| | |
|---|---|
| **Official Protocol Title:** | An Open-Label, Single-Dose Study to Investigate the Influence of Renal Insufficiency on the Pharmacokinetics of MK-7264 |
| **NCT number:** | NCT03108924 |
| **Document Date:** | 09-Jun-2017 |

**Celerion Project No.: CA21631**

**Merck Protocol No.: MK-7264-026-03**

**US IND No.: 123007**

# An Open-Label, Single-Dose Study to Investigate the Influence of Renal Insufficiency on the Pharmacokinetics of MK-7264

**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 |
|---|---|
| 09 June 2017<br>by PPD | Final Protocol, Amendment 3<br><br>The protocol was amended to clarify that a peripheral pharmacokinetic (PK) blood sample will be drawn in addition to the 2 samples from the pre-dialyzer and post-dialyzer blood lines from subjects with end stage renal disease (ESRD) during the hemodialysis (HD) session in Period 2 of Part 2. Thus, a total of 3 blood samples will be taken from subjects with ESRD during each collection time point of the HD session as indicated on the Study Events Flow Chart instead of 2. In Table 3, the number of time points for Blood for MK-7264 will be changed from 49 to 58 and the total blood volume collected from each subject in Part 2 will be changed from 243 mL to 270 mL. All relevant sections of the protocol were updated to reflect this change.<br><br>In addition, the following updates were made:<br><br>*Last post-HD blood sample and last dialysate samples*: Since HD must be running in order to obtain dialysate and post-HD blood sample, the last post-HD blood sample and last dialysate samples cannot be collected **after** HD is stopped and they must be obtained immediately **before** HD is stopped.<br><br>Thus in Section 6.2 Part 2: Subjects with ESRD, footnotes "m" and "n" were updated to reflect these changes as follows (deleted text is presented in ~~strikethrough~~ and added text is in **bold**):<br><br>m. During HD, blood samples for MK-7264 will be collected from both the pre-dialyzer and post-dialyzer blood lines **in addition to the peripheral PK blood draw**; thus ~~2~~ **3** samples per time point during HD will be taken. A blood sample (a pre-dialyzer and post-dialyzer) will also be obtained immediately ~~after~~ **before** the HD is stopped, if this time point does not coincide with a time point that is already scheduled.<br><br>n. Dialysate samples for determination of MK-7264 will be obtained pre-dialysis, post-dialysis (immediately ~~after~~ **before** the HD is stopped), and for 1 minute every half hour during HD.<br><br>*Dialysate samples*: Dialysate is the fluid that contains unwanted waste products from blood after HD, therefore no pre-dialysis and post-dialysis dialysate sample can be obtained every 30 minutes during HD. Thus Section 5 Synopsis, and Section 9.1 Overall Study Design and Plan were updated to reflect this change.<br><br>*Dialysate PK parameters naming*: HD session will be initiated 2 hours after dosing; therefore dialysate will be collected for 4 hours from Hour 2 to Hour 6 in Period 2 of Part 2. Time intervals in PK parameters for dialysates are named relative to start of HD (at Hour 2) instead of dosing (Hour 0), which might be confusing since time |

