Section 6.5).

Prior/Concurrent Clinical Study Experience

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

Diagnostic Assessments

11. Has a QTc interval ≥470 msec (for males) or ≥480 msec (for females).

Other Exclusions

12. Is under the age of legal consent.

13. **Panels A, B, C, and E:** Does not agree to follow the smoking restrictions as defined by the CRU.

14. **Panel D:** Is a smoker and/or has used nicotine or nicotine-containing products (eg, nicotine patch and electronic cigarette) within 3 months of screening.

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

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

17. Is a regular user of any illicit drugs or has a history of drug (including alcohol) abuse within approximately 1 years. Participants must have a negative drug screen prior to randomization.

18. Is unwilling to comply with study restrictions.

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

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

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

5.3.1.1 Diet Restrictions

In each treatment period, participants will fast from all food and drink, except water, for at least 8 hours before study drug administration and at least 1 hour after trial drug administration. Meals and snack(s) will be provided by the investigator at approximately 4 and 10 hours postdose, a snack will be offered at 5 to 7 and 12 to 14 hours postdose in Panels A, B, C, D and E, Period 2. Meals and snack(s) will be provided by the investigator at approximately 1 and approximately 7 hours postdose, a snack will be offered at 2- to 4- and 9-to 11-hours postdose in Panel E, Period 1.

Participants will fast from all food and drink except water between meals and snacks. After the 24-hour postdose procedures have been completed, subsequent meals and snacks will be unrestricted in caloric content, composition and timing.

Instructions on whether to take MK-3402 with or without food and/or drink may be modified during the study based on newly available data.

Laboratory safety blood tests will be performed after at least an 8-hour fast; however, in case of discontinuations or rechecks, a non-fasting assessment may be performed at the discretion of the Investigator.

5.3.1.2 Fruit Juice Restrictions

Participants will refrain from the consumption of grapefruit juice, grapefruits, and grapefruit products beginning approximately 2 weeks before administration of the initial dose of study drug, throughout the study including the washout interval between treatment periods (Panel E) and until the poststudy visit.

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

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

5.3.2.1 Caffeine Restrictions

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

5.3.2.2 Alcohol Restrictions

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

5.3.2.3 Tobacco Restrictions

Panel D only: Smoking (and/or the use of nicotine/nicotine-containing products) is not permitted during the study.

Panels A, B, C, and E: Participants will follow the smoking restrictions (and if applicable, the use of nicotine/nicotine-containing products) defined by the CRU.

5.3.3 Activity Restrictions

Participants will avoid unaccustomed strenuous physical activity (ie, weightlifting, running, bicycling, etc) from the prestudy (screening) visit and until the poststudy visit.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen-failure information may be included, as outlined in the eCRF entry guidelines. Minimal information may include demography, screen-failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements.

5.5 Participant Replacement Strategy

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

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

6 STUDY INTERVENTION

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

Study intervention will be administered by the investigator and/or study staff according to the specification within the study operations manual.

6.1 Study Intervention(s) Administered

The study intervention(s) to be used in this study is outlined in Table 8.

Table 8 Study Interventions

Arm Name	Arm Type	Intervention Name	Inter-vention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Admini-stration	Treatment Period	Use	IMP/ NIMP	Sourcing
All Participants	Experi mental	MK-3402	Drug	Sterile Solution	10 mg/mL	100 mg	IV Infusion	Panels A to D: Day 1 Panel E: Day 1 in Periods 1 and 2	Experi mental	IMP	Provided Centrally by the Sponsor

EEA =European Economic Area; IMP=investigational medicinal product; NIMP=noninvestigational medicinal product.

The classification of IMP and NIMP in this table is based on guidance issued by the European Commission and applies to countries in the EEA. Country differences with respect to the definition/classification of IMP/NIMP may exist. In these circumstances, local legislation is followed.

All supplies indicated in Table 8 will be provided per the "Sourcing" column depending on local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number where possible (eg, not applicable in the case where multiple lots or batches may be required due to the length of the study, etc).

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

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

Specific calculations or evaluations required to be performed to administer the proper dose to each participant are outlined in a separate document provided by the Sponsor. The rationale for selection of doses to be used in this study is in Section 4.3.

6.2.2 Handling, Storage, and Accountability

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

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

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

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

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

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Participants will be assigned an allocation number for a single treatment using the allocation schedule shown in Table 9.

Table 9 Allocation of Participants to Treatment

Panel	Impairment Stage	n	Treatment
A	Mild RI	6	Single IV dose of MK-3402 100 mg
B	Moderate RI	6	Single IV dose of MK-3402 100 mg
C	Severe RI	6	Single IV dose of MK-3402 100 mg
D	Healthy Control	Up to 18	Single IV dose of MK-3402 100 mg
E	ESRD	6	Single IV dose of MK-3402 100 mg for 2 periods
ESRD=end stage renal disease; IV= intravenous; n=sample size; RI=renal impairment			

Participants in this study will be allocated by nonrandom assignment.

6.3.2 Stratification

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

6.3.3 Blinding

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

6.4 Study Intervention Compliance

Interruptions from the protocol-specified treatment plan require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant ID will be confirmed at the time of dosing by a member of the study-site staff other than the person administering the study intervention.

6.5 Concomitant Therapy

Panel D only

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

Concurrent use of any prescription or nonprescription medication, or concurrent vaccination, during the ongoing study (ie, after intervention allocation) must first be discussed between the investigator and Sponsor before administration, unless appropriate medical care necessitates that therapy or vaccination should begin before the investigator and Sponsor can consult. The participant will be allowed to continue in the study if both the Sponsor and the investigator agree.

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

Panels A, B, C, and E

Medications specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medications specifically prohibited, discontinuation from study intervention may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

All prescription or non-prescription medications (including St. John's wort) that are strong inhibitors or strong inducers of CYP3A enzymes, or inhibitors of OATP1B1/1B3 transporters will be prohibited. These enzyme/transporter inhibitors and inducers will not be allowed for at least 14 days and 28 days respectively prior to first dosing and throughout the study. Moderate and weak CYP3A inhibitors or inducers may be deemed acceptable following consultation with the Sponsor Clinical Monitor and the investigator.

