Official Protocol Title:	A 2-Part, Open-Label Trial to Evaluate the Pharmacokinetics of MK-3866 Following the Administration of a Single IV Dose to Subjects with Mild, Moderate, and Severe Renal Impairment and End Stage Renal Disease
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A 2-Part, Open-Label Trial to Evaluate the Pharmacokinetics of MK-3866 Following the Administration of a Single IV Dose to Subjects with Mild, Moderate, and Severe Renal Impairment and End Stage Renal Disease

Compliance Statement

Merck clinical studies will be conducted in compliance with local and/or national regulations and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

Confidentiality Statement

1 PROTOCOL REVISION HISTORY

Date/Name	Description
03 Aug 2017 by PPD	Final Protocol

2 PRINCIPAL INVESTIGATOR AND SPONSOR – SIGNATORIES

A 2-Part, Open-Label Trial to Evaluate the Pharmacokinetics of MK-3866 Following the Administration of a Single IV Dose to Subjects with Mild, Moderate, and Severe Renal Impairment and End Stage Renal Disease

SPONSOR:

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
(hereafter referred to as the Sponsor or Merck)
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SPONSOR'S REPRESENTATIVE:

PPD
Clinical Director
Tel.: PPD
E-mail: PPD

Signature Date

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5 SYNOPSIS

Compound:	MK-3866
Clinical Indication:	Treatment of gram-negative bacterial infections
Study Phase and Type:	Phase 1 - Interventional
Study Objectives and Estimations:	**Primary:** Objective 1: To compare the plasma pharmacokinetics (e.g., AUC0-∞, AUC0-last, AUC0-24, Ceoi (Cmax), Tmax, elimination terminal t½, CL, and Vz) of MK-3866 following a single intravenous (IV) dose in subjects with mild renal impairment (RI) to those of mean healthy matched control subjects. Estimation 1: The AUC0-∞ following a single IV dose of MK-3866 administered to subjects with mild RI will be estimated and compared to the AUC0-∞ when administered to mean healthy matched control subjects. Objective 2: To compare the plasma pharmacokinetics (e.g., AUC0-∞, AUC0-last, AUC0-24, Ceoi (Cmax), Tmax, elimination terminal t½, CL, and Vz) of MK-3866 following a single IV dose in subjects with moderate RI to those of mean healthy matched control subjects. Estimation 2: The AUC0-∞ following a single IV dose of MK-3866 administered to subjects with moderate RI will be estimated and compared to the AUC0-∞ when administered to mean healthy matched control subjects. Objective 3: To compare the plasma pharmacokinetics (e.g., AUC0-∞, AUC0-last, AUC0-24, Ceoi (Cmax), Tmax, elimination terminal t½, CL, and Vz) of MK-3866 following a single IV dose in subjects with severe RI to those of healthy matched control subjects. Estimation 3: The AUC0-∞ following a single IV dose of MK-3866 administered to subjects with severe RI will be estimated and compared to the AUC0-∞ when administered to mean healthy matched control subjects. Objective 4: To compare the plasma pharmacokinetics (e.g., AUC0-∞, AUC0-last, AUC0-24, Ceoi (Cmax), Tmax, elimination terminal t½, CL, and Vz) of MK-3866 following a single IV dose administered after hemodialysis (HD) in subjects

	with end stage renal disease (ESRD) undergoing HD to those of mean healthy matched control subjects. Estimation 4: The AUC0-∞ following a single IV dose of MK-3866 administered after HD to subjects with ESRD will be estimated and compared to the AUC0-∞ when administered to mean healthy matched control subjects. Objective 5: To compare the plasma pharmacokinetics (e.g., AUC0-∞, AUC0-last, AUC0-24, Ceoi (Cmax), Tmax, elimination terminal t½, CL, and Vz) of MK-3866 following a single IV dose administered prior to HD in subjects with ESRD to those of mean healthy matched control subjects. Estimation 5: The AUC0-∞ following a single IV dose of MK-3866 administered prior to HD to subjects with ESRD will be estimated and compared to the AUC0-∞ when administered to mean healthy matched control subjects. **Secondary:** Objective 1: To investigate the extent to which MK-3866 is removed by HD. Estimation 1: The extent to which MK-3866 is removed by HD from the plasma (e.g., Ca, Cv, AUCD, AUC[1-4.5]Ca, AUC[1-4.5]Cv, and CLD,plasma) or the dialysate (e.g., CD, AD, rr, AD,total, and CLD,dialysate) will be estimated. Objective 2: To compare the urine pharmacokinetics (e.g., Ae0-24, Fe, and CLr) of MK-3866 following a single IV dose of MK-3866 to subjects with varying degrees of RI, where possible, to those of healthy matched control subjects. Estimation 2: The Ae0-24, Fe, and CLr following a single IV dose of MK-3866 administered to subjects with varying degrees of RI will be estimated and compared to those estimated in mean healthy matched control subjects. Objective 3: To evaluate the safety and tolerability of the administration of a single IV dose of MK-3866 in subjects with varying degrees of RI. **Exploratory Objective:** Objective: To explore the relationship between eGFR and pharmacokinetics (e.g. CLr and AUC0-∞) of MK-3866 using a model-based approach.

<table>
<tr><td></td><td>Planned Exploratory Biomarker:
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 this study.</td></tr>
<tr><td>Summary of Study Design:</td><td>This is an open-label, 2-part, single dose study in renal impaired and healthy control subjects. Parts 1 and 2 of the study may be conducted concurrently.
Study parts and assignment to a renal function group will be as follows:
<table>
<tr><th>Panel</th><th>Renal Function</th><th>N</th><th>eGFR (mL/min/1.73m^2)*</th></tr>
<tr><td colspan="4">Part 1</td></tr>
<tr><td>A</td><td>Mild</td><td>8</td><td>60 ≤ eGFR< 90</td></tr>
<tr><td>B</td><td>Moderate</td><td>8</td><td>30 ≤ eGFR < 60**</td></tr>
<tr><td>C</td><td>Severe</td><td>8</td><td>< 30 not on dialysis</td></tr>
<tr><td>D</td><td>Healthy Matched Control</td><td>≥ 8 (up to 24)</td><td>≥ 90</td></tr>
<tr><td colspan="4">Part 2</td></tr>
<tr><td>E</td><td>ESRD requiring HD</td><td>8</td><td>requiring HD</td></tr>
<tr><td colspan="4">* Estimated glomerular filtration rate (eGFR) based on Modification of Diet in Renal Disease (MDRD) equation at screening. Baseline eGFR will be obtained by taking the mean of the eGFR obtained from screening and from historical values within a 3-month period from 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 two values will be used for group assignment; the second baseline eGFR sample may be obtained at the time of check-in.
** Reasonable efforts will be made to enroll at least 2 subjects with eGFR values of 30 - 40 mL/min/1.73m^2</td></tr>
</table></td></tr>
</table>

	Part 1: Subjects in Panels A, B, C, and D will receive a single IV dose of MK-3866. Plasma samples will be taken at pre-specified time points up to 72 hours postdose, depending on the panel and urine samples will be collected at pre-specified time points up to 24 hours postdose, where possible, for pharmacokinetic assessment of MK-3866. **Part 2:** Subjects in Panel E will receive a single IV dose of MK-3866 on two separate occasions. In Period 1, subjects will receive a single IV dose of MK-3866 immediately following their normally-scheduled HD, followed by 72 hours plasma sampling and by 24 hours urine collection, where possible, for pharmacokinetic assessment of MK-3866. In Period 2, subjects will receive a single IV dose of MK-3866 approximately 30 minutes prior to their normally scheduled HD followed by 72 hours plasma sampling and by 24 hours urine collection, where possible, for pharmacokinetic assessment of MK-3866. During this dialysis session, additional plasma and dialysate samples will be taken for MK-3866 analysis. There will be a washout period of at least 7 days between MK-3866 dosing in Periods 1 and 2 of Part 2. **Both Parts:** All subjects who received at least one dose of MK-3866 will return to the Clinical Research Unit (CRU) approximately 14 days after the last dose for follow-up procedures, and to determine if any adverse events have occurred since the last study visit.
Blinding:	This is an open-label study.
Number of Subjects:	Subjects with RI: Up to thirty-two (32), adult, male and female (non-childbearing potential only) subjects will be enrolled. Panel A: Eight (8) subjects with mild RI. Panel B: Eight (8) subjects with moderate RI. Panel C: Eight (8) subjects with severe RI. Panel E: Eight (8) subjects with ESRD requiring HD.

	Subjects with mild (Panel A), moderate (Panel B), and severe (Panel C) RI and those with ESRD (Panel E) shall be enrolled in parallel, and each panel shall enroll a minimum of 2 subjects of each gender. Healthy Matched Control Subjects: Panel D: At least 8 (up to 24) healthy subjects (eGFR $\geq$ 90 mL/min/1.73 m^2), matched to the mean age ($\pm$ 15 years), gender, and mean body mass index (BMI; $\pm$ 10%) of subjects in the mild, moderate, severe RI, and subjects with ESRD panels (Panels A, B, C, and E). Enrolment of 8 healthy matched control subjects (Panel D) will commence following the completion of enrolment of Panels A and B. Each healthy control subject will be matched to the mean age ($\pm$ 15 years) and the mean BMI ($\pm$ 10%) of the subjects in Panels A and B combined. There should be a minimum of 2 subjects of each gender in each panel. The data from the already enrolled healthy subjects who satisfy the gender, mean age and BMI matching criteria of the RI subjects in each of Panels C and E will be used. However, if any of the healthy subjects do not meet the matching criteria described above, additional healthy subjects will be enrolled to result in a total of 8 healthy subjects who match the mean age ($\pm$ 15 years) and the mean BMI ($\pm$ 10%) of each of Panels C and E. The gender of the additional healthy subject(s) will be selected to ensure that there is a minimum of 2 subjects of each gender in the group of subjects within Panel D who match with each of the Panels C and E. The pharmacokinetic comparisons between each renally impaired panel (Panels A, B, C, and E) and healthy controls (Panel D) will include only the control subjects who meet the matching criteria for the respective RI panel.
Dosage, Dosage Form, Route, and Dose Regimen:	**Part 1:** Subjects will receive a single IV infusion of 200 mg MK-3866 at Hour 0 on Day 1. **Part 2:** Subjects will receive a single IV infusion of 200 mg MK-3866 at Hour 0 on Day 1, immediately after completion of the scheduled HD (Period 1), and at Hour 0 on Day 1, approximately 30 minutes prior to initiation of the scheduled HD (Period 2).

	Both Parts: Each IV infusion will be administered over 30 minutes (±5 minutes). Hour 0 will be determined as the start of the infusion.
Key Assessments:	**Pharmacokinetics:** The following pharmacokinetic parameters will be calculated for MK-3866 in plasma, as appropriate, in all panels: AUC0-∞, AUC0-last, AUC0-24, Ceoi (Cmax), Tmax, elimination terminal t½, CL, and Vz. The following pharmacokinetic parameters will be calculated for MK-3866 in urine, as appropriate, in all panels: Ae0-24, Fe, and CLr. For subjects with ESRD on HD (Panel E only), the following pharmacokinetic parameters will also be calculated for MK-3866 in plasma, as appropriate: Ca, Cv, AUCD, AUC(1-4.5)Ca, and AUC(1-4.5)Cv, CLD,plasma and in dialysate: CD, AD, rr, AD,total, and CLD,dialysate. **Safety:** Safety will be monitored through physical examination, vital signs, 12-lead electrocardiograms (ECGs), adverse events and clinical laboratory tests. Summary statistics for the laboratory safety tests, 12-lead ECGs, and/or vital signs may also be computed and provided, as deemed clinically appropriate.