| | |
|---|---|
| | intervals for plasma PK parameters are relative to dosing (Hour 0). Thus AUC[0.5-4]Ca, AUC[0.5-4]Cv dialysate PK parameters were changed to AUC[2.5-6]Ca, AUC[2.5-6]Cv and all relevant sections to reflect this change were updated.<br><br>Typographical and grammatical corrections, as well as formatting changes, were made throughout the protocol. |
| 16 May 2017<br>by PPD | Final Protocol, Amendment 2<br><br>The protocol was amended to correct an error in the calculation of the total blood volume drawn from subjects in Part 2 as listed in Table 3 Blood Volume Drawn During the Study in Part 2.<br><br>In Period 2 of Part 2 of the study, some blood samples for MK-7264 are scheduled to be collected during hemodialysis (HD). As stated in Section 5 Synopsis, Section 6.2 Part 2: Subjects with ESRD, Section 9.1 Overall Study Design and Plan, and Section 10.1.5 Hemodialysis (ESRD Subjects Only), the blood samples taken during HD will be collected from both the pre-dialyzer and post-dialyzer blood lines; therefore 2 blood samples per time point will be collected during HD. In Amendment 1 of this protocol, only 1 sample per time point during HD was accounted for in Table 3 Blood Volume Drawn During the Study in Part 2. To correct this mistake in Table 3, the number of time points for Blood for MK-7264 was corrected from 40 to 49 and the total blood volume collected from each subject in Part 2 was corrected from 216 mL to 243 mL.<br><br>Additionally, in Section 6.2 Part 2: Subjects with ESRD, footnote "m" was added to the 6-hour time point for Blood for MK-7264 Pharmacokinetics to clarify that blood samples (pre-dialyzer and post-dialyzer) will be collected immediately after HD is stopped. An "X" was also added to the 6-hour time point for Dialysate for MK-7264 Pharmacokinetics and footnote "n" was updated to clarify that a dialysate sample will be collected immediately after HD is stopped. Lastly, footnote "o" was updated and the "X" in the Hemodialysis row was extended until the 6-hour column to clarify that HD will be approximately 4 hours in duration as correctly indicated in Section 10.1.5 Hemodialysis (ESRD Subjects Only).<br><br>Typographical corrections were also made throughout the protocol. |
| 04 May 2017<br>by PPD | Final Protocol, Amendment 1<br><br>The protocol was amended to document the addition of Part 2 to the study to assess pharmacokinetics of MK-7264 in subjects with end stage renal disease (ESRD) requiring hemodialysis (HD). Updates were applied throughout the protocol.<br><br>Typographical and grammatical corrections, as well as formatting changes, were made throughout the protocol. |

| | |
|---|---|
| 22 Mar 2017<br>by PPD | Final Protocol |

## 2 PRINCIPAL INVESTIGATOR AND SPONSOR – SIGNATORIES

**An Open-Label, Single-Dose Study to Investigate the Influence of Renal Insufficiency on the Pharmacokinetics of MK-7264**

**SPONSOR:**

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. (hereafter referred to as the Sponsor or Merck)
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## 4 TABLE OF CONTENTS

**LIST OF APPENDICES**



**LIST OF TABLES**

## 5 SYNOPSIS

| | |
|---|---|
| Compound: | MK-7264 |
| Clinical Indication: | Cough |
| Study Phase and Type: | Phase I – Interventional |
| Study Objectives and Estimation: | **Primary:**<br>**Both Parts:**<br>Objective: To evaluate the plasma pharmacokinetics of MK-7264 administered to subjects with varying degrees of renal insufficiency (RI) compared to healthy matched control subjects.<br>Estimation: In subjects with moderate and severe RI, and subjects with ESRD, pharmacokinetic parameters (AUC0-∞, AUC0-last, Cmax, CL/F, and CLr, as appropriate) of MK-7264 following administration of a single 50 mg dose will be estimated and compared to those observed in healthy matched control subjects.<br>**Part 2 Only:**<br>Objective: To investigate the extent of MK-7264 removal by hemodialysis.<br>Estimation: The extent to which MK-7264 is removed from plasma by hemodialysis will be estimated following administration of a single 50 mg dose of MK-7264 in subjects with ESRD requiring hemodialysis.<br>**Secondary (Both Parts):**<br>Objective: To evaluate the safety and tolerability of MK-7264 in subjects with moderate and severe RI (Part 1) and in subjects with ESRD on hemodialysis (Part 2).<br>**Exploratory:**<br>Objective 1 (both parts): To estimate and compare the pharmacokinetic parameters (AUC0-12, AUC0-24, AUC0-48, Ae0-24, Ae0-48, Tmax, Vz/F, apparent terminal t½, and Fe, as applicable) between subjects with various degrees of RI and healthy matched control subjects.<br>Objective 2 (both parts): Analyze the potential relationship between appropriate MK-7264 pharmacokinetic parameters and renal function.<br>Objective 3 (Part 2 only): To estimate pharmacokinetic parameters (AUCD, AUC[2.5-6]Ca, AUC[2.5-6]Cv, $CL_{D,plasma}$, $CL_{D,dialysate}$, AD, and $AD_{,total}$) for MK-7264 in subjects with ESRD following dosing, as appropriate. |