Participants who are taking certain prescription medications to treat manifestations of renal disease or medications needed to treat stable diseases (eg, angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists, beta-blockers, diuretics) may be allowed to participate in the study at the discretion of the investigator and following consultation with the Sponsor Clinical Monitor. Participants must be on a stable regimen for at least 2 weeks (or 5 half-lives of the concomitant medication, whichever is longer) prior to dosing and be able to withhold the use 4 hours prior to and 4 hours postdose of study drug. If a participant is prescribed prohibited medication, upon discussion between the Sponsor and the investigator, the investigator may substitute the previously prescribed medication to an allowed one for the purpose of this study.

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

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements or other specific categories of interest) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Sponsor Clinical Director should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1 Rescue Medications and Supportive Care

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

CRUs will be staffed with medically trained personnel with appropriate access to full service acute-care hospitals to facilitate rapid institution of medical intervention.

6.6 Dose Modification (Escalation/Titration/Other)

See Section 8.10.6 for modifications permitted within protocol parameters.

6.6.1 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 investigator), a substantial amendment will be submitted for approval.

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

2. Two (2) or more participants within a Panel (at the same dose level) report Severe Nonserious AEs considered related to the study intervention by the investigator.

If the below stopping rule is met, the study will be paused and no further dosing will occur until the data have been reviewed by a cardiologist. The study may continue at either the planned dose or a lower dose based on the cardiologist review and upon agreement of the Sponsor and investigator.

- An individual shows evidence of complete heart block (i.e., 3rd degree AV block) in 12-lead ECG or 1-minute ECG after study drug administration.

6.7 Intervention After the End of the Study

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

6.8 Clinical Supplies Disclosure

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

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

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

Panel E: Discontinuation of study intervention does not represent withdrawal from the study.

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention before completion of the protocol-specified treatment period/vaccination regimen will still continue to participate in the study as specified in Section 1.3 and Section 8.10.3.

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study intervention discontinuation are provided in Section 8.1.9 and Section 8.10.3.

A participant must be discontinued from study intervention, but continue to be monitored in the study, for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The participant has a confirmed positive serum pregnancy test.
- The participant has a positive drug screen at any time during the course of the study. The drug screen can be confirmed by a recheck at the discretion of the investigator after discussion with the Sponsor.

7.2 Participant Withdrawal From the Study

A participant must be withdrawn from the study if the participant or participant's legally acceptable representative withdraws consent from the study.

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

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

7.3 Lost to Follow-up

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

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.
- Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the prespecified statistical data handling and analysis guidelines.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study-site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All study-related medical decisions must be made by an investigator who is a qualified physician.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be used for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

The maximum amount of blood collected from each participant over the duration of the study will not exceed 99 mL for Panels A to D and 223 mL for Panel E (Appendix 8).

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

8.1 Administrative and General Procedures

8.1.1 Informed Consent

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

8.1.1.1 General Informed Consent

Informed consent by the participant or their legally acceptable representative 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 (or his/her legally acceptable representative) and of the person conducting the consent discussion.

A copy of the signed and dated informed consent form should be given to the participant (or their legally acceptable representative) before participation in the study.

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

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

8.1.2 Inclusion/Exclusion Criteria

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

8.1.3 Participant Identification Card

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

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

8.1.4 Medical History

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

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review before medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 2 weeks before first dose of study intervention.

8.1.5.2 Concomitant Medications

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

8.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur before intervention allocation. Each participant will be assigned only 1 screening number. Screening numbers must not be reused for different participants.

8.1.7 Assignment of Treatment/Randomization Number

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

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

8.1.8 Study Intervention Administration

Study intervention(s) will be administered by the investigator and/or study staff according to the specifications within the study operations manual.

8.1.8.1 Timing of Dose Administration

MK-3402 solutions for IV infusion will be prepared per instructions in the Study Operations manual and dosed in the morning.

8.1.9 Discontinuation and Withdrawal

The investigator or study coordinator must notify the Sponsor when a participant has been discontinued/withdrawn from the study and/or intervention. If a participant discontinues for any reason at any time during the course of the study and/or intervention, the participant may be asked to return to the clinic (or be contacted) for a poststudy visit as per the number of days described in Section 8.10.4 to have the applicable procedures conducted. However, the investigator may decide to perform the poststudy procedures at the time of discontinuation or as soon as possible after discontinuation. If the poststudy visit occurs prior to the safety follow-up time frame as specified in Section 8.4.1, the investigator should perform a follow-up telephone call at the end of the follow-up period (Section 8.4.1) to confirm if any AEs have occurred since the poststudy clinic visit. Any AEs that are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.9.1 Withdrawal From Future Biomedical Research

Participants may withdraw their consent for FBR. Participants may withdraw consent at any time by contacting the investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the participant's consent for FBR will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the participant of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed 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 main study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main study records) or the specimens have been completely anonymized, there will no longer be a link between the participant's personal information and their specimens. In this situation, the request for specimen withdrawal cannot be processed.

8.1.10 Participant Blinding/Unblinding

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

8.1.11 Domiciling

Participants will report to the CRU the evening before the scheduled day of study intervention administration for each treatment period and remain in the unit until 24 hours postdose. At the discretion of the investigator, participants may be requested to remain in the CRU longer.

8.1.12 Calibration of Equipment

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

8.2 Efficacy/Immunogenicity Assessments

There are no direct efficacy assessments in this study.

8.3 Safety Assessments

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

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

8.3.1 Physical Examinations

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

BMI

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

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

8.3.2 Vital Signs

- BP and HR measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- VS measurements should be taken before blood collection for laboratory tests.

8.3.2.1 Resting Vital Signs

Vital Sign Measurements (Heart Rate and Blood Pressure)

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

The predose (baseline) HR and BP will be triplicate measurements, obtained at least 1 to 2 minutes apart within 3 hours of dosing MK-3402 for Panels A, B, C, D, and E, Period 2. The predose (baseline) HR and BP will be triplicate measurements, obtained at least 1 to 2 minutes apart within 6 hours of dosing MK-3402 for Panel E, Period 1. The mean of these measurements will be used as the baseline to calculate change from baseline for safety evaluations (and for rechecks, if needed). Postdose VS measurements will be single measurements.