6 STUDY EVENTS FLOW CHART

6.1 Subjects with Mild (Panel A), Moderate (Panel B), and Severe (Panel C) RI and Healthy Subjects (Panel D) – Part 1

Study Procedures [a]	S [b]	Study Days																				FU [c]
Days →		-2 /-1	1														2		3		4	
Hours →		(C-I) [d]	P	0	0.5	0.75	1	1.5	2	3	4.5	6	8	10	12	24	36	48	60	72	
Administrative Procedures																						
Informed Consent	X																				
Informed Consent for Future Biomedical Research	X																				
Inclusion/Exclusion Criteria	X	X																			
Medical History	X																				
Safety Evaluations																					
Full Physical Examination [e]	X	X														X [f]		X [f]		X [f]	X
Height	X																				
Weight	X	X																			X
Assessment of Renal Function [g]	X																				
12-Lead Electrocardiogram [h]	X		X [i]		X				X							X [f]		X [f]		X [f]	
Vital Signs (heart rate & blood pressure)	X		X [i]		X				X			X				X [f]		X [f]		X [f]	X
Vital Signs (respiratory rate & temperature)	X																				
Hematology, Ser Chemistry [j], and UA	X	X														X					X
Serum Pregnancy Test (female subjects only)	X	X																			
Serum FSH (postmenopausal females only)	X																				
Urine or Saliva Drug and Cotinine Screen	X	X																			
Urine or Breath Alcohol Screen	X	X																			
HIV/Hepatitis Screen	X																				
Adverse Events Monitoring	X----------X																				
Prior and Concomitant Medication Monitoring	X----------X																				

Study Procedures [a]	S [b]	Study Days																				FU [c]
Days →		-2 /-1	1														2		3		4	
Hours →		(C-I) [d]	P	0	0.5	0.75	1	1.5	2	3	4.5	6	8	10	12	24	36	48	60	72	
Study Drug Administration / Pharmacokinetics																						
MK-3866 IV Administration				X	----	X																
Blood for MK-3866 Pharmacokinetics [k]			X		X [l]	X	X	X	X	X	X	X	X	X	X	X [k]	X	X [k]	X	X [k]		
Urine for MK-3866 Pharmacokinetics [m]			X	X	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	X							
Other Procedures																						
Blood for Genetic Analysis [n]			X																			
Confinement in the CRU for Healthy		X	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	X							
Confinement in the CRU for mild and moderate RI		X	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	X			
Confinement in the CRU for severe RI		X	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	X	
Visit and Post-Trial Visit	X																					X

a. For details on Procedures, refer to Section 10 and/or corresponding appendices.

b. Within 28 days prior to dosing.

c. All subjects who received at least one dose of MK-3866 will return to the Clinical Research Unit (CRU) approximately 14 days after the last dose for follow-up procedures, and to determine if any adverse events have occurred since the last study visit.

d. Check-in: Subjects will be admitted to the CRU on Day -2 or Day -1, at the time indicated by the CRU.

e. Symptom-driven physical examinations may be performed at other times, at the Investigator's or designee discretion.

f. To be performed only once as the last study procedure for each panel: at 24 hours post start of infusion for healthy controls (Panel D); 48 hours for subjects with mild and moderate RI (Panel A and B), and 72 hours for subjects with severe RI (Panel C), or prior to early termination from the study.

g. Baseline eGFR will be obtained by taking the mean of the eGFR obtained from screening and from historical values within a 3 months period from 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 two values will be used for group assignment; the second baseline eGFR sample may be obtained at the time of check-in.

h. Triplicate 12-lead ECGs to be performed at screening and for predose ECG measurement. Single 12-lead ECGs to be performed for all postdose ECG measurements.

i. To be performed within 24 hours prior to dosing.

j. Samples for serum chemistry will be obtained following a fast of at least 8 hours; however, in case of discontinuations or rechecks, subjects may not have fasted for 8 hours prior the serum chemistry sample is taken. For subjects who are anuric, urine samples for urinalysis will not be collected.

k. The plasma pharmacokinetic sampling time points will be completed at 24 hours post start of infusion for healthy controls (Panel D); 48 hours for subjects with mild and moderate RI (Panel A and B), and 72 hours for subjects with severe RI (Panel C).

l. The 0.5 hour blood sample for MK-3866 pharmacokinetic should be collected at the end of the infusion.

m. Urine collection intervals are: pre-dose (spot collection), 0 - 4, 4 - 8, 8 – 12, and 12 - 24 hours postdose. For subjects with RI, urine samples will be collected whenever possible, as subjects may not be able to produce urine at each interval. For subjects who are anuric, urine samples will not be collected.

n. This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at the site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for future biomedical research if the subject signs the FBR consent. 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.

Abbreviations: C-I = Check-in, CRU = Clinical Research Unit, FU = Follow-Up, FSH = Follicle Stimulating Hormone, HIV = Human Immunodeficiency Virus, IV = Intravenous, P = Predose, RI = Renal Impairment, S = Screening, Ser = Serum, UA = Urinalysis

6.2 Subjects with ESRD on Dialysis (Panel E, Period 1 + Period 2) – Part 2

Study Procedures [a]	**S** [b]	**Study Days in Period 1 (MK-3866 Administered Post-Dialysis)** [c]																			
Days →		**-2 /-1**	**1**														**2**		**3**		**4**
Hours →		**(C-I)** [d]	**P**	**0**	**0.5**	**0.75**	**1**	**1.5**	**2**	**3**	**4**	**4.5**	**6**	**8**	**10**	**12**	**24**	**36**	**48**	**60**	**72**
Administrative Procedures																					
Informed Consent	X																				
Informed Consent for Future Biomedical Research	X																				
Inclusion/Exclusion Criteria	X	X																			
Medical History	X																				
Safety Evaluations																					
Full Physical Examination [e]	X	X																			X [f]
Height	X																				
Weight	X	X																			
12-Lead Electrocardiogram [g]	X		X [h]		X				X								X				X [f]
Vital Signs (heart rate & blood pressure)	X		X [h]		X				X				X				X				X [f]
Vital Signs (respiratory rate & temperature)	X																				
Hematology, Serum Chemistry [i], and UA	X	X															X				X [f]
Serum Pregnancy Test (female subjects only)	X	X																			
Serum FSH (postmenopausal females only)	X																				
Urine or Saliva Drug and Cotinine Screen	X	X																			
Urine or Breath Alcohol Screen	X	X																			
HIV/Hepatitis Screen	X																				
Adverse Events Monitoring	X----------X																				
Prior and ConMed Monitoring	X----------X																				
Study Drug Administration/ Pharmacokinetics																					
MK-3866 IV Administration				X------X [j]																	
Blood for MK-3866 Pharmacokinetics			X [k]		X [l]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X [m]
Urine for MK-3866 Pharmacokinetics [n]				X----------X																	
Other Procedures																					
Blood for Genetic Analysis [o]			X																		
Confinement in the CRU		X----------X																			
Visit	X																				

Study Procedures [a]	Study Days in Period 2 (MK-3866 Administered Pre-Dialysis) [c]																						FU [p]
Days →	-2 /-1	1																2		3		4	
Hours →	(C-I) [d]	P	0	0.5	0.75	1	1.5	2	2.5	3	3.5	4	4.5	6	8	10	12	24	36	48	60	72	
Safety Evaluations																							
Full Physical Examination [e]	X																					X [f]	X
Weight	X																						X
12-Lead Electrocardiogram [g]		X [h]																					
Vital Signs (heart rate & blood pressure)		X [h]		X				X						X								X [f]	X
Vital Signs (respiratory rate & temperature)	X																						
Hematology, Serum Chemistry [i], and UA	X																	X				X [f]	X
Serum Pregnancy Test (female subjects only)	X																						
Urine/Saliva/Blood Drug Screen	X																						
Urine or Breath Alcohol Screen	X																						
Adverse Events Monitoring	X----------X																						
Prior and ConMed Monitoring	X----------X																						
Study Drug Administration / Pharmacokinetics																							
MK-3866 IV Administration			X----X																				
Blood for MK-3866 Pharmacokinetics		X		X [l]	X [q]	X [q]	X [q]	X [q]	X [q]	X [q]	X [q]	X [q]	X [q]	X	X	X	X	X	X	X	X	X [m]	
Dialysate for MK-3866 Pharmacokinetics [r]				X		X	X	X	X	X	X	X	X										
Urine for MK-3866 Pharmacokinetics [n]			X----------X																				
Other Procedures																							
Hemodialysis [s]					X----------X																		
Confinement in the CRU	X----------X																						
Post-Trial Visit																							X

a. For details on Procedures, refer to Section 10 and/or corresponding appendices.

b. Screening: Within 28 days prior to the first dose.

c. There will be a period of at least 7 days between MK-3866 dosing in Period 1 and Period 2.

d. Check-in: Subjects will be admitted to the CRU on Day -2 or Day -1, at the time indicated by the CRU.

e. Symptom-driven physical examinations may be performed at other times, at the Investigator's discretion.

f. To be performed on Day 4 or prior to early termination from the study.

g. Triplicate 12-lead ECGs to be performed at screening and for predose ECG measurements. Single 12-lead ECGs to be performed all postdose ECG measurements.

h. To be performed within 24 hours prior to dosing.

i. Samples for serum chemistry will be obtained following a fast of at least 8 hours; however, in case of discontinuations or rechecks, subjects may not have fasted for 8 hours prior the serum chemistry sample is taken. For subjects who are anuric, urine samples for urinalysis will not be collected.

j. IV infusion will start immediately following the end of the scheduled HD in Period 1.

k. The predose sample should be collected after HD and prior to the start of the infusion.

l. The 0.5 hour blood sample for MK-3866 should be collected at the end of the infusion.

m. If the next scheduled HD must be initiated prior the 72 hours postdose, a sample for MK-3866 analysis will be collected prior to HD.

n. Urine collection intervals are: pre-dose (spot collection), 0 - 4, 4 - 8, 8 – 12, and 12 - 24 hours postdose. Urine samples will be collected whenever possible, as subjects may not be able to produce urine at each interval. For subjects who are anuric, urine samples will not be collected.

o. This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at the site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for future biomedical research if the subject signs the FBR consent. 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.

p. All subjects who received at least one dose of MK-3866 will return to the Clinical Research Unit (CRU) approximately 14 days after the last dose for follow-up procedures, and to determine if any adverse events have occurred since the last study visit.

q. During HD, blood samples for MK-3866 will be collected from both the pre-dialyzer and post-dialyzer blood lines; thus 2 plasma samples per time point during HD will be taken. A blood sample (a pre-dialyzer and post-dialyzer) will also be obtained immediately before the HD is stopped, if this time point does not coincide with a time point that is already scheduled.

r. Dialysate samples for determination of MK-3866 will be obtained pre-dialysis, post-dialysis (before the HD is stopped), and for 1 minute every half hour during HD.

s. HD session will be initiated immediately following the 0.5-hour postdose blood draw.

Abbreviations: ConMed = Concomitant Medication, CRU = Clinical Research Unit, FU = Follow-Up, FSH = Follicle Stimulating Hormone, HIV = Human Immunodeficiency Virus, IV = Intravenous, HD = Hemodialysis P = Predose, RI = Renal Impairment, S = Screening, UA = Urinalysis

7 BACKGROUND AND RATIONALE

7.1 Background

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 β-lactamases (BLs) poses a growing threat to the clinical utility of all β-lactams. There are 4 major classes of BLs; classes A, B, C, and D. Classes A, C, and D are serine-based enzymes, while class B are metallo-enzymes with a zinc active site required for hydrolysis of the β-lactam ring.

MK-3866 is a potent small molecule class B metallo-β-lactamase inhibitor (MBLi) which is being developed as part of combination therapy with β-lactam antibiotics to restore their antibacterial activity against resistant metallo-β-lactamase (MBL)-expressing gram-negative bacteria. The ability to improve treatment of infections caused by resistant organisms through the addition of a β-lactamase inhibitor (BLi) is well-established by clinically used β-lactam/BLi combinations that inhibit class A (clavulanic acid, sulbactam, tazobactam) and classes A and C (avibactam, relebactam) enzymes. There are currently no clinically available inhibitors of class B MBLs and no good treatment options for MBL-expressing gram-negative bacterial infections. Therefore, the addition of an MBLi component to current and future treatment regimens would address a growing unmet medical need and represent a significant advance in the treatment of resistant gram-negative bacterial infections.

MK-3866 [redacted] of many MBLs. [redacted]

[redacted]

MK-3866 has a low potential to cause drug-drug interactions (DDIs) as a perpetrator by inhibition or induction of cytochrome P450 enzymes (CYPs) and major transporters, [redacted]

MK-3866 has recently completed dosing the first-in-human (FIH) single ascending dose trial (PN001), and the multiple ascending dose trial (PN002) commenced dosing on 01-Jun-2017. [redacted]

Sixteen healthy adult subjects have received at least one dose of MK-3866 in PN001. MK-3866 in single doses up to 1200 mg, and divided doses up to 2000 mg (2 x 1000 mg, administered 6 hours apart) was generally well-tolerated, with no reported serious adverse experiences (SAEs), AEs leading to discontinuation, or events of clinical interest. [redacted]

Please refer to the Confidential Clinical Investigator's Brochure (IB) for detailed background information on MK-3866 in the following areas:

- Physical, Chemical, and Pharmaceutical Properties and Formulation
- Nonclinical Pharmacology
- Safety Pharmacology and Supplemental Safety Pharmacology Studies
- Pharmacokinetics and Product Metabolism in Animals
- Toxicology (Preclinical Safety Assessment)
- Effects in Humans and Clinical Experience

7.2 Rationale

7.2.1 Rationale for this Study and Study Design

[redacted]

MK-3866 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 study is thus to understand the effect of RI on the pharmacokinetics of MK-3866 in order to guide dosing recommendations in these patients. [redacted]

Renal clearance is expected to be the major elimination pathway for MK-3866. Parameter estimates were obtained from an interim pharmacokinetic analysis indicating that ~65% of MK-3866 is excreted in the urine following a single IV dose. Simulations conducted predict that the effect of RI on single dose pharmacokinetic will be a reduction in clearance, thereby increasing the terminal half-life and AUC. A change in the peak plasma concentration

(Cmax) following a single dose is not anticipated. However, these predictions do not take into consideration the role of hepatic elimination, which is anticipated to be a significant elimination pathway for MK-3866 as well. It is established that RI can affect the non-renal clearance of compounds like MK-3866, that are partially hepatically cleared, and so this trial will provide insight into the role of non-renal clearance mechanisms in the setting of RI.