<table>
<tr><td></td><td>Planned Exploratory Biomarker (Both Parts):<br>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 Part 1, the pharmacokinetics of MK-7264 will be evaluated in subjects with moderate and severe RI compared to healthy matched control subjects. In Part 2, the pharmacokinetics of MK-7264 will be evaluated in subjects with ESRD requiring HD under dialysis and non-dialysis conditions. Parts 1 and 2 of the study may be conducted concurrently.<br>Assignment to a renal function group will be as follows:
<table>
<tr><th>Group</th><th>N</th><th>eGFR (mL/min/1.73m$^2$)*</th></tr>
<tr><td colspan="3">Part 1</td></tr>
<tr><td>Severe Insufficiency</td><td>6</td><td><30 **, not on dialysis</td></tr>
<tr><td>Moderate Insufficiency</td><td>6</td><td>30 – 59 ***</td></tr>
<tr><td>Healthy Matched Control</td><td>6</td><td>≥90****</td></tr>
<tr><td colspan="3">Part 2</td></tr>
<tr><td>ESRD requiring HD</td><td>6</td><td>requiring HD</td></tr>
</table>
* Estimated glomerular filtration rate (eGFR) based on Modification of Diet in Renal Disease (MDRD) equation at screening. Baseline eGFR will be obtained twice during the screening period, 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.<br>** Reasonable efforts will be made to enroll at least 2 subjects with eGFR values of < 20 mL/min/1.73m$^2$<br>*** Reasonable efforts will be made to enroll at least 2 subjects with eGFR values of 30 - 45 mL/min/1.73m$^2$<br>**** Healthy control subjects are within ± 10 years of the mean age and within ± 10 kg (where the weight is rounded to the nearest kg) of the mean weight for the pooled severe RI, moderate RI, and ESRD groups. For healthy subjects a creatinine clearance computed over a 24 hour urine collection for subjects that do not qualify with ≥90 eGFR may be done for confirmation purposes.<br>Part 1:<br>On Day 1, a single oral dose of MK-7264 will be administered followed by pharmacokinetic sampling for 72 hours. Urine samples will be collected for 48 hours postdose, if possible.</td></tr>
</table>

| | |
|---|---|
| | **Part 2:**<br><br>Subjects with ESRD requiring HD will receive a single dose of MK-7264 on two occasions.<br><br>On Day 1 of Period 1, subjects with ESRD requiring HD will receive a single oral dose of MK-7264 immediately following their scheduled HD, followed by pharmacokinetic sampling for 72 hours. Subjects will initiate the next HD immediately following the 72-hour blood draw on Day 4. If the next scheduled HD must be initiated before 72 hours postdose, a sample for MK-7264 analysis will be collected prior to HD. Urine samples will be collected for 48 hours postdose, if possible.<br><br>On Day 1 of Period 2, subjects with ESRD requiring HD will receive a single oral dose of MK-7264 approximately 2 hours prior to their scheduled HD followed by pharmacokinetic sampling for 72 hours. The HD session will initiate immediately following the 2-hour blood draw. During this dialysis session, pre- and post-dialyzer plasma samples will be collected every 30 minutes and dialysate samples will be collected pre-dialysis, post-dialysis, and for 1 minute every 30 minutes during HD for MK-7264 analysis. Urine samples will be collected for 48 hours postdose, if possible.<br><br>There will be a washout period of approximately 7 days (with 3 dialysis sessions) between MK-7264 dosing in Periods 1 and 2.<br><br>**Both Parts:**<br><br>The clinic will contact all subjects (including those who terminate the study early) approximately 14 days after the last study drug administration to determine if any adverse events have occurred since last visit. |
| Blinding: | This is an open-label study. |
| Number of Subjects: | Twenty-four (24), adult, male and female subjects between 18 and 80 years of age (inclusive) will be enrolled; 6 subjects with ESRD requiring HD, 6 subjects with severe RI, 6 subjects with moderate RI, and 6 healthy matched control subjects.<br><br>Once subjects with severe and moderate RI and subjects with ESRD are enrolled, the healthy matched control subjects will be enrolled. Each healthy control subject will be matched to the mean age (±10 years) and weight (±10 kg, where the weight is rounded to the nearest kg) of subjects with RI. |