Body Temperature

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

8.3.3 Electrocardiograms

- All 12-lead ECG will be obtained and reviewed by an investigator or medically qualified designee (consistent with local requirements) as outlined in the SoA using an ECG machine that automatically calculates the HR and measures PR, QRS, QT, and [QTc] intervals. For Panel D, refer to Appendix 9 for evaluation and withdrawal criteria and additional [QTc] readings that may be necessary. For Panels A, B, C, and E, abnormalities will be evaluated by the investigator.

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

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

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

The correction formula to be used for QTc is Fridericia.

If repeat ECGs are required, the clinical site will decide whether to leave the electrodes in place or mark the position of the electrodes for subsequent ECGs. To mark the position of the

electrodes, 12-lead electrode sites will be marked on the skin of each participant with an ECG skin-marker pen to ensure reproducible electrode placement.

Predose ECGs will be obtained in triplicate at least 1 to 2 minutes apart within 3 hours before dosing MK-3402 in Panels A, B, C, D and E, Period 2. Predose ECGs will be obtained in triplicate at least 1 to 2 minutes apart within 6 hours before dosing MK-3402 in Panel E Period 1. The mean of these measurements will be used as the baseline to calculate change from baseline for safety evaluations (and for rechecks, if needed). In addition, a 1 minute ECG limited lead rhythm strip will be collected as specified on the SoA and as per site SOP.

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

During each treatment period, if a participant demonstrates a QTc interval ≥500 msec on a postdose ECG, the ECG will be repeated twice within 5 minutes. The mean value of the QTc interval from the 3 ECGs will represent the value at that time point. If the mean QTc interval is ≥500 msec, the Sponsor should be notified and the ECGs should be reviewed by a cardiologist. The participant should be telemetry monitored (until the QTc is <500 msec) or should be considered for transfer to a location where closer monitoring and definitive care (eg, a CCU or ICU) is available.

If the QRS duration from any postdose ECG is 20% greater than the mean baseline QRS duration and is >120 msec (and change is not considered rate related or pacing induced) or there appears to be new onset intermittent bundle branch block, then the ECG will be immediately repeated twice within 5 minutes. The mean value of the QRS interval from the 3 ECGs will represent the value at that time point. If the mean OR median QRS interval increase from baseline for any postdose time point is >20%, the participant will continue to be monitored by repeat 12-lead ECGs every 15 minutes for at least 1 hour or until the QRS is within 20% of baseline. If a >20% prolongation of the QRS interval persists, a consultation with a cardiologist may be appropriate and the Sponsor should be notified.

If at any time the QRS duration is prolonged ≥200 msec (and change is not considered rate related or pacing induced), then the Sponsor should be notified. The ECGs should be reviewed by a cardiologist and the participant should be considered for transfer to a location where closer monitoring and definitive care (eg, a CCU or ICU) is available.

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

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

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

8.3.4 Clinical Safety Laboratory Assessments

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

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

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

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

- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 14 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

8.3.5 Photograph of Rash

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

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

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

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

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

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

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

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

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

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

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

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 10.

Table 10 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

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

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

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

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

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

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

8.4.4 Regulatory Reporting Requirements for SAE

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

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

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

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

8.4.5 Pregnancy and Exposure During Breastfeeding

Information in this section is not applicable since participants are WONCBP or males and partner pregnancy/lactation information is not required.

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

Not Applicable.

8.4.7 Events of Clinical Interest

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

Events of clinical interest for this study include:

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

13. An elevated AST or ALT laboratory value that is greater than or equal to 3X the 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 must trigger an additional evaluation for an underlying etiology. The study-site guidance for assessment and follow up of these criteria can be found in the Investigator Study File Binder (or equivalent).

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

8.5 Treatment of Overdose

For purposes of this study, an overdose will be defined as any dose of any drug administered as part of the study exceeding the dose prescribed by the protocol. It is up to the investigator or the reporting physician to decide whether a dose is to be considered an overdose, in consultation with the Sponsor.

8.6 Pharmacokinetics

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

8.6.1 Blood Collection for Plasma MK-3402

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

8.6.2 Urine Collection for Urinary MK-3402

Sample collection, processing, storage and shipment instructions for urine samples will be provided in the study operations manual. For participants with RI, urine samples will be collected whenever possible, as participants may not be able to produce urine at each interval. For participants who are anuric, urine samples will not be collected.

8.6.3 Dialysate Collection (Panel E, Period 2)

For ESRD participants only, sample collection, processing, storage and shipment instructions for plasma samples will be provided in the study operations manual.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Biomarkers

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

- Blood for genetic analysis

8.8.1 Planned Genetic Analysis Sample Collection

The planned genetic analysis sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at the site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for FBR if the participant provides documented informed consent for FBR. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.

Sample collection, storage, and shipment instructions for planned genetic analysis samples will be in the Operations/Laboratory Manual.

8.9 Future Biomedical Research Sample Collection

If the participant provides documented informed consent for FBR, the following specimens will be obtained as part of FBR:

- Leftover DNA for future research

8.10 Visit Requirements

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

8.10.1 Screening

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

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

8.10.2 Treatment Period

Following confirmation that each participant meets inclusion/exclusion criteria and that all predose procedures have been completed, participants will be assigned a unique allocation number associated with a specific treatment sequence as defined by a computer allocation schedule.

Before each treatment, participants will report to the CRU on Day -1 or at a time specified by the investigator. Participants will fast from all food and drink except for water, for a at least 8 hours before study drug administration and at least 1 hour after study drug administration (refer to Section 5.3.1 for specific dietary restrictions during dosing).

Participants will remain in the CRU up to 24 hours postdose. Participants may be required to remain in the CRU for longer than 24-hours postdose at the discretion of the investigator.

Participants in Panels A to D will be administered the assigned treatment in the morning. The exact clock time of dosing should be recorded.

ESRD participants on HD (Panel E) will receive HD as per their regular schedule and blood and dialysate sampling be collected as outlined in the SoA (Section 1.3).

Dosing in Period 1 will occur immediately following completion of a normally scheduled HD session. Panel E will have a washout period of at least 6 days between the dosing of study drug in each treatment period. Dosing in Period 2 will occur approximately 30 minutes prior to the normally scheduled HD session. The subsequent HD session should initiate immediately following the 30-minute blood draw, VS and ECG.