Based on the predominance of renal elimination of MK-3866 and the simulations performed, it is expected that RI will affect to varying degrees the pharmacokinetic of MK-3866, with the likely requirement for dosing adjustment(s). A full pharmacokinetic study design has thus been selected and will enable the estimation of the impact on pharmacokinetic across the spectrum of RI, in order to inform dose adjustments needed in each of mild, moderate, and severe RI, as well as the establishment of recommendations for dosing with respect to HD [1].

Given the limited developmental and reproductive toxicity data available for MK-3866, enrollment shall be restricted to adult males and females of non-childbearing potential who meet the study's eligibility criteria. Healthy subjects and subjects with RI, but not patients with acute bacterial infection, will be enrolled to allow the assessment of pharmacokinetics, safety, and tolerability of MK-3866; these assessments may be confounded in the presence of active infection.

7.2.2 Rationale for the Dose Selection

MK-3866 is currently undergoing evaluation in clinical trials with healthy subjects; therefore the planned clinical dose has not yet been established. At the time of writing this protocol, the projected clinical dose is approximately 300 mg. However, a 200 mg dose has been selected for this study on the grounds that it is sufficiently close to the projected clinical dose so as to enable prediction of pharmacokinetic at the clinical dose, yet is anticipated to be well-tolerated by all study subjects, regardless of renal function.

Because both renal (~65%) and hepatic (~35% predicted) pathways are involved in the elimination of MK-3866, the evaluation at the maximum possible dose (as limited by the tolerability considerations below) is preferred in order to maximize insight into the effect of RI on pharmacokinetic, in particular the impact of reduced renal clearance on hepatic elimination.

In the FIH study (PN001) of MK-3866 in healthy subjects, [redacted] single doses of up to 1200 mg and divided doses of up to 2000 mg (2 x 1000 mg, six hours apart) were generally well-tolerated, [redacted]

In consideration of the tolerability of MK-3866 in subjects with RI, the dose of study drug in this trial has been selected so that the exposure in all subjects is not expected to exceed the exposure at 800 mg in healthy subjects (AUC0-∞ of 272 µM*hr and Ceoi of 97 µM). Modeling projections predict that a 200 mg dose in ESRD subjects will produce an AUC0-∞

of 202 µM*hr (1.3X exposure margin) and Ceoi of 24 µM. There is additional confidence in the tolerability of the selected dose on the basis of the acceptable tolerability [redacted] of a single 1200 mg dose in healthy subjects, which produced an AUC0-∞ of 439 µM*hr (2.2 x exposure margin for the 200 mg dose in subjects with ESRD) and Ceoi of 152 µM.

7.2.3 Rationale for Planned Exploratory Biomarker Research

7.2.3.1 Planned Genetic Analysis

Understanding genetic determinants of drug response and the molecular basis of disease is an important endeavor during medical research. This research will evaluate whether genetic variation within a clinical trial population correlates with response to the treatment(s) under evaluation and/or disease. If genetic variation is found to predict efficacy or adverse events, the data might inform optimal use of therapies in the patient population. Knowledge of the molecular basis of disease contributes to the development of novel biomarkers and the identification of new drug targets. This research contributes to understanding molecular basis of disease and the genetic determinants of efficacy and safety associated with the treatments in this study.

7.2.3.2 Rationale for Future Biomedical Research

The Sponsor will conduct Future Biomedical Research on DNA specimens consented for future biomedical research during this clinical trial.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented subjects. The objective of collecting/retaining specimens for Future Biomedical Research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that subjects receive the correct dose of the correct drug/vaccine at the correct time. The details of this Future Biomedical Research sub-trial are presented in Appendix 2 - Collection and Management of Specimens for Future Biomedical Research.

8 STUDY OBJECTIVES, ESTIMATIONS AND ENDPOINTS

8.1 Objectives and Estimations

8.1.1 Primary

Objective 1: To compare the plasma pharmacokinetics (e.g., AUC0-∞, AUC0-last, AUC0-24, Ceoi (Cmax), Tmax, elimination terminal t½, CL, and Vz) of MK-3866 following a single IV dose in subjects with mild RI to those of mean healthy matched control subjects.

Estimation 1: The AUC0-∞ following a single IV dose of MK-3866 administered to subjects with mild RI will be estimated and compared to the AUC0-∞ when administered to mean healthy matched control subjects.

Objective 2: To compare the plasma pharmacokinetics (e.g., AUC0-∞, AUC0-last, AUC0-24, Ceoi (Cmax), Tmax, elimination terminal t½, CL, and Vz) of MK-3866 following a single IV dose in subjects with moderate RI to those of mean healthy matched control subjects.

Estimation 2: The AUC0-∞ following a single IV dose of MK-3866 administered to subjects with moderate RI will be estimated and compared to the AUC0-∞ when administered to mean healthy matched control subjects.

Objective 3: To compare the plasma pharmacokinetics (e.g., AUC0-∞, AUC0-last, AUC0-24, Ceoi (Cmax), Tmax, elimination terminal t½, CL, and Vz) of MK-3866 following a single IV dose in subjects with severe RI to those of healthy matched control subjects.

Estimation 3: The AUC0-∞ following a single IV dose of MK-3866 administered to subjects with severe RI will be estimated and compared to the AUC0-∞ when administered to mean healthy matched control subjects.

Objective 4: To compare the plasma pharmacokinetics (e.g., AUC0-∞, AUC0-last, AUC0-24, Ceoi (Cmax), Tmax, elimination terminal t½, CL, and Vz) of MK-3866 following a single IV dose administered after HD in subjects with ESRD to those of mean healthy matched control subjects.

Estimation 4: The AUC0-∞ following a single IV dose of MK-3866 administered after HD to subjects with ESRD will be estimated and compared to the AUC0-∞ when administered to mean healthy matched control subjects.

Objective 5: To compare the plasma pharmacokinetics (e.g., AUC0-∞, AUC0-last, AUC0-24, Ceoi (Cmax), Tmax, elimination terminal t½, CL, and Vz) of MK-3866 following a single IV dose administered prior to HD in subjects with ESRD to those of mean healthy matched control subjects.

Estimation 5: The AUC0-∞ following a single IV dose of MK-3866 administered prior to HD to subjects with ESRD will be estimated and compared to the AUC0-∞ when administered to mean healthy matched control subjects.

8.1.2 Secondary

Objective 1: To investigate the extent to which MK-3866 is removed by HD.

Estimation 1: The extent to which MK-3866 is removed by HD from the plasma (e.g., Ca, Cv, AUCD, AUC[1-4.5]Ca, AUC[1-4.5]Cv, and CLD,plasma) or the dialysate (e.g., CD, AD, rr, AD,total, and CLD,dialysate) will be estimated.

Objective 2: To compare the urine pharmacokinetics (e.g., Ae0-24, Fe, and CLr) of MK-3866 following a single IV dose of MK-3866 to subjects with varying degrees of RI, where possible, to those of healthy matched control subjects.

Estimation 2: The Ae0-24, Fe, and CLr following a single IV dose of MK-3866 administered to subjects with varying degrees of RI, as appropriate, will be estimated and compared to those estimated in mean healthy matched control subjects.

Objective 3: To evaluate the safety and tolerability of the administration of a single IV dose of MK-3866 in subjects with varying degrees of RI.

8.1.3 Exploratory Objective

Objective: To explore the relationship between eGFR and pharmacokinetics (e.g. CLr and AUC0-∞) of MK-3866 using a model-based approach.

8.1.4 Planned Exploratory Biomarker

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 this study.

8.2 Analysis Endpoints

Pharmacokinetics:

Part 1 and Part 2

The pharmacokinetic parameters AUC0-∞, AUC0-last, AUC0-24, Ceoi (Cmax), Tmax, elimination terminal t½, CL, and Vz in plasma, and Ae0-24, Fe, and CLr in urine, as appropriate, for MK-3866 will be computed.

Part 2

In addition, in Part 2, the following pharmacokinetic parameters will be calculated during HD for plasma MK-3866: Ca, Cv, AUCD, AUC(1-4.5)Ca, AUC(1-4.5)Cv, and CLD,plasma and for dialysate MK-3866: CD, AD, rr, AD,total, and CLD,dialysate.

Safety:

Safety endpoints will include adverse events, physical examinations, vital signs, 12-lead ECGs, and clinical laboratory tests.

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is an open-label, 2-part, single dose study in renal impaired and healthy control subjects. Part 1 will include subjects with mild, moderate, and severe RI and healthy control subjects, and Part 2 will include subjects with ESRD undergoing HD. Parts 1 and 2 of the study may be conducted concurrently.

Screening of subjects will occur within 28 days prior to dosing in Part 1 or prior to the first dose in Part 2. Up to thirty-two (32), adult, male and female (non-childbearing potential only) subjects with RI, and at least 8 (up to 24) age- and BMI-matched healthy control adult male and female subjects will be enrolled.

Study parts and assignment to a renal function group will be as follows:

Panel	RI Group	N	eGFR (mL/min/1.73m^2)*
Part 1			
A	Mild	8	60 ≤ eGFR < 90
B	Moderate	8	30 ≤ eGFR < 60**
C	Severe	8	< 30, not on dialysis
D	Healthy Matched Control	≥ 8	≥ 90
Part 2			
E	ESRD requiring HD	8	requiring HD

* eGFR based on MDRD equation at screening. Baseline eGFR will be obtained by taking the mean of the eGFR obtained from screening and from historical values within a 3-month period from 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 two values will be used for group assignment; the second baseline eGFR sample may be obtained at the time of check-in.

** Reasonable efforts will be made to enroll at least 2 subjects with eGFR values of 30 - 40 mL/min/1.73m^2

Subjects 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 subjects of each gender.

Panel D: At least 8 and up to 24 healthy subjects (eGFR ≥ 90 mL/min/1.73 m^2), matched to the gender, mean age (± 15 years) and BMI (± 10%) of subjects in the mild, moderate, severe RI, and subjects with ESRD panels (Panels A, B, C, and E) as follows:

Enrolment of 8 healthy matched control subjects (Panel D) will commence following the completion of enrolment of Panels A and B. Each healthy control subject will be matched to

the mean age (± 15 years) and the mean BMI (± 10%) of the subjects in Panels A and B combined. There should be a minimum of 2 subjects of each gender in each panel.

The data from the already enrolled healthy subjects who satisfy the gender, mean age and BMI matching criteria of the RI subjects in each Panel (C and E) will be used. However, if any of the healthy subjects do not meet the matching criteria described above, additional healthy subjects will be enrolled to result in a total of 8 healthy subjects who match the mean age (± 15 years) and the mean BMI (± 10%) of each Panel C and E. The gender of the additional healthy subject(s) will be selected to ensure that there is a minimum of 2 subjects of each gender in the group of subjects within Panel D who match with Panels C and E.

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

In both Parts, MK-3866 will be administered IV over 30 minutes (± 5 minutes).

Part 1:

Subjects in Panels A, B, C, and D will receive a single IV dose of MK-3866. Plasma samples will be taken at pre-specified time points up to 72 hours postdose, depending on the panel and urine samples will be collected over pre-specified time intervals up to 24 hours postdose, where possible, for pharmacokinetic assessment of MK-3866.

Part 2:

Subjects in Panel E will receive a single IV dose of MK-3866 on two separate occasions.