| | |
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| Dosage, Dosage Form, Route, and Dose Regimen: | **Part 1:**<br>Subjects will receive a single oral dose of 50 mg MK-7264 (1 x 50 mg tablet) at Hour 0 on Day 1.<br>**Part 2:**<br>Subjects will receive a single oral dose of 50 mg MK-7264 (1 x 50 mg tablet) at Hour 0 on Day 1 in Period 1, immediately following the scheduled HD, and at Hour 0 on Day 1 in Period 2, approximately 2 hours prior to initiation of the scheduled HD.<br>**Both Parts:**<br>MK-7264 will be administered following an overnight fast, with approximately 240 mL of water. |
| Key Assessments: | **Pharmacokinetics:**<br>The following pharmacokinetic parameters will be calculated for MK-7264 in plasma, as appropriate: AUC0-∞, AUC0-last, AUC0-12, AUC0-24, AUC0-48, Cmax, Tmax, apparent terminal t½, CL/F, and Vz/F.<br>For subjects with ESRD (Part 2 only), the following PK parameters will also be calculated for MK-7264 in plasma following dosing, as appropriate: AUCD, AUC(2.5-6)Ca, AUC(2.5-6)Cv, CLD,plasma, CLD,dialysate, AD, and AD,total.<br>The following pharmacokinetic parameters will be calculated for MK-7264 in urine (Part 1 and Part 2), as appropriate: Ae0-24, Ae0-48, Fe, and CLr.<br>**Safety:**<br>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 Part 1: Healthy Subjects and Subjects with Severe and Moderate RI

| Study Procedures [a] | Screening [b] | Study Days | | | | | | | | | | | | | | | | FU [c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Days → | | -2 /-1 | 1 | | | | | | | | | | | | 2 | | 3 | 4 | |
| Hours → | | (C-I)[d] | P | 0 | 0.25 | 0.5 | 1 | 2 | 3 | 4 | 6 | 8 | 12 | 16[e] | 24 | 36 | 48 | 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 [f] | X | | | | | | | | | | | | | | | | | X [g] | |
| Height | X | | | | | | | | | | | | | | | | | | |
| Weight | X | X | | | | | | | | | | | | | | | | | |
| Assessment of Renal Function [h] | X | | | | | | | | | | | | | | | | | | |
| 12-Lead Electrocardiogram | X | | X [i] | | | | | | | | | | | | | | | X [g] | |
| Vital Signs (heart rate & blood pressure) | X | | X [i] | | | | X | | | | | | | | | | | X [g] | |
| Vital Signs (respiratory rate & temperature) | X | | | | | | | | | | | | | | | | | | |
| Hematology, Serum Chemistry [j], and Urinalysis | X | X | | | | | | | | | | | | | X | | | X [g] | |
| Serum Pregnancy Test (female subjects only) | X | X | | | | | | | | | | | | | | | | | |
| Serum FSH (postmenopausal females only) | X | | | | | | | | | | | | | | | | | | |
| Urine or Saliva Drug Screen | X | X | | | | | | | | | | | | | | | | | |
| Urine or Breath Alcohol Screen | X | X | | | | | | | | | | | | | | | | | |
| HIV/Hepatitis Screen | X | | | | | | | | | | | | | | | | | | |
| Adverse Events Monitoring | | X | | | | | | | | | | | | | | | | | |
| Concomitant Medication Monitoring | | X | | | | | | | | | | | | | | | | | |
| **Study Drug Administration / Pharmacokinetics** | | | | | | | | | | | | | | | | | | | |
| MK-7264 Administration | | | | X | | | | | | | | | | | | | | | |
| Blood for MK-7264 Pharmacokinetics | | | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Urine for MK-7264 Pharmacokinetics [k] | | | X | X | | | | | | | | | | | | | | | |
| **Other Procedures** | | | | | | | | | | | | | | | | | | | |
| Blood for Genetic Analysis [l] | | | X | | | | | | | | | | | | | | | | |
| Confinement in the CRU | | X | | | | | | | | | | | | | | | | | |
| Visit | X | | | | | | | | | | | | | | | | | | |

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

b. Within 28 days prior to the study drug administration.

c. The clinic will contact all subjects (including subjects who terminate early) approximately 14 days after the study drug administration to determine if any adverse events have occurred since the last study visit.