In Period 2, the HD period will be approximately 4 hours for all participants. Blood samples collected during HD will be collected from both the pre-dialyzer and post-dialyzer blood lines.

The blood flow, dialysate flow, and the make and model of the dialyzer will be recorded.

8.10.3 Discontinued Participants Continuing to be Monitored in the Study

At any point if a participant discontinues from treatment (Panel E) but continues to be monitored in the study, a subset of study procedures specified in the SoA may be completed at the discretion of the investigator and with Sponsor agreement. The subset of study procedures completed will be communicated in a PCL.

8.10.4 Poststudy

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

8.10.5 Critical Procedures Based on Study Objectives: Timing of Procedure

For this study, the blood sample for MK-3402 is the critical procedure.

At any postdose time point, the blood sample for MK-3402 needs to be collected as close to the exact time point as possible. The sample at 0.5-hour blood sample should be collected as close as possible to end of infusion. All other procedures should be completed as close to the prescribed/scheduled time as possible. Study procedures can be performed prior or after the prescribed/scheduled time.

The order of priority can be changed during the study with joint agreement of the investigator and the Sponsor Clinical Director.

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

The following variance in procedure collection times will be permitted.

- PK Collection as outlined in Table 11.

Table 11 Pharmacokinetic (Blood/Urine) Collection Windows

PK Collection	PK Collection Window
0 - <1 hour	5 min; The 30 minute samples taken after the infusion will have window of 15 minutes.
1 - <24 hour	15 minute
24 - 48 hour	1 hour

- Predose standard safety evaluations:
  - VS and ECG up to 3 hours (Panels, A, B, C, D and E, Period 2)
  - VS and ECG up to 6 hours (Panel E, Period 1)
  - Laboratory safety tests up to 72 hours predose to confirm eligibility at Visit 1 and 24 hours for Panel E, Period 2
  - Physical exam up to 24 hours
- Postdose standard safety evaluations: VS, ECG, laboratory safety tests, and physical exam
  - <24-hour postdose may be obtained within 15 minutes of the theoretical sampling time
  - 24 hour to <48-hour postdose may be obtained within 1 hour of the theoretical sampling time
- Study intervention administration: IV infusion should take 30 minutes (± 5 minutes)

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

This is a Phase 1 assessment of MK-3402 in humans, and the PK, pharmacodynamic, and safety profiles of the compound are still being elucidated. This protocol is written with some flexibility to accommodate the inherent dynamic nature of Phase 1 clinical studies. Modifications to the dose, dosing regimen, and/or clinical or laboratory procedures currently outlined may be required to achieve the scientific goals of the study objectives and/or to ensure appropriate safety monitoring of the study participants.

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

- Decrease in the dose of the study intervention administered in any given panel(s) or period(s)
- Entire period(s) or panel(s) may be omitted
- Adjustment of the dosing interval (eg, divided doses [bid to qd, qd to bid, tid, or vice versa])
- Lengthening of the washout period between doses
- Instructions to take study intervention 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 to another panel or period

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

Up to additional 50 mL of blood may be drawn for safety, PK, and/or pharmacodynamic analyses. The total blood volume withdrawn from any single participant will not exceed the maximum allowable volume during his/her participation in the entire study (Appendix 8).

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

It is understood that the current study may 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 investigator for retention. The letter may be forwarded to the IRB/IEC at the discretion of the investigator.

9 STATISTICAL ANALYSIS PLAN

9.1 Statistical Analysis Plan Summary

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

Primary PK analysis

If a different group of healthy matched control participants are needed to match the mean age and BMI for the RI and ESRD groups, then separate analyses will be performed for the populations as follows:

- Mild RI and moderate RI versus an appropriate group of healthy matched control participants;

- Severe RI versus an appropriate group of healthy matched control participants;

- ESRD participants (non-HD and HD) versus an appropriate group of healthy matched control participants.

If a single set of healthy matched control participants can be used for comparison with all RI and ESRD groups, the following analysis pooled over all populations will be used.

Separately for each PK parameter, individual values of plasma MK-3402 AUC0-inf and Ceoi will be natural log-transformed and evaluated with a linear fixed-effects model containing a categorical effect for populations. The REPEATED statement with the GROUP=Population option will be used in SAS PROC MIXED to estimate separate variances for each population. The Kenward and Roger adjustment will be used to calculate the denominator degrees of freedom for the fixed-effect (DDFM=KR).

Ninety-five percent (95%) CIs for the least squares means for each population will be constructed on the natural log scale and will reference the t-distribution. Exponentiating the least-squares means and their corresponding 95% CIs will yield estimates for the population geometric means and CIs about the geometric means on the original scale.

To compare participants with RI in each of the renal categories (mild RI, moderate RI, severe RI, ESRD non-HD and ESRD HD) to matching participants with normal renal function, a 2-sided 90% confidence interval for the true difference in means (RI-normal renal function) will be calculated for each PK parameters (AUC0-inf and Ceoi) using the mean square error from the model and referencing a t-distribution. For each of the RI populations, these confidence limits will be exponentiated to obtain the 90% CI for the true ratio of geometric means (RI/normal renal function) for each PK parameter.

Sample Size and Power Calculations

The precision of the estimated ratios of geometric means (renal impairment/normal renal function) of PK parameters obtained from this study can be assessed by calculating the half-width of the 90% CIs expected for the given sample size and assumed variability. The pooled between-subject standard deviation (on the natural log scale) for MK-3402 AUC0-inf after administration of 25 to 1100 mg MK-3402 observed in P001 is 0.112 ln(μM•hr). Assuming a sample size of 6 participants per population and observed between-subject SDs as given above, then the half width of the 90% CIs of GMRs for MK-3402 AUC0-inf on the log scale will be 0.11. The lower and upper 90% confidence limits for the true GMRs will be given by OBS/1.12 and OBS*1.12 for AUC0-inf, where OBS is the observed GMR. Thus, for example, if the observed GMR for AUC0-inf was 1.50, then the 90% CI for the GMR would be 1.33 to 1.68.