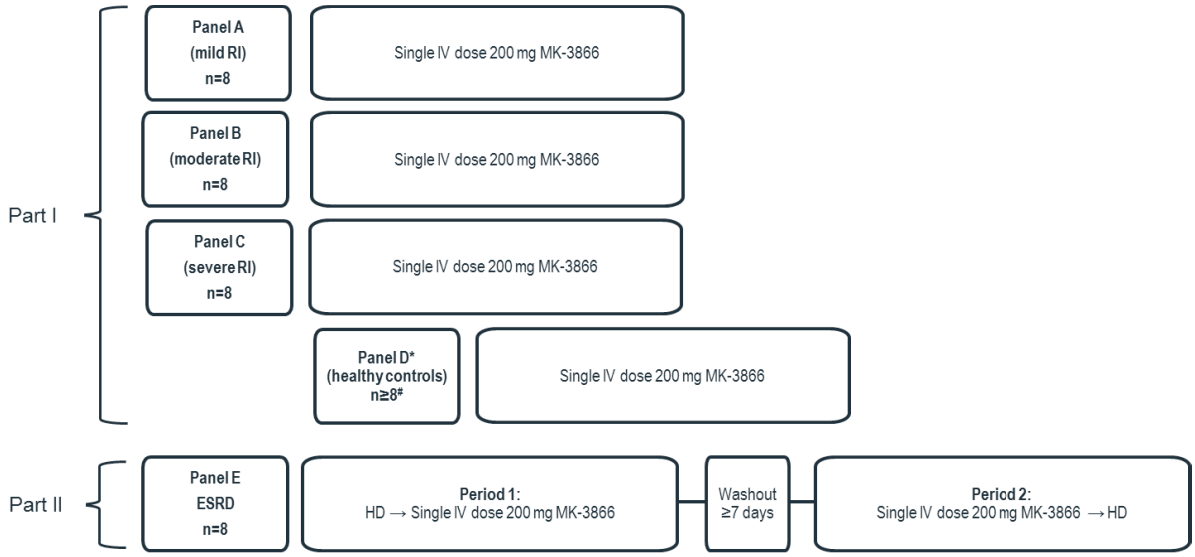
In Period 1, subjects will receive a single IV dose of MK-3866 immediately following completion of their normally-scheduled HD, followed by 72 hours plasma sampling and by 24 hours urine collection, where possible, for pharmacokinetic assessment of MK-3866.

In Period 2, subjects will receive a single IV dose of MK-3866 approximately 30 minutes prior to their normally scheduled HD followed by 72 hours plasma sampling and by 24 hours urine collection, where possible, for pharmacokinetic assessment of MK-3866. During this dialysis session, additional plasma and dialysate samples will be taken for MK-3866 analysis.

There will be a washout period of at least 7 days between MK-3866 dosing in Periods 1 and 2 of Part 2.

The figure below represents a summary of the study design.

Figure 1: Study design schematic



*Panel D is to commence enrollment following completion of enrollment of Panels A and B
#Subjects will be enrolled into Panel D as per the protocol-specified matching criteria. The total number of subjects in this Panel will be ≥8, but will not exceed 24.

Subjects who are discontinued may be replaced at the discretion of the Sponsor.

9.1.1 Confinement, Return Visit(s), and Follow-up

In each part and in each period, subjects will be housed from either Day -2 or Day – 1 at the time indicated by the CRU, until after the last study procedures of that part. At all times, a subject may be required to remain at the CRU for longer at the discretion of the Investigator.

All subjects who received at least one dose will return to the CRU approximately 14 days after the last dose for follow-up procedures, and to determine if any adverse events have occurred since the last study visit.

9.1.2 Study Duration

The duration of Part 1 of the study from screening to Day 4 is approximately 4.5 weeks. The duration of Part 1 of the study from screening to follow-up is approximately 6 weeks.

The duration of Part 2 of the study from screening to Day 4 of Period 2 is approximately 5.5 weeks. The duration of Part 2 of the study from screening to follow-up is approximately 7 weeks.

9.2 Selection of Study Population

9.2.1 Inclusion Criteria

9.2.1.1 Renal Impaired Subjects

Subjects must fulfill all of the following inclusion criteria to be eligible for participation in the study, unless otherwise specified:

1. Adult male or female (non-childbearing potential only) subjects, 18-75 years of age, inclusive, at screening.

2. Has a BMI $\geq$ 18.0 and $\leq$ 40.0 kg/m^2, at screening.

3. Have a stable baseline health, based on medical history, physical examination, vital sign measurements, 12-lead ECGs, and clinical laboratory safety tests performed at screening. Subjects who do not qualify based on a reversible condition or mild intercurrent illness may be re-screened after the underlying condition is resolved.

4. Liver function tests (serum alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) and serum bilirubin (total and direct) must be within the upper limit of normal for the laboratory used by the clinical site.

5. Females must be of non-childbearing potential and are defined as:

    - Postmenopausal: defined as, without menses for at least 1 year and has a documented follicle stimulating hormone (FSH) level in the postmenopausal range at screening.

    - Surgically sterile: defined as, status post hysterectomy or oophorectomy, or tubal ligation.

      NOTE: These procedures must be confirmed with medical records or via pelvic exam or ultrasound scan, as applicable. In the absence of documentation, oophorectomy may be confirmed by hormone levels, particularly FSH in the postmenopausal range, but tubal ligation subjects without records should be excluded. Information must be captured appropriately within the site's source documents.

6. Male subjects with female partner(s) of child-bearing potential must agree to use a medically acceptable method of contraception during the study and for 90 days after dosing. If their partner is pregnant, males must agree to use a condom; if their partner is of child-bearing potential, their partner must additionally be using one of the following methods: hormonal contraception, intra-uterine device, diaphragm, or cervical cap. Spermicides alone are not an acceptable method of contraception

7. Male subjects must agree not to donate sperm from the first dose until 90 days after dosing.

8. Have adequate venous access, as determined by the Investigator or designee, at screening.

9. Understands the study procedures in the informed consent forms (ICFs), is willing and able to comply with the protocol, and provide written informed consent to the study. Future Biomedical Research participation is voluntary and is not required in order to participate in the study.

10. ***For Panel A only:*** Baseline eGFR is ≥60 and <90 mL/min/1.73m^2 based on the MDRD equation at screening defined as follows (for females multiply result by 0.742, if African American multiply result by 1.212).

    The MDRD equation is:

    $$eGFR = 175 \times (S_{cr,std})^{-1.154} \times (Age)^{-0.203}$$

    $S_{cr, std}$: serum creatinine (mg/dL) measured with a standardized assay.

    Baseline eGFR will be obtained by taking the mean of the eGFR obtained from screening and from historical values within a 3-month period from 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 two values will be used for group assignment; the second baseline eGFR sample may be obtained at the time of check-in.

11. ***For Panel B only:*** Baseline eGFR is ≥30 and <60 mL/min/1.73m^2 based on the MDRD equation at screening. Reasonable efforts will be made to enroll at least 2 subjects with eGFR values of 30 - 45 mL/min/1.73m^2.

    The MDRD equation to be used will be as above. Baseline eGFR will be obtained by taking the mean of the eGFR obtained from screening and from historical values within a 3-month period from 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 two values will be used for group assignment; the second baseline eGFR sample may be obtained at the time of check-in.

12. ***For Panel C only:*** Baseline eGFR is <30 mL/min/1.73m^2 based on the MDRD equation, but not on HD at screening.

    The MDRD equation to be used will be as above. Baseline eGFR will be obtained by taking the mean of the eGFR obtained from screening and from historical values within a 3-month period from 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 two values will be used for group assignment; the second baseline eGFR sample may be obtained at the time of check-in.

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

14. ***For Panel E only***: subject has ESRD maintained on stable regimen of at least three times per week HD for at least 3 months prior to first dosing.

9.2.1.2 Healthy Subjects

Subjects must fulfill all of the following inclusion criteria to be eligible for participation in the study, unless otherwise specified:

1. Healthy adult male or female (non-childbearing potential only) subjects, 18-75 years of age, inclusive, at screening. Age must be within ± 15 years of the mean age of subjects within the RI panel(s) to which the subject is matched.

2. Has a BMI ≥18.0 and ≤40.0 kg/m^2, at screening. BMI must be within ± 10 % of the mean BMI of subjects within the RI panel(s) to which the subject is matched.

3. Medically healthy with no clinically significant medical history, physical examination, vital signs, 12-lead ECGs, and clinical laboratory safety tests performed at screening.

4. Blood urea nitrogen, liver function tests (ALT, AST, alkaline phosphatase [ALP]), and serum bilirubin (total and direct) must be within the upper limit of normal for the laboratory used by the clinical site. Abnormal serum creatinine and urinalysis results must be determined to not be clinically significant by the Investigator.

5. Females must be of non-childbearing potential and are defined as:

    - Postmenopausal: defined as, without menses for at least 1 year and has a documented FSH level in the postmenopausal range at screening.

    - Surgically sterile: defined as, status post hysterectomy or oophorectomy, or tubal ligation.

      NOTE: These procedures must be confirmed with medical records or via pelvic exam or ultrasound scan, as applicable. In the absence of documentation, oophorectomy may be confirmed by hormone levels, particularly FSH in the postmenopausal range, but tubal ligation subjects without records should be excluded. Information must be captured appropriately within the site's source documents.

6. Male subjects with female partner(s) of child-bearing potential must agree to use a medically acceptable method of contraception during the study and for 90 days after

dosing. If their partner is pregnant, males must agree to use a condom; if their partner is of child-bearing potential, their partner must additionally be using one of the following methods: hormonal contraception, intra-uterine device, diaphragm, or cervical cap. Spermicides alone are not an acceptable method of contraception.

7. Male subjects must agree not to donate sperm from the first dosing until 90 days after dosing.

8. Have adequate venous access, as determined by the Investigator or designee, at screening.

9. Understands the study procedures in the ICFs, is willing and able to comply with the protocol, and provide written informed consent to the study. Future Biomedical Research participation is voluntary and is not required in order to participate in the study.
10. Baseline eGFR ≥90 mL/min/1.73 m^2 based on MDRD equation at screening.

    The MDRD equation to be used will be as above. Baseline eGFR will be obtained by taking the mean of the eGFR obtained from screening and from historical values within a 3 months period from 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 two values will be used for group assignment; the second baseline eGFR sample may be obtained at the time of check-in.

9.2.2 Exclusion Criteria

9.2.2.1 Renal Impaired Subjects

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

1. Is under the age of legal consent.

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

3. Has a history of clinically significant endocrine, gastrointestinal, cardiovascular, hematological, hepatic, immunological, renal, respiratory, genitourinary or major neurological (including stroke within 1 year and chronic seizures) abnormalities or diseases. Subjects with a history of minor limited disease in the past (e.g., uncomplicated kidney stones, as defined as spontaneous passage and no recurrence in the last 5 years, uncomplicated appendectomy or childhood asthma) may be enrolled in the study at the discretion of the Investigator.

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

5. Has a clinically significant history of cancer. Remote history with full cure or limited disease with complete resection (cure) may be included at the discretion of the Investigator.

6. Is a smoker and/or has used nicotine or nicotine-containing products (e.g., nicotine patch) within 3 months prior to screening.

7. Has QTcF ≥460 msec (for males) or ≥470 msec (for females) or has ECG findings deemed abnormal with clinical significance by the PI or designee at screening.

8. Is a regular user of cannabis or any illicit drug(s) or has a history of drug (including alcohol) abuse within approximately 1 year.

9. Has a history or presence of hypersensitivity or idiosyncratic reaction to the study drug or related compounds.

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

11. Female subjects who are of childbearing potential, pregnant, or lactating.

12. Positive results for the urine or saliva drug screen and/or urine or breath alcohol screen at screening or check-in, unless the positive drug screen is due to prescription drug use that is approved by the Investigator and Sponsor's Clinical Monitor.

13. Positive urine or saliva cotinine (as per site standard operating procedures) at screening.

14. Positive results at screening for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C virus (HCV).

15. Is unable to refrain from or anticipates the use of any medication or substance (including prescription or over-the-counter, vitamin supplements, natural or herbal supplements) as indicated in Section 9.3.1 for the prohibited time period.

16. Consumes more 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, within 6 months of screening. Subjects who consume 4 glasses of alcoholic beverages per day may be enrolled at the discretion of the Investigator.

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

18. Has been on a diet incompatible with the on-study diet, in the opinion of the Investigator, within the 30 days prior to dosing in Part 1 or first dose in Part 2 and throughout the study.

19. Has had major surgery, donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks prior to screening.

20. Has donated plasma within 7 days prior to dosing in Part 1 or first dose in Part 2.

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

22. Has participated in another clinical trial within 28 days (or 5 half-lives of the study drug administration in another clinical trial), whichever is greater, prior to dosing in Part 1 or first dose in Part 2. The minimum of a 28-day window will be derived from the date of the last dose in the previous study.

23. Is considered for any reason by the investigator to be inappropriate for safe participation in the study.

24. ***For Panels A, B, and C:*** Has had a failed renal transplant or has had nephrectomy.

25. ***For Panels A, B, and C:*** Has rapidly fluctuating renal function, as determined by historical measurements; or has demonstrated or suspected renal artery stenosis. Rapidly fluctuating renal function is defined as creatinine clearance or estimated GFR that differs by more than 30% within 3 months of the screening eGFR or creatinine clearance determination. If historical measurements are not available, then the 2 screening measurements will be used to demonstrate stability.

26. ***For Panel E only:*** Has required frequent emergent HD (≥3) within a year prior to first dosing.