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

e. The 16-hour time point following dosing on Day 1 will be either on Day 1 or Day 2, depending on the time of dosing on Day 1.

f. A symptom-driven physical examination may be performed at other times, at the Investigator's discretion.

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

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

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 dropouts or rechecks, subjects may not have fasted for 8 hours before the serum chemistry sample is taken.

k. Urine collection intervals are: pre-dose (spot collection), 0 - 12 hours, 12 - 24 hours post-dose, and 24 -48 hours. For subjects with renal insufficiency, urine samples will be collected whenever possible, as they may not be able to produce urine at each interval. For subjects who are anuric, urine samples for urinalysis will not be collected.

l. 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, DNA = deoxyribonucleic acid, eGFR = Estimated glomerular filtration rate, FBR = Future Biomedical Research, FSH = Follicle-stimulating hormone, FU = Follow-Up, HIV = Human immunodeficiency virus, IRB/IEC = Institutional review board/independent ethics committee, P = Predose, PK = Pharmacokinetic.

## 6.2 Part 2: Subjects with ESRD

| Study Procedures [a] | S [b] | Study Days in Period 1 of Part 2 [c] | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Days → | | -2 /-1 | 1 | | | | | | | | | | | | | | | | | 2 | | 3 | 4 |
| Hours → | | (C-I) [d] | P | 0 | 0.25 | 0.5 | 1 | 2 | 2.5 | 3 | 3.5 | 4 | 4.5 | 5 | 5.5 | 6 | 8 | 12 | 16 [e] | 24 | 36 | 48 | 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 [f] | X | | | | | | | | | | | | | | | | | | | | | | X |
| Height | X | | | | | | | | | | | | | | | | | | | | | | |
| Weight | X | X | | | | | | | | | | | | | | | | | | | | | |
| 12-Lead Electrocardiogram | X | | X [g] | | | | | | | | | | | | | | | | | | | | X |
| Vital Signs (heart rate & blood pressure) | X | | X [g] | | | | X | | | | | | | | | | | | | | | | X |
| Vital Signs (respiratory rate & temperature) | X | | | | | | | | | | | | | | | | | | | | | | |
| Hematology, Serum Chemistry [h], and Urinalysis | X | X | | | | | | | | | | | | | | | | | | X | | | X |
| Serum Pregnancy Test (female subjects only) | X | X | | | | | | | | | | | | | | | | | | | | | |
| Serum FSH (postmenopausal females only) | X | | | | | | | | | | | | | | | | | | | | | | |
| Urine or Saliva Drug Screen | X | X | | | | | | | | | | | | | | | | | | | | | |
| Urine or Breath Alcohol Screen | X | X | | | | | | | | | | | | | | | | | | | | | |
| HIV/Hepatitis Screen | X | | | | | | | | | | | | | | | | | | | | | | |
| Adverse Events Monitoring | | X | | | | | | | | | | | | | | | | | | | | | |
| Concomitant Medication Monitoring | | X | | | | | | | | | | | | | | | | | | | | | |
| **Study Drug Administration / Pharmacokinetics** | | | | | | | | | | | | | | | | | | | | | | | |
| MK-7264 Administration | | | | X [i] | | | | | | | | | | | | | | | | | | | |
| Blood for MK-7264 Pharmacokinetics | | | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X [j] |
| Urine for MK-7264 Pharmacokinetics [k] | | | X | | X | | | | | | | | | | | | | | | | | | |
| **Other Procedures** | | | | | | | | | | | | | | | | | | | | | | | |
| Blood for Genetic Analysis [l] | | | X | | | | | | | | | | | | | | | | | | | | |
| Confinement in the CRU | | X | | | | | | | | | | | | | | | | | | | | | |
| Visit | X | | | | | | | | | | | | | | | | | | | | | | |