9.2 Responsibility for Analyses

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

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

9.3 Hypotheses/Estimation

Primary Estimation:

MK-3402 AUC0-inf following a single IV dose of MK-3402 administered to participants with varying degrees of RI (mild, moderate, severe, ESRD before HD, ESRD after HD) will be estimated and compared to MK-3402 AUC0-inf when administered to healthy matched control participants.

Secondary Estimation:

The extent to which MK-3402 is removed by hemodialysis from the plasma (plasma MK-3402 $CL_{D,plasma}$ or the dialysate C_D, AE_D, AE_D (%dose), and $CL_{D,dialysis}$) will be estimated.

MK-3402 Ae0-24, Fe, and CLr following a single IV dose of MK-3402 administered to participants with varying degrees of RI, as appropriate, will be estimated and compared to those estimated in healthy matched control participants.

9.4 Analysis Endpoints

The primary PK endpoints are plasma MK-3402 AUC0-inf, Ceoi, Tmax, elimination terminal t1/2, CL, and Vd following a single MK-3402 IV dose in participants with mild, moderate, severe renal impairment, ESRD or in healthy matched control participants.

The secondary PK endpoints are plasma MK-3402 $CL_{D,plasma}$ or the dialysate C_D, AE_D, AE_D (%dose), and $CL_{D,dialysis}$ and urine MK-3402 Ae0-24, Fe, and CLr following a single MK-3402 IV dose in participants with mild, moderate, severe impairments, ESRD or in healthy matched control participants.

The secondary safety endpoints are AEs, VS, 12-lead ECGs, and laboratory safety tests.

The exploratory endpoint is eGFR at baseline.

9.5 Analysis Populations

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

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

Per-Protocol (PP): The Per-Protocol Population consists of the subset of participants who comply with the protocol sufficiently to ensure that generated data will be likely to exhibit the effects of treatment, according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements and absence of important protocol deviations. Important protocol deviations will be identified to the extent possible prior to unblinding by individuals responsible for data collection/compliance, and its

analysis and interpretation. Any participants or data values excluded from analysis will be identified, along with their reason for exclusion, in the CSR. At the end of the study, all participants who are compliant with the study procedure as aforementioned and have available data considered sufficient to exhibit the effect of treatment will be included in the Per-Protocol dataset. This population will be used for the PK analyses.

9.6 Statistical Methods

Pharmacokinetics:

Primary Analysis

If a different group of healthy matched control participants is needed to match the mean age and BMI for the RI and ESRD groups, then separate analyses will be performed for the populations as follows:

- Mild RI and moderate RI versus an appropriate group of healthy matched control participants;
- Severe RI versus an appropriate group of healthy matched control participants;
- ESRD participants (non-HD and HD) versus an appropriate group of healthy matched control participants.

If a single set of healthy matched control participants can be used for comparison with all RI and ESRD groups, the following analysis pooled over all populations will be used.

Separately for each pharmacokinetic parameter, individual values of plasma MK-3402 AUC0-inf and Ceoi will be natural log-transformed and evaluated with a linear fixed-effects model containing a categorical effect for populations. The REPEATED statement with the GROUP=Population option will be used in SAS PROC MIXED to estimate separate variances for each population. The Kenward and Roger adjustment will be used to calculate the denominator degrees of freedom for the fixed-effect (DDFM=KR).

Ninety-five percent (95%) CIs for the least squares means for each population will be constructed on the natural log scale and will reference the t-distribution. Exponentiating the least-squares means and their corresponding 95% CIs will yield estimates for the population GMs and CIs about the GMs on the original scale.

To compare participants with RI in each of the renal categories (mild RI, moderate RI, severe RI, ESRD non-HD and ESRD HD) to matching participants with normal renal function, a 2-sided 90% CI for the true difference in means (RI - normal renal function) will be calculated for each PK parameters (AUC0-inf and Ceoi) using the mean square error from the model and referencing a t-distribution. For each of the RI populations, these confidence limits will be exponentiated to obtain the 90% CI for the true GMRs (RI/normal renal function) for each PK parameter.

Figures showing individual PK values with GMs (95% CIs) by population, plotted on the natural log scale, will be provided for AUC0-inf and Ceoi.

Secondary Analysis

To evaluate the extent to which MK-3402 is removed from plasma by HD, a linear mixed effect model with population (ESRD non-HD, ESRD HD) as a fixed effect will be used. An unstructured covariance matrix will be used to allow for unequal treatment variances and to model the correlation between the 2 treatment measurements within each participant via the REPEATED statement in SAS PROC MIXED. Kenward and Roger's method will be used to calculate the denominator degrees of freedom for the fixed effects (DDFM=KR).

A natural log transformation will be applied to AUC0-inf and Ceoi. For each PK parameter, 95% confidence intervals for the least squares means will be constructed on the natural log scale and will reference the t-distribution. Exponentiating the least-squares means and their corresponding 95% CIs will yield estimates for the population GMs and CIs about the GMs on the original scale.

A 2-sided 90% CI for the true difference in means (ESRD HD – ESRD non-HD) will be calculated for each pharmacokinetic parameter (AUC0-inf and Ceoi) using the mean square error from the model and referencing a t-distribution. These confidence limits will be exponentiated to obtain the 90% confidence interval for the true ratio (GMR) of geometric means (ESRD HD / ESRD non-HD) for each PK parameter.

Plots with individual ratios overlaid with GMR and corresponding 90% CI will be provided for AUC0-inf and Ceoi.

Separately for each urine PK parameter, where possible, individual values of Ae0-24, Fe and CLr will be natural log-transformed and evaluated with a linear fixed-effects model, which is described in the primary analysis. Ninety-five percent (95%) CIs intervals for the least squares means for each population will be constructed. To compare participants with RI in each of the renal categories (mild RI, moderate RI, severe RI, ESRD non-HD and ESRD HD) to matching participants with normal renal function, a 2-sided 90% CI for the true ratio of means (RI/normal renal function) will be calculated for each urine PK parameter (Ae0-24, Fe and CLr).

Exploratory Regression Analysis

In addition to running the primary regression analysis below using BSA normalized eGFR as the measure of renal function for each participant, the analysis will also be run using BSA un-normalized eGFR and CrCL from CG equation.