9.2.2.2 Healthy Subjects

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

1. Is under the age of legal consent.

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

3. Has a history of clinically significant endocrine, gastrointestinal, cardiovascular, hematological, hepatic, immunological, renal, respiratory, genitourinary or major neurological (including stroke within the previous 1 year and chronic seizures) abnormalities or diseases. Subjects with a history of minor limited disease in the past

(e.g., uncomplicated kidney stones, as defined as spontaneous passage and no recurrence in the last 5 years, uncomplicated appendectomy or childhood asthma) may be enrolled in the study at the discretion of the Investigator.

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

5. Has a clinically significant history of cancer. Remote history with full cure or limited disease with complete resection (cure) may be included at the discretion of the Investigator.

6. Is a smoker and/or has used nicotine or nicotine-containing products (e.g., nicotine patch) within 3 months prior to screening.

7. Has QTcF ≥460 msec (for males) or ≥470 msec (for females) or has ECG findings deemed abnormal with clinical significance by the PI or designee at screening.

8. Is a regular user of cannabis or any illicit drug(s) or has a history of drug (including alcohol) abuse.

9. Has a history or presence of hypersensitivity or idiosyncratic reaction to the study drug or related compounds.

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

11. Female subjects who are of childbearing potential, pregnant, or lactating.

12. Positive results for the urine or saliva drug screen and/or urine or breath alcohol screen at screening or check-in, unless the positive drug screen is due to prescription drug use that is approved by the Investigator and Sponsor's Clinical Monitor.

13. Positive urine or saliva cotinine (as per site standard operating procedures) at screening.

14. Positive results at screening for HIV, HBsAg, or HCV.

15. Is unable to refrain from or anticipates the use of any medication or substance (including prescription or over-the-counter, vitamin supplements, natural or herbal supplements) as indicated in Section 9.3.1 for the prohibited time period.

16. Consumes more 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, within 6 months of screening. Subjects who consume 4 glasses of alcoholic beverages per day may be enrolled at the discretion of the Investigator.

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

18. Has been on a diet incompatible with the on-study diet, in the opinion of the Investigator, within the 30 days prior to dosing and throughout the study.

19. Has had major surgery, donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks prior to screening.

20. Has donated plasma within 7 days prior to dosing.

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

22. Has participated in another clinical trial within 28 days (or 5 half-lives of the study drug administration), whichever is greater, prior to dosing. The minimum of a 28-days window will be derived from the date of the last dose in the previous study.

23. Is considered for any reason by the investigator to be inappropriate for safe participation in the study.

24. Has had a renal transplant or has had nephrectomy.

9.2.3 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be discontinued from the trial at the discretion of the Investigator should any untoward effect occur. In addition, a subject may be withdrawn by the Investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal procedures, including specific details regarding withdrawal from Future Biomedical Research, are provided in Section 9.2.3.1.

Discontinuation is “permanent”. Once a subject is discontinued, he/she shall not be allowed to enroll again.

Subjects who are discontinued may be replaced at the discretion of the Sponsor.

A subject must be discontinued from the study for any of the following reasons:

- The subject withdraws consent.
- The subject has a confirmed positive serum pregnancy test.
- The subject has a medical condition or personal circumstance which, in the opinion of the Investigator and/or Sponsor, places the subject at unnecessary risk through continued participation in the trial or does not allow the subject to adhere to the requirements of the protocol.

A subject may be discontinued from the study for any of the following reasons:

- Adverse events.
- Difficulties in blood collection.
- Protocol violation (other than those listed above).

9.2.3.1 Withdrawal/Discontinuation

The Investigator or designee must notify the Sponsor when a subject has been discontinued/withdrawn from the study. If a subject discontinues for any reason at any time during the course of the study, the procedures scheduled at early termination (as outlined in Section 6) will be performed. Furthermore, the subject will be asked to return to the clinic, for a follow-up (approximately 14 days after dosing in Part 1 or last dose in Part 2), to determine if any adverse events have occurred since the last visit. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 10.1.7.

9.2.3.1.1 Withdrawal from Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research. Subjects may withdraw consent at any time by contacting the Principal Investigator for the main trial. If medical records for the main trial are still available, the Investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the subject's consent for Future Biomedical Research will be withdrawn. A letter will be sent from the Sponsor to the Investigator confirming the withdrawal. It is the responsibility of the Investigator to inform the subject of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

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

9.3 Study Restrictions

9.3.1 Prohibitions and Concomitant Medication

Consumption of foods and beverages containing the following substances will be prohibited as indicated:

- Xanthines/Caffeine: 24 hours prior to dosing until the last pharmacokinetic sample collection in Part 1 and 24 hours prior to each dosing in Part 2 until the last pharmacokinetic sample collection following each dosing;

- Alcohol: 48 hours prior to dosing until the last pharmacokinetic sample collection in Part 1 and 24 hours prior to each dosing in Part 2 until the last pharmacokinetic sample collection following each dosing;
- Grapefruit/Seville orange: 14 days prior to dosing in Part 1 and first dose in Part 2 and throughout the study.

Concurrent medication during the course of the protocol including both prescription and non-prescription drugs must first be discussed with the Investigator and Sponsor Clinical Monitor prior to dosing in Part 1 or first dose in Part 2, unless appropriate medical care necessitates that therapy should begin before the Investigator and Sponsor Clinical Monitor can be consulted. Once dosed with study drug, acetaminophen (up to 2 g per 24 hours) may be administered at the discretion of the Investigator.

Appropriate sources will be consulted by the Investigator or designee to confirm lack of pharmacokinetic/pharmacodynamic interaction with the study drug. If deviations occur, the Investigator will decide on a case-by-case basis whether the subject may continue participation in the study based on the time the study drug and concomitant medication was administered and its pharmacology.

All medications taken by subjects during the course of the study will be recorded.

For Renal Impaired Subjects:

All prescription or non-prescription medications (including St. John's Wort) that are strong inhibitors or strong inducers of CYP3A enzyme, 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.

Subjects who are taking certain prescription medications to treat manifestations of renal disease or medications needed to treat stable diseases (e.g., angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists, beta-blockers, diuretics) may be allowed to participate in the study at the discretion of the Investigator and following consultation with the Sponsor Clinical Monitor. Subjects must be on a stable regimen for at least 2 weeks (or 5 half-lives of the concomitant medication, whichever is longer) prior to dosing in Part 1 or first dose in Part 2 and is able to withhold the use 4 hours prior to and 4 hours postdose of study drug. If a subject 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 (e.g., cimetidine) must be discontinued at least 2 weeks (or 5 half-lives of the compound, whichever is longer) prior to dosing in Part 1 or first dose in Part 2 and throughout the study.

For Healthy Subjects:

Any medication or substance (including prescription or over-the-counter, vitamin supplements, natural or herbal supplements) which cannot be discontinued at least 14 days prior to dosing and throughout the study are prohibited. All prescription or non-prescription medications (including St. John's wort) that are strong inhibitors or strong inducers of CYP 3A enzyme, or inhibitors of OATP1B1/1B3 transporters will be prohibited for at least 14 days (for inhibitors) and 28 days (for inducers) prior to dosing and throughout the study. Moderate and weak CYP 3A inhibitors or inducers may be deemed acceptable following consultation with the Sponsor Clinical Monitor and the Investigator. Subjects who are taking medications for stable diseases for ~1 month for prior to dosing may be allowed to participate in the study at the discretion of the Investigator.

9.3.2 Meals

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

Subjects will fast for at least 1 hour prior to dosing in Part 1 or each dose in Part 2. Subjects will continue the fast for at least 1 hour postdose.

On all days that subjects are confined in the CRU, standard meals and snacks will be provided at appropriate times. When confined in the CRU, subjects will fast from all food and drink except water between meals and snacks.

Each meal and/or snacks served at the CRU will be standardized, and will be similar in caloric content and composition.

9.3.3 Activity

Subjects will remain ambulatory or seated upright for the first 4 hours following study drug administration, except when they are supine or semi-reclined for study procedures.

However, should adverse events occur at any time, subjects may be placed in an appropriate position or will be permitted to lie down on their right side.

Subjects will be instructed to refrain from strenuous physical activity which could cause muscle aches or injury, including contact sports at any time from screening until completion of the study.

9.4 Treatments

9.4.1 Treatments Administered

Please refer to the Study Operations Manual provided by the Sponsor for details of preparation and dispensing procedures.

Part 1:

Subjects will receive a single IV infusion of 200 mg MK-3866 at Hour 0 on Day 1.

Part 2:

Subjects will receive a single IV infusion of 200 mg MK-3866 at Hour 0 on Day 1, immediately after completion of the scheduled HD (Period 1), and at Hour 0 on Day 1, approximately 30 minutes prior to initiation of the scheduled HD (Period 2).

Both Parts:

Each IV infusion will be administered over 30 minutes (±5 minutes).

Hour 0 will correspond to the start of the IV infusion.

The time at which the IV infusion starts and ends will be recorded.

The pharmacy at the CRU will provide the IV dose ready for infusion for each subject and for each study period.

Each IV infusion will be administered using an IV infusion pump system over 30 minutes (± 5 minutes), while subjects are seated or in a semi-reclined position, except when a supine position is dictated by study procedures. Should the need arise to change the infusion rate (i.e., due to an adverse event), changes to the infusion rate and the times at which those changes are made will be documented.

9.4.2 Method of Assigning Subjects to Treatment Groups

Each subject will be assigned a unique identification number upon screening. Subjects who complete the study screening assessments and meet all the eligibility criteria will receive MK-3866 according to allocation schedule generated by Celerion.

If replacement subjects are used, the replacement subject number will be 100 more than the original (e.g., allocation number 0101 will replace allocation number 0001).

9.4.3 Blinding

This is an open-label study.

9.4.4 Treatment Compliance

MK-3866 IV infusion will be performed by a qualified designee. The qualified designee will visually inspect the infusion pump device prior and after IV infusion, to ensure that the subject has received the entire dose. Should an infusion dosing be interrupted or incomplete for any reason (e.g., distal occlusion, proximal air, infiltration, large droplet of study medication on the surface of the skin), the initial start and stop times of the infusion, as well as all reinitiating start and stop times of the infusion will be recorded. Additionally, the pre-and post-infusion bag weights will be recorded.

10 STUDY PROCEDURES

The Study Events Flow Chart (Section 6) summarizes the clinical procedures to be performed at each visit. Individual clinical procedures are described in detail below. Additional evaluations/testing may be deemed necessary by the Investigator and/or the Sponsor for reasons related to subject safety.

For this study, the blood collection for MK-3866 is the critical parameter and needs to be collected as close to the exact time point as possible. All other procedures should be completed as close to the prescribed/scheduled time as possible, but can be performed prior or after the prescribed/scheduled time.

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

10.1 Safety Assessment

10.1.1 Screening

Within 28 days prior to dosing, medical history and demographic data, including name, sex, age, race, ethnicity, body weight (kg), height (cm), BMI (kg/m^2) and history of tobacco use will be recorded. Each subject will have a physical examination, vital sign measurements (heart rate, blood pressure, temperature, and respiratory rate), 12-lead ECG, and the laboratory tests of hematological, hepatic and renal function and additional tests as noted in Section 10.1.6.

10.1.2 Physical Examination

A full physical examination will be performed as outlined in the Study Events Flow Chart (Section 6). Symptom-driven physical examinations may be performed at other times, if deemed necessary by the Investigator or designee.

10.1.3 Vital Signs

Single measurements of body temperature, respiratory rate, blood pressure, and heart rate, will be measured as outlined in the Study Events Flow Chart (Section 6).

Vital signs may be taken at any other times, if deemed necessary. Blood pressure and heart rate measurements will be performed with subjects in a seated position for at least 1 minute, except when they are supine or semi-reclined because of study procedures and/or adverse events (e.g., nausea, dizziness) or if deemed necessary by the Investigator or designee.

Blood pressure and heart rate will be measured within 24 hours prior to Day 1 dosing for the predose time point. When scheduled postdose, vital signs will be performed within approximately 15 minutes of the scheduled time point.

10.1.4 ECG Monitoring

Triplicate 12-lead ECGs will be performed at screening and predose; single 12-lead ECGs will be performed as outlined in the Study Events Flow Chart (Section 6), at all other times.

Predose triplicate 12-lead ECGs will be measured within 24 hours prior to dosing. The average value from the triplicate 12-lead ECGs collected prior to dosing will be considered the baseline ECG.

Timing and recording technique for triplicate 12-lead ECGs will be standardized for all subjects. Subjects will be required to lie quietly in a supine position with minimal movement and minimal exposure to noise and other environmental stimuli prior to and during ECG extraction. ECGs will be interpreted, signed, and dated by the Investigator or his/her designee. The ECGs will be classified as normal, abnormal but not clinically significant, or having a clinically significant abnormality. In addition, ECG parameter values of ventricular rate, PR interval, QRS duration, and QT interval (corrected and uncorrected) from the automated reading will be noted on the case report form (CRF). All clinically significant findings will be recorded as AEs for subjects enrolled in the study. An average for QTcF interval will be calculated for each triplicate.

Single 12-lead ECGs will be performed within approximately 20 minutes of the scheduled time point. Single ECGs will be performed with subjects in a supine position for at least 5 minutes. All ECG tracings will be reviewed by the Study Physician or his/her designee.

A subject will be withdrawn from the study by the Study Physician if, in their medical judgment, ECG findings are present which make continued study participation not in the subject's best interest.

10.1.5 Hemodialysis (ESRD Subjects Only)

ESRD subjects on HD will receive HD as per their regular schedule and blood and dialysate sampling be collected as outlined in the Study Events Flow Chart (Section 6).

Dosing in Period 1 will occur immediately following completion of a normally scheduled HD session. For subjects following a Monday, Wednesday, Friday HD schedule, MK-3866 will be administered immediately following their Friday HD session. For subjects following a Tuesday, Thursday, Saturday HD schedule, MK-3866 will be administered immediately following their Saturday HD session. The 72-hour HD (either Monday or Tuesday) should initiate immediately following the 72-hour blood draw. If HD must be initiated prior to 72 hours postdose, a sample for MK-3866 analysis will be collected prior to HD, and the time recorded.

Dosing in Period 2 will occur approximately 30 minutes prior to the normally scheduled HD session. For subjects following a Monday, Wednesday, Friday HD schedule, MK-3866 will be administered prior to their Friday HD session. For subjects following a Tuesday, Thursday, Saturday HD schedule, MK-3866 will be administered prior to their Saturday HD

session. The subsequent HD session should initiate immediately following the 30 minute blood draw.

In Period 2, the HD period will be approximately 4 hours for all subjects. 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.

10.1.6 Laboratory Tests

All tests listed below will be performed as outlined in the Study Events Flow Chart (Section 6). In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the Investigator.

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

Serum Chemistry*
- Blood urea nitrogen
- Bilirubin (total and direct)
- ALP
- AST
- ALT
- Albumin
- Sodium
- Potassium
- Chloride
- Glucose (fasting)
- Creatinine**

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

Additional Tests
- HIV test
- HBsAg
- HCV
- Urine or saliva drug screen
  - Opiates
  - Amphetamines
  - Barbiturates
  - Benzodiazepines
  - Cocaine
  - Cannabinoids
- Urine or breath alcohol screen
- Urine or saliva cotinine test
- Serum pregnancy test (for females only)
- FSH (for postmenopausal females only)

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

** At screening, eGFR will be calculated based on MDRD for renal classification assignment. Baseline eGFR will be obtained by taking the mean of the eGFR obtained from screening and from historical values within a 3 months period from 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 two values will be used for group assignment; the second baseline eGFR sample may be obtained at the time of check-in.

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

§ Any unexplained drug-related hematuria or evidence of triphosphate crystals should be referred to a nephrologist.

10.1.7 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Sponsor's product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

Sponsor's product includes any pharmaceutical product, biological product, device, diagnostic agent, or protocol-specified procedure whether investigational or marketed, manufactured by, licensed by, provided by or distributed by the Sponsor for human use.

Adverse events may occur during clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse, and from withdrawal.

For allocated subjects only, all adverse events that occur after the consent form is signed but before allocation must be reported by Investigator if they are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet treatment, or a procedure. From the time of allocation through 14 days following cessation of treatment, all adverse events must be reported by the Investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in Section 10.1.7.3.1. The Investigator will make every attempt to follow all subjects with non-serious adverse events for outcome. Any unexplained drug-related hematuria or evidence of triphosphate crystals should be referred to a nephrologist.

Electronic reporting procedures can be found in the Electronic Data Capture (EDC) data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

10.1.7.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor

The subject has taken (accidentally or intentionally) any drug administered as part of the protocol and exceeding the dose as 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.

If an adverse event(s) is associated with ("results from") the overdose of Sponsor's product or vaccine, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of Sponsor's product or vaccine meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with or without an adverse event must be reported by the Investigator within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

10.1.7.2 Reporting of Pregnancy and Lactation to the Sponsor

Although pregnancy and lactation are not considered adverse events, it is the responsibility of Investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial.

Pregnancies and lactations that occur after the consent form is signed but before allocation must be reported by the Investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, treatment or a procedure. Pregnancies and lactations that occur from the time of allocation through 14 days following cessation of Sponsor's product must be reported by the Investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

10.1.7.3 Immediate Reporting of Adverse Events

10.1.7.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that has the following outcome:

- Death
- Immediately life threatening
- Persistent or significant disability/incapacity
- Inpatient hospitalization or prolongation of hospitalization
- Congenital anomaly/birth defect
- Other important medical event

Note: In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same timeframe as serious adverse events to meet certain local requirements. Therefore, these events are considered serious by the Sponsor for collection purposes.

- Cancer
- Overdose

Refer to Table 1 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, treatment or a procedure.

For the time period beginning at treatment allocation through 14 days following cessation of treatment, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Additionally, any serious adverse event, considered by an Investigator who is a qualified physician to be related to the Sponsor's product that is brought to the attention of the Investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor.

All subjects with serious adverse events must be followed up for outcome.

10.1.7.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as ECI and must be reported to the Sponsor.

For the time period beginning when the consent form is signed until treatment allocation, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, treatment or a procedure.

For the time period beginning at treatment allocation through 14 days following cessation of treatment, any ECI, or follow up to an ECI, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor, either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Events of clinical interest for this trial include:

- an overdose of Sponsor's product, as defined in Section 10.1.7.1 that is not associated with clinical symptoms or abnormal laboratory results.
- an elevated AST or ALT laboratory value that is greater than or equal to three times (3X) the upper limit of normal (ULN) and an elevated total bilirubin laboratory value that is greater than or equal to 2X the ULN and, at the same time, an alkaline phosphatase laboratory value that is less than 2X the ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

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

10.1.7.4 Evaluating Adverse Events

An Investigator who is a qualified physician will evaluate all adverse events with respect to the elements outlined in Table 1. The Investigator's assessment of causality is required for each adverse event. Refer to Table 1 or instructions in evaluating adverse events.

Table 1: Evaluating Adverse Events

Maximum Intensity (Severity)	**Mild**	awareness of sign or symptom, but easily tolerated (for pediatric trials, awareness of symptom, but easily tolerated)
	Moderate	discomfort enough to cause interference with usual activity (for pediatric trials, definitely acting like something is wrong)
	Severe	incapacitating with inability to work or do usual activity (for pediatric trials, extremely distressed or unable to do usual activities)
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that:	
	†**Death**; or	
	†**Immediately life threatening**; or places the subject, in the view of the Investigator, at immediate risk of death from the event as it occurred [Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.]; or	
	†**Persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Inpatient hospitalization or prolongation of 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 [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse event.); or	
	†**Congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis); or	
	Cancer; or	
	Overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. An overdose that is not associated with an adverse event is considered a non-serious ECI and must be reported within 24 hours.	
	Other important medical event that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
	None	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units.	
Action Taken	The action taken is in reference to the either the Sponsor's Product or the Interacting Drug. Did the adverse event cause the Sponsor's product or the Interacting Drug to be:	
	None	
	Reduced	
	Interrupted	
	Discontinued	
	Increased	
	Not Applicable	
	Unknown	

<table>
<tr><td>Relationship to Sponsor's Product</td><td colspan="2">Did the Sponsor's product cause the adverse event? The determination of the likelihood that the Sponsor's product caused the adverse event 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 adverse event form, ensures that a medically qualified assessment of causality was done. This initialled 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 drug and the adverse event based upon the available information.</td></tr>
<tr><td></td><td colspan="2">The following components are to be used to assess the relationship between the Sponsor's product and the adverse event; 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 adverse event:</td></tr>
<tr><td></td><td>Exposure</td><td>Is there evidence that the subject 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?</td></tr>
<tr><td></td><td>Time Course</td><td>Did the adverse event follow in a reasonable temporal sequence from administration of the Sponsor's product?
Is the time of onset of the adverse event compatible with a drug-induced effect (applies to trials with investigational medicinal product)?</td></tr>
<tr><td></td><td>Likely Cause</td><td>Is the adverse event not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors</td></tr>
<tr><td></td><td>Dechallenge</td><td>Was the Sponsor's product discontinued or dose/exposure/frequency reduced?
If yes, did the adverse event 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 adverse event resulted in death or permanent disability; (2) the adverse event resolved/improved despite continuation of the Sponsor's product; (3) the trial is a single-dose drug trial; or (4) Sponsor's product(s) is/are only used one time.)</td></tr>
<tr><td></td><td>Rechallenge</td><td>Was the subject re-exposed to the Sponsor's product in this trial?
If yes, did the adverse event 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 adverse event resulted in death or permanent disability, or (2) the trial is a single-dose drug trial; or (3) Sponsor's product(s) is/are used only one time.)
NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH 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 SUBJECT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE U.S. CLINICAL MONITOR AND THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.</td></tr>
<tr><td></td><td>Consistency with Trial Treatment Profile</td><td>Is the clinical/pathological presentation of the adverse event consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?</td></tr>
<tr><td colspan="3">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.</td></tr>
<tr><td colspan="2">Record one of the following:</td><td>Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).</td></tr>
</table>

Related (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 adverse event onset relative to the administration of the Sponsor's product is reasonable. The adverse event is more likely explained by the Sponsor's product than by another cause.
Not Related (there is not a reasonable possibility of Sponsor's product relationship)	Subject did not receive the Sponsor's product OR temporal sequence of the adverse event onset relative to administration of the Sponsor's product is not reasonable OR there is another obvious cause of the adverse event. (Also entered for a subject with overdose without an associated adverse event.)

10.1.7.5 Sponsor Responsibility for Reporting Adverse Events

All adverse events will be reported to regulatory authorities, IRB or independent ethics committees (IECs), and Investigators in accordance with all applicable global laws and regulations i.e., per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.

10.2 Pharmacokinetic Assessment

10.2.1 Blood Sampling and Processing

For all subjects, blood samples for the determination of MK-3866 will be collected at scheduled time points as delineated in the Study Events Flow Chart (Section 6).

Instructions for blood sampling, collection, processing, and sample shipment for MK-3866 will be provided separately.

Blood collections outside the following windows will be considered deviations:

Hour	Deviation window
0 to 1 hour	± 5 minutes
> 1 to < 24 hour	± 15 minutes
≥24 hour	± 30 minutes

10.2.2 Urine Collection

Prior to the predose sample, each subject will be instructed as to urine collection methods.

Urine samples for determination of MK-3866 concentrations will be collected over selected intervals as outlined in the Study Events Flow Chart (Section 6). For subjects with mild, moderate, and severe RI, and subjects with ESRD, urine samples will be collected whenever possible, as subjects may not be able to produce urine within each interval. For subjects who are anuric, urine samples for urinalysis will not be collected.

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

After administration of MK-3866, during the 24 hour period, all urine will be collected completely. Urine portions will be pooled per subject within any planned collection interval. Just prior to the end of each sampling interval, subjects will be encouraged to void their bladder again to complete the collection. If they void at any time during the collection interval, the time should be documented. Should this be the case, subjects need to attempt to void again at the end of the collection period, as scheduled. However, should subjects be unable to void, this will be documented as well.

Urine will be refrigerated during the collection intervals. The weight of an empty urine collection container and total weight of urine collected during each timed interval will be recorded.

Instructions for urine collection, processing, and sample shipment for MK-3866 will be provided separately.

10.2.3 Dialysate Collection (Part 2 only)

For ESRD subjects only, dialysate samples will be collected at scheduled time points as delineated in the Study Events Flow Chart (Section 6).

Instructions for dialysate sampling, collection, processing, and sample shipment for MK-3866 will be provided separately.

10.3 Planned Genetic Analysis Sample Collection

Sample collection, storage and shipment instructions for Planned Genetic Analysis samples will be provided separately.

10.4 Future Biomedical Research Samples

The following specimens are to be obtained as part of Future Biomedical Research:

- DNA for future research

10.5 Blood Volume Drawn for Study Assessments

Table 2: Blood Volume Drawn During the Study in Part 1

Sample Type	Number of Time Points	Approximate Volume per Time Point * (mL)	Approximate Sample Volume Over Course of Study (mL)
Screening laboratory safety tests (including hematology, serum chemistry, serology), FSH (for postmenopausal female subjects only) and serum pregnancy (for female subjects only).	1	12.5	12.5
Blood for Planned Genetic Analysis	1	8.5	8.5
On-study hematology and serum chemistry (including serum pregnancy for female subjects only when scheduled at the same time)	3	12.5	37.5
Blood for MK-3866 (healthy subject)	13	6	78
Blood for MK-3866 (subject with mild or moderate RI)	15	6	90
Blood for MK-3866 (subject with severe RI)	17	6	102
Total Blood Volume Healthy Subject (mL)→			136.5[§]
Total Blood Volume Subject with Mild or Moderate RI (mL)→			148.5[§]
Total Blood Volume Subject with Severe RI (mL)→			160.5[§]

* Represents the largest collection tube that may be used for this (a smaller tube may be used).