Separately for each PK parameter, individual values of plasma MK-3402 AUC0-inf and Ceoi will be evaluated with a linear fixed effects model containing eGFR as a continuous variable. The participant’s mean renal function value derived from 2 serum creatinine measurements at Screening will be used for the analysis. Estimates of the slope and intercept, together with corresponding ninety five percent (95%) CIs will be obtained. The estimated mean and

corresponding 95% CI for each renal impairment group will be predicted at the midpoint of the defined eGFR range for each group (60, 45, and 22.5 for mild, moderate, and severe, respectively). However, for the normal renal function group, the estimated mean and corresponding 95% CI will be predicted at the median of the observed eGFR values. Sample SAS code is given below.

Proc mixed data=pk ;

model AUC= eGFR / s cl DDFM=KR alpha=**0.05** outpm=normres;
estimate "predicted AUC in severe" int **1** eGFR 22.5/alpha=**0.1** cl e;

estimate "predicted AUC in moderate" int **1** eGFR **45**/alpha=**0.1** cl e;

estimate "predicted AUC in mild" int **1** eGFR **60**/alpha=**0.1** cl e;

estimate "predicted AUC in normal" int **1** eGFR xx /alpha=**0.1** cl e;

*xx is median eGFR for normal renal function group***;**run**;

The data will be examined for departures from the assumptions of the model. The residuals from the model will be examined for normality using diagnostic plots such as residuals vs predicted values and normal probability plots of residuals. Lack of fit will also be visually assessed.

If the model used does not fit the data adequately, other models, such as natural log-transformed PK vs renal function or natural log-transformed PK vs natural log-transformed renal function, will be explored. Other transformations or nonlinear models will also be considered.

Additionally, plots of MK-3402 PK parameter values (AUC0-inf, Ceoi) versus eGFR along with a regression line and 95% confidence bands for regression line will be constructed. Different symbols will be used to identify different renal function groups. Separate plots of AUC0-inf and Ceoi values vs age and body weight will be provided.

Summary Statistics using BSA un-normalized eGFR: The participants will be recategorized into different renal categories based on their BSA un-normalized eGFR and nonmodel based summary statistics by population will be provided for (plasma AUC0-inf, Ceoi, Tmax, elimination terminal t1/2, CL, and Vd, and urine Ae0-24, Fe, and CLr, as applicable).

Analysis using CrCl (CG equation): The participants will be recategorized into different renal categories based on their CrCl obtained from CG equation and nonmodel based summary statistics by population will be provided for (plasma AUC0-inf, Ceoi, Tmax, elimination terminal t1/2, CL, and Vd, and urine Ae0-24, Fe, and CLr, as applicable).

Individual values will be listed for each PK parameter (plasma MK-3402 AUC0-inf, Ceoi, Tmax, elimination terminal t1/2, CL, and Vd, plasma MK-3402 $CL_{D,plasma}$ or the dialysate C_D, AE_D, AE_D (%dose), and $CL_{D,dialysis}$, and urine MK-3402 Ae0-24, Fe, and CLr) by population, and the following (nonmodel-based) descriptive statistics will be provided: N

(number of subjects with nonmissing data), arithmetic mean, standard deviation, arithmetic percent CV (calculated as 100 x standard deviation/arithmetic mean), median, minimum, maximum, geometric mean, and geometric percent CV (calculated as 100 x sqrt(exp(s^2) - 1), where s^2 is the observed variance on the natural log-scale).

Safety: The safety and tolerability of MK-3402 will be monitored by clinical assessment of adverse experiences and other safety measurements (eg, labs, VS, ECGs).

9.7 Interim Analyses

Not applicable.

9.8 Multiplicity

There is no prespecified hypothesis; therefore, no multiplicity adjustment is needed.

9.9 Sample Size and Power Calculations

The sample size selected for each population to evaluate the effect of RI on the PK of MK-3402 was not chosen to satisfy any a priori statistical requirement. This sample size (n= 6 participants per panel) has historically been shown to be sufficient for studies of this type and should provide adequate data to support the planned analyses. Nevertheless, estimates of the expected precision of the estimates, based on these sample sizes are presented below.

The precision of the estimated ratios of geometric means (renal impairment / normal renal function) of PK parameters obtained from this study can be assessed by calculating the half-width of the 90% CIs expected for the given sample size and assumed variability. The pooled between-subject standard deviation (on the natural log scale) for MK-3402 AUC0-inf after administration of 25 to 1100 mg MK-3402 observed in P001 is 0.112 ln(µM•hr). Assuming a sample size of 6 participants per population and observed between-subject SDs as given above, then the half width of the 90% CIs of GMRs for MK-3402 AUC0-inf on the log scale will be 0.11. The lower and upper 90% confidence limits for the true GMRs will be given by OBS/1.12 and OBS*1.12 for AUC0-inf, where OBS is the observed GMR. Thus, for example, if the observed GMR for AUC0-inf was 1.50, then the 90% CI for the GMR would be 1.33 to 1.68.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Code of Conduct for Clinical Trials

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

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (including all applicable data protection laws and regulations), and International Council for Harmonisation Good Clinical Practice (ICH-GCP), and also in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Highest ethical and scientific standards shall be endorsed for all clinical interventional investigations sponsored by MSD irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials that are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials, which are not under the full control of MSD.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of MSD or comparator products. Alternatively, MSD may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine patient preferences, etc.

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

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

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

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

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish the primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the pre-specified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing; in such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

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

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

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

B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care.

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Participants may withdraw from an MSD trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices.

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

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

10.1.3 Data Protection

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

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

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

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

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

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

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

10.1.3.3 Confidentiality of IRB/IEC Information

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

10.1.4 Publication Policy

The results of this study may be published or presented at scientific meetings. The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

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

Authorship will be determined by mutual agreement and in line with ICMJE authorship requirements.

10.1.5 Compliance with Study Registration and Results Posting Requirements

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

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

10.1.6 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GCP (eg, ICH GCP: Consolidated Guideline and other generally accepted standards of GCP); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical study.