[§] If additional safety or pharmacokinetic analysis is necessary or if larger collection tubes are required to obtain sufficient plasma/serum for analysis, additional blood may be obtained (up to a maximum of 50 mL).

Table 3: Blood Volume Drawn During the Study in Part 2

Sample Type	Number of Time Points	Approximate Volume per Time Point * (mL)	Approximate Sample Volume Over Course of Study (mL)
Screening laboratory safety tests (including hematology, serum chemistry, serology), FSH (for postmenopausal female subjects only) and serum pregnancy (for female subjects only).	1	12.5	12.5
Blood for Planned Genetic Analysis	1	8.5	8.5
On-study hematology and serum chemistry (including serum pregnancy for female subjects only when scheduled at the same time)	7	12.5	87.5
Blood for MK-3866	47	6	282
		Total Blood Volume (mL)→	390.5[§]

* Represents the largest collection tube that may be used for this (a smaller tube may be used).

§ If additional safety or pharmacokinetic analysis is necessary or if larger collection tubes are required to obtain sufficient plasma/serum for analysis, additional blood may be obtained (up to a maximum of 50 mL).

11 DATA ANALYSIS

11.1 Pharmacokinetic Parameters

11.1.1 Plasma

For all subjects, the following pharmacokinetic parameters for plasma MK-3866 will be calculated as appropriate:

AUC0-∞:	Area under the concentration versus time curve from 0 to infinity after single dosing
AUC0-last:	Area under the concentration versus time curve, from 0 to the time of the last quantifiable (above LLOQ) sample
AUC0-24:	Area under the concentration versus time curve, from 0 to 24 hours after dosing
Ceoi:	Concentration at end of infusion
Cmax:	Maximum observed plasma concentration after the administration of a given dose.
CL:	Clearance
Tmax:	Time to maximum observed plasma drug concentration
t½:	Elimination terminal half-life
Vz:	Volume of distribution

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

No values for pharmacokinetic parameters will be estimated for subjects with 2 or fewer consecutive time points with detectable concentrations.

Individual and mean plasma concentration time curves (both linear and log-linear) will be included in the final report.

11.1.2 Urine

For all subjects, values for the following pharmacokinetic parameters for urine MK-3866 will be estimated as appropriate:

Ae0-24:	Total amount of drug excreted unchanged in the urine over the period of 24 hours, obtained by adding the amounts excreted over each collection interval
CLr:	Renal clearance calculated as Ae(t'-t")/AUC(t'-t") where t'-t" is the longest interval of time during which Ae and AUC are both obtained
Fe:	Fraction of MK-3866 excretion during each collection interval. Obtained by dividing the amount of MK-3866 excreted in each collection interval by the dose

11.1.3 Hemodialysis: Plasma and Dialysate

For subjects in Panel E, the following pharmacokinetic parameters for plasma MK-3866 will be calculated as appropriate:

Ca:	Concentration in plasma entering the dialyzer line (arterial or pre-dialyzer line)
Cv:	Concentration in plasma exiting the dialyzer (venous or post-dialyzer line)
AUCD:	Plasma AUC values determined from Ca versus time profile during the dialysis period (0.5-4.5 hours) using 'linear up, log down' calculation method option in WinNonlin
AUC(1-4.5)Ca:	Plasma AUC values determined from Ca versus time profile during the dialysis period from 1 hour to 4.5 hours using 'linear up, log down' calculation method option in WinNonlin
AUC(1-4.5)Cv:	Plasma AUC values determined from Cv versus time profile during the dialysis period from 1 hour to 4.5 hours using 'linear up, log down' calculation method option in WinNonlin
CLD,plasma:	Dialysis clearance based on plasma, calculated as Q x R x (AUC[1-4.5]Ca – AUC[1-4.5]Cv)/ AUC(1-4.5)Ca, where Q is the flow rate of blood through the dialyzer, and R is the ratio of blood drug concentration to plasma drug concentration

For subjects in Panel E, the following pharmacokinetic parameters for dialysate MK-3866 will be calculated as appropriate:

CD:	Concentration in dialysate samples
AD:	Amount of drug recovered from each dialysate collection, calculated as: CD x dialysate volume
rr:	Rate of drug removal, calculated as: (CD x dialysate flow rate)
AD,total:	Cumulative amount of drug recovered from the dialysate will be obtained by integrating the rr versus time profile over the dialysis session duration, using actual times relative to the start time of dialysis
CLD,dialysate:	HD clearance based on dialysate, calculated as: AD,total/AUCD

11.2 Statistical Methods

The statistical analysis of the data obtained from this study will be the responsibility of the Data Management and Biometrics department at Celerion.

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

Additional statistical analyses, other than those described in this section, may be performed if deemed appropriate.

11.2.1 Determination of Sample Size

The sample size selected for each population to evaluate the effect of RI on the pharmacokinetic of MK-3866 was not chosen to satisfy any a priori statistical requirement. This sample size (N=8 per group) has historically been shown to be sufficient for studies of this type and should provide adequate data to support the planned analyses. Nevertheless, estimates of the expected precision of the estimates, based on these sample sizes are presented below.

The precision of the estimates of ratios of geometric means obtained from this study can be assessed by calculating the half-width of the 90% confidence intervals expected for the given sample size and assumed variability. The estimated between-subject variance for log AUC0-∞ is 0.0196 log ng*hr/mL from the FIH study (PN001). Since the between subject variability in subjects with severe RI has historically been seen to be 2-3 fold higher in many studies, the between subject variability obtained from healthy subjects was inflated by a factor of 2 for subjects with severe RI and was used for the following calculations. With 8 renally impaired subjects and 8 healthy matched subjects, the half-width of the 90%

confidence interval for the arithmetic mean AUC0-∞ on the log scale will be 0.151 log ng*hr/mL. The lower and upper 90% confidence limits for the true ratio of geometric means will be given by OBS/1.163 and OBS x 1.163, where OBS is the observed ratio of geometric means. Thus, for example, if the observed ratio of geometric means was 1.5, the 90% confidence interval would be (1.29, 1.74).

11.2.2 Subjects to Analyze

The decision as to which plasma samples collected will be assayed for evaluation of pharmacokinetics/pharmacodynamics will be collaboratively determined by the Departments of Quantitative Pharmacology and Pharmacometrics and Translational Pharmacology. If indicated, these samples may also be assayed and/or pooled for assay in an exploratory manner for metabolites and/or additional pharmacodynamic markers.

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

All Subjects as Treated: All subjects who received at least one dose of the investigational drug. This population will be used for assessments of safety and tolerability.

Per-Protocol: The set of data generated by the subset of subjects who comply with the protocol sufficiently to ensure that these data will be likely to exhibit the effects of treatment, according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements and absence of major protocol violations. Any subjects 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 subjects who are compliant with the study procedure as aforementioned and have available data will be included in the primary analysis dataset. This population will be used for the pharmacokinetic analyses.

11.2.3 Analysis Overview

11.2.3.1 Interim analysis

An interim statistical analysis of the pharmacokinetic data obtained in moderate RI subjects will be performed, including a comparison with data in healthy control subjects from this study.

For this interim statistical analysis, values for the pharmacokinetic parameters AUC0-∞, AUC0-last, AUC0-24, and Ceoi (Cmax) of MK-3866 will be estimated and compared to concurrent healthy control subjects. A Linear Fixed Effects (LFE) Model will be used for the analysis of natural log-transformed pharmacokinetic parameters: AUC0-∞, AUC0-last, AUC0-24, and Ceoi (Cmax) separately. The LFE model will contain a categorical factor for population (moderate RI and healthy control subjects), and possible covariates for age, gender, and BMI, if statistically significant. A two-sided 90% confidence interval for the mean differences of AUC0-∞, AUC0-last, AUC0-24, and Ceoi (Cmax), of MK-3866 will be calculated based on the above model. These confidence limits will then be exponentiated to

obtain confidence intervals for the GMR (moderate RI /healthy) for AUC0-∞, AUC0-last, AUC0-24, and Ceoi (Cmax) of MK-3866. Individual and mean concentrations versus time plots profiles will be also be provided.

11.2.3.2 Primary Analysis

If a different group of healthy matched control subjects 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 subjects;
- Severe RI versus an appropriate group of healthy matched control subjects;
- ESRD subjects (non HD and HD) versus an appropriate group of healthy matched control subjects.

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

Separately for each pharmacokinetic parameter, individual values of AUC0-∞, AUC0-last, AUC0-24, Ceoi (Cmax), and CL 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%) confidence intervals for the least squares means for each population will be constructed on the natural log scale and will reference the t-distribution. Exponentiating the least-squares means and their corresponding 95% confidence intervals will yield estimates for the population geometric means and confidence intervals about the geometric means on the original scale.

To compare subjects with RI in each of the renal categories (mild RI, moderate RI, severe RI, ESRD nonHD and ESRD HD) to matching subjects with normal renal function, a two sided 90% confidence interval for the true difference in means (RI/normal renal function) will be calculated for each PK parameters (AUC0-∞, AUC0-last, AUC0-24, Ceoi (Cmax), and CL) 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% confidence interval for the true ratio of geometric means (RI/normal renal function) for each pharmacokinetic parameter.

Figures showing individual pharmacokinetic values with GMs (95% confidence intervals) by population, plotted on the natural log scale, will be provided for AUC0-∞, AUC0-last, AUC0-24, Ceoi (Cmax), and CL.

Individual values will be listed for each pharmacokinetic parameter (AUC0-∞, AUC0-last, AUC0-24, Ceoi (Cmax), Tmax, elimination terminal t½, CL, Vz, and Fe) by population, and the following (non-model-based) descriptive statistics will be provided: N (number of subjects with non-missing data), arithmetic mean, standard deviation, arithmetic percent CV (calculated as 100 x standard deviation/arithmetic mean), median, minimum, maximum, geometric mean, and geometric percent CV (calculated as 100 x sqrt(exp(s^2) - 1), where s^2 is the observed variance on the natural log-scale).

11.2.3.3 Secondary Analysis

Objective 1

To evaluate the extent to which MK-3866 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 two treatment measurements within each subject 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 CL, AUC0-∞, AUC0-last, and Ceoi (Cmax). For each pharmacokinetic parameter, 95% confidence intervals for the least squares mean will be constructed on the natural log scale and will reference the t-distribution. Exponentiating the least-squares means and their corresponding 95% confidence intervals will yield estimates for the population geometric means and confidence intervals about the geometric means on the original scale.

A two sided 90% confidence interval for the true difference in means (ESRD HD - ESRD non HD) will be calculated for each pharmacokinetic parameter (AUC0-∞, AUC0-last, Ceoi [Cmax], and CL) 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 pharmacokinetic parameter.

Plots with individual ratios overlaid with GMR and corresponding 90% confidence interval will be provided for CL, AUC0-∞, AUClast, and Ceoi (Cmax).

Individual listings and descriptive statistics for CLD,plasma, CLD,dialysate, AD, AD(%dose), AUCD, AUC(1-4.5)Ca, AUC(1-4.5)Cv following a single-dose administration of MK-3866 will be provided for subjects with ESRD receiving HD.

Individual listings and descriptive summary statistics may be provided for CLr for those ESRD subjects in whom it is possible to determine CLr.

Objective 2

Separately for each urine pharmacokinetic 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%) confidence intervals for the least squares means for each population will be constructed. To compare subjects with RI in each of the renal categories (mild RI, moderate RI, severe RI, ESRD nonHD and ESRD HD) to matching subjects with normal renal function, a two sided 90% confidence interval for the true difference in means (RI/normal renal function) will be calculated for each urine pharmacokinetic parameter (Ae0-24, Fe and CLr).

Individual values will be listed for each urine pharmacokinetic parameter (Ae0-24, Fe and CLr) by population, and non-model-based descriptive statistics will be provided.

11.2.3.4 Exploratory Analysis

For this analysis, all the data from Part 1 will be included.

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

Separately for each pharmacokinetic parameter, individual values of AUC0-∞, AUC0-last, AUC0-24, Ceoi (Cmax), CL, and CLr will be evaluated with a linear mixed effects model containing eGFR as a continuous variable. The subject'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 95% confidence intervals will be obtained. The estimated mean and corresponding 95% confidence interval for each RI group will be predicted at the midpoint of the defined eGFR range for each group (75, 45, and 15 for mild, moderate and severe, respectively). However, for the normal renal function subjects, the estimated mean and corresponding 95% confidence interval will be predicted at the median of the observed eGFR values.

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 pharmacokinetic versus renal function or natural log transformed pharmacokinetic versus natural log transformed renal function, will be explored. Other transformations or non-linear models will also be considered.

Additionally, plots of MK-3866 pharmacokinetic parameter values AUC0-∞, AUC0-last, AUC0-24, Ceoi (Cmax), CL, and CLr 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. Additionally, separate plots of AUC0-∞ and Ceoi (Cmax) values vs age and body weight will be provided.

Summary Statistics using BSA un-normalized eGFR: The subjects will be re-categorized into different renal categories based on their BSA un-normalized eGFR and non-model based

summary statistics by population will be provided for (AUC0-∞, AUC0-last, AUC0-24, Ceoi (Cmax), Tmax, CL, Vz, elimination terminal t½, CLr, and Fe, as applicable).

Analysis using CLcr (C-G equation): The subjects will be re-categorized into different renal categories based on their CLcr obtained from C-G equation and non-model based summary statistics by population will be provided for (AUC0-∞, AUC0-last, AUC0-24, Ceoi (Cmax), Tmax, CL, Vz, elimination terminal t½, CLr, and Fe, as applicable).

11.3 Safety Evaluation

The safety and tolerability of MK-3866 will be evaluated by clinical assessment of adverse events and other safety measurements. Summary statistics for the laboratory safety tests, ECGs, and/or vital signs may also be computed and provided, as deemed clinically appropriate.

12 STUDY ADMINISTRATION

12.1 Ethics

12.1.1 Institutional Review Board

This protocol will be reviewed by the PPD and the study will not start until the IRB has approved the protocol or a modification thereof. The IRB is constituted and operates in accordance with the principles and requirements described in the US Code of Federal Regulations (21 CFR Part 56). The IRB is compliant with the International Conference on Harmonization (ICH), and may be reached at:

PPD

12.1.2 Ethical Conduct of the Study

This research will be carried out in accordance with the protocol, US Code of Federal Regulations, GCP, 21 CFR Parts 50, 56, and 312, the ethical principles set forth in the Declaration of Helsinki, and the ICH harmonized tripartite guideline regarding GCP (E6 Consolidated Guidance, April 1996).

12.1.3 Subject Information and Consent

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

Subjects will be given a copy of their ICF.

The initial ICF, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB approval/favorable opinion in advance of use. The subject should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. 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 subject's dated signature.

The informed consent will adhere to IRB/Ethics Research Committee (ERC) requirements, applicable laws and regulations and Sponsor requirements.

12.1.4 Consent and Collection of Specimens for Future Biomedical Research

The Investigator or qualified designee will explain the Future Biomedical Research consent to the subject, answer all of his/her questions, and obtain written informed consent before performing any procedure related to the Future Biomedical Research sub-trial. A copy of the informed consent will be given to the subject.

12.2 Termination of the Study

Celerion and/or Merck reserve the right to terminate the study in the interest of subject welfare.

12.2.1 Clinical Criteria for Early Trial Termination

There are no pre-specified criteria for terminating the trial early.

12.3 Data Quality Assurance

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

The CSR will be audited by the quality assurance (QA) department and the QA audit certificate will be included in the study report.

All clinical data will undergo a 100% quality control check prior to clinical database lock. Edit checks are then performed for appropriate databases as a validation routine using SAS® to check for missing data, data inconsistencies, data ranges etc. Corrections are made prior to database lock.

CRFs are printed off directly from the database. Each CRF is reviewed and signed by the Investigator.

12.4 Data Management

The Investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the Investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the Investigator confirms that all recorded data have been verified as accurate.

Detailed information regarding Data Management procedures will be outlined in Celerion Data Management Plan.

12.5 Direct Access to Source Data/Documents

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

12.6 Drug Supplies, Packaging and Labeling

The Sponsor will supply sufficient quantities of MK-3866 and to allow completion of this study. The lot numbers and expiration dates (where available) of the drugs supplied will be recorded in the final report.

Records will be made of the receipt and dispensing of the drugs supplied. At the conclusion of the study, any unused MK-3866 drugs will be returned to the Sponsor unless otherwise specified by the Sponsor. If no supplies remain, this fact will be documented in the pharmacy product accountability records.

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 investigational product in accordance with the protocol and any applicable laws and regulations.

Clinical supplies will be affixed with a clinical label and in accordance with regulatory requirements.

12.7 Data Handling and Record Keeping

Celerion's Merck library CRFs will be supplied.

12.8 Report Format

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

12.9 Compliance With Law, Audit, And Debarment

By signing this protocol, the Investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GCP (e.g., International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by Merck, is provided in Appendix 1.

The Investigator also agrees to allow monitoring, audits, IRB/ERC review and regulatory authority inspection of trial-related documents and procedures and provide for direct access to all trial-related source data and documents.

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

The Investigator shall prepare and maintain complete and accurate trial documentation in compliance with GCP standards and applicable federal, state and local laws, rules and regulations; and, for each subject participating in the trial, provide all data, and, upon completion or termination of the clinical trial, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Trial documentation will be promptly and fully disclosed to the Sponsor by the Investigator upon request and also shall be made available at the trial 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 as a result of an audit to cure deficiencies in the trial documentation and worksheets/case report forms.

The Investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, Investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. By signing this protocol, the Investigator agrees that documentation shall be retained until at least 2 years after the last approval of a marketing application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Because the clinical development and marketing application process is variable, it is anticipated that the retention period can be up to 15 years or longer after protocol database lock. The Sponsor will determine the minimum retention period and notify the Investigator when documents may be destroyed. The Sponsor also recognizes that documents may need to be retained for a longer period if required by local regulatory requirements. All trial documents shall be made available if required by relevant regulatory authorities. The Investigator must consult with and obtain written approval by the Sponsor prior to discarding trial and/or subject files.

ICH GCP guidelines recommend that the Investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

The Investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this trial.

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

In the event the Sponsor prematurely terminates a particular trial site, the Sponsor will promptly notify that trial site's IRB/IEC.

According to European legislation, a Sponsor must designate an overall coordinating Investigator for a multi-center trial (including multinational). When more than one trial site is open in an EU country, Merck, as the Sponsor, will designate, per country, a national principal coordinator (Protocol CI), responsible for coordinating the work of the Investigators at the different trial sites in that Member State, according to national regulations. For a single-center trial, the Protocol CI is the Investigator. In addition, the Sponsor must designate a principal or coordinating Investigator to review the trial report that summarizes the trial results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the trial [CSR CI]. The Sponsor may consider one or more factors in the selection of the individual to serve as the Protocol CI and or CSR CI (e.g., availability of the CI during the anticipated review process, thorough understanding of clinical trial methods, appropriate enrollment of subject cohort, timely achievement of trial milestones). The Protocol CI must be a participating trial Investigator.

12.10 Publication Policy

The Sponsor will provide separate guidance on the criteria for publication of clinical trial data when contacted for permission to publish.

12.11 Privacy Notice

In order to comply with government regulations governing clinical studies, as well as ICH GCP 3.2.1, Merck & Co., Inc., and its corporate affiliates ("Sponsor"), is required to record the name and address of each IRB or IEC member that reviews and approves this study. The Sponsor is also required to document that each IRB or 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 (ICH GCP 8.2.8).

13 REFERENCES

1. Food and Drug Administration: Center for Drug Evaluation and Research (CDER). Guidance for Industry - Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling (March 2010).

Appendix 1: Merck* Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

Merck, 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 subject safety is the overriding concern in the design of clinical trials. In all cases, Merck clinical trials will be conducted in compliance with local and/or national regulations and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Such standards shall be endorsed for all clinical interventional investigations sponsored by Merck 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 which are observational in nature, or which are retrospective. Further, this Code does not apply to Investigator-initiated trials which are not under the control of Merck.

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

The design (i.e., subject population, duration, statistical power) must be adequate to address the specific purpose of the trial. Research subjects must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

Merck selects investigative sites based on medical expertise, access to appropriate subjects, adequacy of facilities and staff, previous performance in Merck trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by Merck personnel to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice. Merck reviews clinical data for accuracy, completeness and consistency. Data are verified versus source documentation according to standard operating procedures. Per Merck policies and procedures, if fraud, misconduct or serious GCP-non-Compliance are suspected, the issues are promptly investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified and data disclosed accordingly.

B. Publication and Authorship

To the extent scientifically appropriate, Merck seeks to publish the results of trials it conducts. 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 of multiplicity.

Merck's policy on authorship is consistent with the requirements outlined in the ICH-Good Clinical Practice guidelines. 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. Merck funding of a trial will be acknowledged in publications.

III. Subject Protection

A. IRB/ERC review

All clinical trials will be reviewed and approved by an independent IRB/ERC prior being initiated at each site. Significant changes or revisions to the protocol will be approved by the IRB/ERC prior to implementation, except that changes required urgently to protect subject safety and well-being may be enacted in anticipation of IRB/ERC approval. For each site, the IRB/ERC and Merck will approve the subject informed consent form.

B. Safety

The guiding principle in decision-making in clinical trials is that subject welfare is of primary importance. Potential subjects 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. Subjects are never denied access to appropriate medical care based on participation in a Merck clinical trial.

All participation in Merck clinical trials is voluntary. Subjects are enrolled only after providing informed consent for participation. Subjects may withdraw from a Merck 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

Merck is committed to safeguarding subject confidentiality, to the greatest extent possible. Unless required by law, only the Investigator, Sponsor (or representative) and/or regulatory authorities will have access to confidential medical records that might identify the research subject by name.

D. Genomic Research

Genomic Research will only be conducted in accordance with informed consent and/or as specifically authorized by an Ethics Committee.

IV. Financial Considerations

A. Payments to Investigators

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

Merck does not pay for subject referrals. However, Merck may compensate referring physicians for time spent on chart review to identify potentially eligible subjects.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by Merck, and that the Investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local IRB/ERC may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, publications resulting from Merck trials will indicate Merck 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 including, in the U.S., those established by the American Medical Association (AMA).

V. Investigator Commitment

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

* In this document, "Merck" refers to Merck Sharp & Dohme Corp. and Schering Corporation, each of which is a subsidiary of Merck & Co., Inc. Merck is known as MSD outside of the United States and Canada. As warranted by context, Merck also includes affiliates and subsidiaries of Merck & Co., Inc.

Appendix 2: 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 trial as outlined in Section 10.4- Future Biomedical Research Samples 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 drugs/vaccines may interact with
- 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. Subjects for Enrollment

All subjects enrolled in the clinical trial will be considered for enrollment in the Future Biomedical Research sub-trial.

b. Informed Consent

Informed consent for specimens (i.e., DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all subjects or legal guardians, at a trial visit by the investigator or his or her designate. Informed consent for Future Biomedical Research should be presented to the subjects on the visit designated in the trial flow chart. If delayed, present consent at next possible Subject Visit. Consent forms signed by the subject will be kept at the clinical trial site under secure storage for regulatory reasons.

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

c. CRF Documentation for Future Biomedical Research Specimens

Documentation of subject consent for Future Biomedical Research will be captured in the Case Report Forms (CRFs). 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 trial flow chart. In general, if additional blood specimens are being collected for Future Biomedical Research, these will usually be obtained at a time when the subject is having blood drawn for other trial purposes.

4. Confidential Subject 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 subject' clinical information with future test results. In fact little or no research can be conducted without connecting the clinical trial data to the specimen. The clinical data allow specific analyses to be conducted. Knowing subject characteristics like gender, age, medical history and treatment 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 trial 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 subject identifiers and this unique code will be held at the trial site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses utilizing the Future Biomedical Research specimens may be performed by the Sponsor, or an additional third party (e.g., a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third party analyses will conform to the specific scope of analysis outlined in this sub-trial. 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

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

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject'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 trial 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 trial, the trial 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 trial 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 Subjects

No information obtained from exploratory laboratory studies will be reported to the subject, family, or physicians. Principle reasons not to inform or return results to the subject include: Lack of relevance to subject 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 subjects. Subjects 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 subjects diagnosed and treated on Sponsor clinical trials for Future Biomedical Research.

11. Risks versus Benefits of Future Biomedical Research

For Future Biomedical Research, risks to the subject have been minimized. No additional risks to the subject have been identified as no additional specimens are being collected for Future Biomedical Research (i.e., only leftover samples are being retained).

The Sponsor has developed strict security, policies and procedures to address subject 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 e-mailed directly to clinical.specimen.management@merck.com.

13. References

1. National Cancer Institute: http://www.cancer.gov/dictionary/?searchTxt=biomarker
2. International Conference on Harmonization: DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES - E15; 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. 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. Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/