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

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

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

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

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

10.1.7 Data Quality Assurance

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

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

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

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

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

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

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

Records and documents, including participants' documented informed consent, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8 Source Documents

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

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

10.1.9 Study and Site Closure

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

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

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 12 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 12 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit			WBC count with Differential (absolute): Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Chemistry	BUN	Potassium	AST/SGOT	Total bilirubin (and direct bilirubin, if total bilirubin is above the ULN)
	Albumin	Bicarbonate	Chloride	Phosphorous
	Creatinine	Sodium	ALT/SGPT	Total Protein
	Glucose (fasting)	Calcium	Alkaline phosphatase	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, [bilirubin, urobilinogen, nitrite, leukocyte esterase] by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• FSH (as needed in WONCBP only) • Urine/saliva drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, and benzodiazepines) if applicable • Serology [(HIV antibody, HBsAg, and hepatitis C virus antibody)]			

ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; FSH=follicle-stimulating hormone; HBsAg=hepatitis B surface antigen; hCG=human chorionic gonadotropin; HIV=human immunodeficiency virus; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; RBC=red blood cell; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; ULN=upper limit of normal; WBC=white blood cell; WONCBP=women of nonchildbearing potential

The investigator (or medically qualified designee) must document their review of each laboratory safety report.

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

10.3.1 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.
- Note: For purposes of AE definition, study intervention (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, diagnostic agent, medical device, combination product, or protocol specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of 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.
- Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.2 Definition of SAE

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

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

1. **Results in death**

2. **Is life-threatening**

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

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

   - Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a 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 an MSD product and is documented in the participant's medical history.

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

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

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

5. Is a congenital anomaly/birth defect

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

6. Other important medical events

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

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

10.3.3 Additional Events Reported

Additional events that require reporting

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

- Is a cancer

- Is associated with an overdose

10.3.4 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.

- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.

- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.

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

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

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

Assessment of intensity

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

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

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

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

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

Assessment of causality

- Did the Sponsor's product cause the AE?

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

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

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

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

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

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

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

    - If yes, did the AE resolve or improve?
    - If yes, this is a positive dechallenge.
    - If no, this is a negative dechallenge.

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

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

    - If yes, did the AE recur or worsen?
    - If yes, this is a positive rechallenge.
    - If no, this is a negative rechallenge.

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

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR, AND IF REQUIRED, THE IRB/IEC.

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

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

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

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

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

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

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

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

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

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

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

Follow-up of AE and SAE

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

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

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

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

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

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

SAE reporting to the Sponsor via paper CRF

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

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

Not Applicable

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Women of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

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

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

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens consented and/or collected in this study as outlined in Section 8.8.1 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

a. Participants for Enrollment

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

b. Informed Consent

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

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

c. eCRF Documentation for Future Biomedical Research Specimens

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

d. Future Biomedical Research Specimen(s)

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

4. Confidential Participant Information for Future Biomedical Research

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

To maintain privacy of information collected from specimens obtained for future biomedical research, the Sponsor has developed secure policies and procedures. All specimens will be single-coded per ICH E15 guidelines as described below.

At the clinical study site, unique codes will be placed on the future biomedical research specimens. This code is a random number which does not contain any personally identifying information embedded within it. The link (or key) between participant identifiers and this unique code will be held at the study site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses using the future biomedical research specimens may be performed by the Sponsor, or an additional third party (eg, a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third party analyses will conform to the specific scope of analysis outlined in future biomedical research protocol and consent. Future biomedical research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research

Participants may withdraw their consent for future biomedical research and ask that their biospecimens not be used for future biomedical research. Participants may withdraw consent at any time by contacting the investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to main study use only. If specimens were collected from study participants specifically for future biomedical research, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

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

7. Retention of Specimens

Future biomedical research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the main study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the study site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not utilized in a particular study, the study site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility which

operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated study administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards to protect against unauthorized access.

9. Reporting of Future Biomedical Research Data to Participants

No information obtained from exploratory laboratory studies will be reported to the participant, family, or physicians. Principle reasons not to inform or return results to the participant include: lack of relevance to participant health, limitations of predictive capability, and concerns regarding misinterpretation.

If important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to rapidly report this information to doctors and participants. Participants will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population

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

11. Risks Versus Benefits of Future Biomedical Research

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

The Sponsor has developed strict security, policies, and procedures to address participant data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation, there is risk that the information, like all medical information, may be misused.

12. Questions

Any questions related to the future biomedical research should be emailed directly to clinical.specimen.management@merck.com.

13. References

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

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

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

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

10.7 Appendix 7: Country-specific Requirements

Not Applicable.

10.8 Appendix 8: Blood Volume Table

Panels A to D	Prestudy	Treatment Periods	Poststudy	Total Collections	mL Per Collection	Total mL/ Test
Laboratory Safety Tests	2	1		3	10	30
HIV/Hepatitis Screen (at the discretion of the investigator)	1			1	8.5	8.5
Blood for Planned Genetic Analysis OR Blood (DNA) for FBR	1			1	8.5	8.5
Blood for MK-3402		13			4	52
	Total Blood Volume per Participant for Panels A to D[a]					99 mL

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

Panel E	Prestudy	Treatment Periods	Poststudy	Total Collections	mL Per Collection	Total mL/ Test
Laboratory Safety Tests	3	2		5	10	50
HIV/Hepatitis Screen (at the discretion of the investigator)	1			1	8.5	8.5
Blood for Planned Genetic Analysis OR Blood (DNA) for FBR	1			1	8.5	8.5
Blood for MK-3402 Period 1		13		13	4	52
Blood for MK-3402 Period 2		26		26	4	104
	Total Blood Volume per Participant for Panel E[a]					223 mL

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

10.9 Appendix 9: 12-Lead Electrocardiogram Abnormality Criteria for Panel D

	Screen Failure Criteria	Potentially Significant Postrandomization Findings (clarification on action to take)
RHYTHM		
Sinus Tachycardia	>110 bpm	HR >110 bpm and HR increase of ≥25 bpm from baseline
Sinus Bradycardia	<40 bpm	HR <40 bpm and HR decrease of ≥5 bpm from baseline
Sinus Pause/Arrest	>2.0 seconds	>2.0 seconds
Atrial Premature Complex	> 1 beat	≥ 3 beats
Ventricular Premature Complex	All	≥ 3 beats
Ectopic Atrial Rhythm	None	None
Junctional Rhythm	Junctional Rhythm with HR <40 bpm	Junctional Rhythm with HR <40 bpm
Idioventricular Rhythm	All	All
Atrial Fibrillation	All	All
Atrial Flutter	All	All
Supraventricular Tachycardia	All	All
Ventricular Tachycardia	All	All
AXIS		
Left Axis Deviation	RBBB With LAHB	New Onset LAHB
Right Axis Deviation	RBBB With LPHB	New Onset LPHB
CONDUCTION		
1st Degree AV Block	PR ≥230 ms	PR ≥ 230 ms + Increase of >15 ms; or PR Increase of >25%
2nd Degree AV Block	All (i.e., both Mobitz Type I and Type II)	Mobitz Type II
3rd Degree AV Block	All	All
LBBB	All	All
RBBB	RBBB With LAHB/LPHB as Defined Above	New Onset RBBB (Not Including Rate-related)
ICRBBB (QRS <120 ms)	No Exclusion	Nothing
Short PR/Preexcitation Syndrome	Delta Wave + PR <120 ms	Delta Wave + PR <120 ms
Other Intra-Ventricular Conduction Delay	QRS ≥130 ms	QRS ≥130 ms + Increase of ≥10 ms
QTc (B or F)		
Male	QTc ≥470 ms	QTc ≥500 ms or Increase of ≥60 ms From Baseline
Female	QTc ≥480 ms	QTc ≥500 ms or Increase of ≥60 ms From Baseline
HYPERTROPHY		
Atrial Abnormalities	Definite Evidence of P Mitrale or P Pulmonale	Definite Evidence of P Mitrale or P Pulmonale
Ventricular Abnormalities	Voltage Criteria for LVH Plus Strain Pattern	Voltage Criteria for LVH Plus Strain Pattern

	Screen Failure Criteria	Potentially Significant Postrandomization Findings (clarification on action to take)
MYOCARDIAL INFARCTION		
Acute or Recent	All	All
Old	All	All
ST/T MORPHOLOGY		
ST Elevation Suggestive of Myocardial Injury	In 2 or more contiguous leads	In 2 or more contiguous leads
ST Depression Suggestive of Myocardial Ischaemia	In 2 or more contiguous leads	In 2 or more contiguous leads
T-wave Inversions Suggestive of Myocardial Ischaemia	In 2 or more contiguous leads	In 2 or more contiguous leads
Non-specific ST-T Changes (In 2 or More Leads)	No exclusion	In 2 or more contiguous leads
PACEMAKER	All	All

AV=atrioventricular; bpm=beats per minute; HR=heart rate: ICRBBB=incomplete right bundle branch block; LAHB=left anterior hemiblock; LPHB=left posterior hemiblock; LVH=left ventricular hypertrophy; mm=millimeter; ms=milliseconds, PR=pulse rate; QTcB=QT correction using Bazett's formula; QTcF=QT correction using Fredericia formula; RBBB=right bundle branch block; ST/T=ST-segment/T wave.
Baseline is defined as Predose Day 1

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

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

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

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

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

    1. The participant may be excluded from the study;

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

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

    OR

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

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

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

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

10.11 Appendix 11: Abbreviations

Abbreviation	Expanded Term
Ae0-24	amount recovered in urine from 0 to 24 hours
AE	adverse event
AE_D	Amount of drug recovered from the dialysate
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APaT	All-Participants-as-Treated
AR	adverse reaction
AST	aspartate aminotransferase
AUC	area under the curve
bid	twice daily
BL	β-lactamase
BLI	β-lactamase inhibitor(s)
BMI	body mass index
BP	blood pressure
BSA	body surface area
CAC	Clinical Adjudication Committee
CCU	cardiac care unit
Ceoi	concentration at the end of infusion
CG	Cockcroft-Gault
CI	confidence interval
Cmax	maximum plasma concentration
CL	clearance
$CL_{D, diasylsate}$	hemodialysis clearance
$CL_{D, plasma}$	dialysis clearance based on plasma
CLr	renal clearance
CrCl	creatinine clearance
CRF	Case Report Form
CRU	clinical research unit
CSR	Clinical Study Report
CT	computed tomography
CV	coefficient of variation
CYP	cytochrome P450
DDI	drug-drug interaction
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
EDC	electronic data collection
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
ESRD	end stage renal disease
EVB	ectopic ventricular beats
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
Fe	fraction of dose recovered in urine
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal

Abbreviation	Expanded Term
GM	geometric mean
GMR	geometric mean ratio
HABP	hospital-acquired bacterial pneumonia
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HD	hemodiaysis
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
ICU	intensive care unit
ID	identification
IEC	Independent Ethics Committee
IMP	imipenemase
IND	Investigational New Drug
IRB	Institutional Review Board
IRT	interactive response technology
IV	intravenous(ly)
MAD	maximum administered dose
MBL	metallo-β-lactamase
MBLI	metallo-β-lactamase inhibitor(s)
MDRD	Modification of Diet in Renal Disease
MIC	minimum inhibitory concentration
NCS	not clinically significant
NDA	New Drug Application
NDM	New Delhi metallo-β-lactamase
OATP1B1/1B3	Organic anion transporting polypeptides 1B1 and 1B3
OBS	Observed
PCL	protocol clarification letter
PD	pharmacodynamics
PK	pharmacokinetic
po	orally
PP	per-protocol
q8hr	every 8 hours
REL	relebactam
RI	renal impairment
RNA	ribonucleic acid
RR	respiratory rate
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transminase
SLAB	supplemental laboratory test(s)
SoA	schedule of activities
SOP	Standard Operating Procedures
SUSAR	suspected unexpected serious adverse reaction
SW	study week

Abbreviation	Expanded Term
Tmax	time to maximum plasma concentration
t1/2	half life
ULN	upper limit of normal
VABP	ventilator-associated bacterial pneumonia
Vd	volume of distribution
VIM	verona integron-encoded metallo-β-lactamase
VS	vital sign(s)
WBC	white blood cell
WOCBP	woman/women of childbearing potential
WONCBP	woman/women of nonchildbearing potential

11 REFERENCES

Not Applicable.