| Study Procedures [a] | Study Days in Period 2 of Part 2 [c] | | | | | | | | | | | | | | | | | | | | | | FU [q] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Days → | -2 /-1 | 1 | | | | | | | | | | | | | | | | | 2 | | 3 | 4 | |
| Hours → | (C-I)[d] | P | 0 | 0.25 | 0.5 | 1 | 2 | 2.5 | 3 | 3.5 | 4 | 4.5 | 5 | 5.5 | 6 | 8 | 12 | 16[e] | 24 | 36 | 48 | 72 | |
| **Safety Evaluations** | | | | | | | | | | | | | | | | | | | | | | | |
| Full Physical Examination [f] | | | | | | | | | | | | | | | | | | | | | | X [p] | |
| 12-Lead Electrocardiogram | | X [g] | | | | | | | | | | | | | | | | | | | | X [p] | |
| Vital Signs (heart rate & blood pressure) | | X [g] | | | | X | | | | | | | | | | | | | | | | X [p] | |
| Vital Signs (respiratory rate & temperature) | | | | | | | | | | | | | | | | | | | | | | | |
| Hematology, Serum Chemistry [h], and Urinalysis | X | | | | | | | | | | | | | | | | | | X | | | X [p] | |
| Urine or Saliva Drug Screen | X | | | | | | | | | | | | | | | | | | | | | | |
| Urine or Breath Alcohol Screen | X | | | | | | | | | | | | | | | | | | | | | | |
| Adverse Events Monitoring | X | | | | | | | | | | | | | | | | | | | | | | |
| Concomitant Medication Monitoring | X | | | | | | | | | | | | | | | | | | | | | | |
| **Study Drug Administration / Pharmacokinetics** | | | | | | | | | | | | | | | | | | | | | | | |
| MK-7264 Administration | | | X | | | | | | | | | | | | | | | | | | | | |
| Blood for MK-7264 Pharmacokinetics | | X | | X | X | X | X [m] | X [m] | X [m] | X [m] | X [m] | X [m] | X [m] | X [m] | X [m] | X | X | X | X | X | X | X | |
| Urine for MK-7264 Pharmacokinetics [k] | | X | X | | | | | | | | | | | | | | | | | | | | |
| Dialysate for MK-7264 Pharmacokinetics [n] | | | | | | | X | X | X | X | X | X | X | X | X | | | | | | | | |
| **Other Procedures** | | | | | | | | | | | | | | | | | | | | | | | |
| Hemodialysis [o] | | | | | | | X | | | | | | | | | | | | | | | | |
| Confinement in the CRU | X | | | | | | | | | | | | | | | | | | | | | | |
| Visit | | | | | | | | | | | | | | | | | | | | | | | |

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

b. Within 28 days prior to the first study drug administration.

c. There will be a washout period of approximately 7 days (with 3 dialysis sessions) between MK-7264 dosing in Period 1 and Period 2.

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

e. The 16-hour time point following dosing on Day 1 will be either on Day 1 or Day 2, depending on the time of dosing on Day 1.

f. A symptom-driven physical examination may be performed at other times, at the Investigator's discretion.

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

h. Samples for serum chemistry will be obtained following a fast of at least 8 hours; however, in case of dropouts or rechecks, subjects may not have fasted for 8 hours before the serum chemistry sample is taken.

i. To be administered immediately following scheduled HD.

j. If the next scheduled HD must be initiated before 72 hours postdose, a sample for MK-7264 analysis will be collected prior to HD.

k. Urine collection intervals are: pre-dose (spot collection), 0 - 12 hours, 12 - 24 hours post-dose, and 24 -48 hours. Urine samples will be collected whenever possible, as some subjects with ESRD may not be able to produce urine at each interval. For subjects who are anuric, urine samples for urinalysis will not be collected.

l. 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.

m. During HD, blood samples for MK-7264 will be collected from both the pre-dialyzer and post-dialyzer blood lines in addition to peripheral PK blood draw; thus 3 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.

n. Dialysate samples for determination of MK-7264 will be obtained pre-dialysis, post-dialysis (immediately before the HD is stopped), and for 1 minute every half hour during HD.

o. The HD session will be initiated immediately following the 2-hour postdose blood draw and the HD period will be approximately 4 hours in duration.

p. To be performed on Day 4 of Period 2 or prior to early termination from the study.

q. The clinic will contact all subjects (including subjects who terminate early) approximately 14 days after the last study drug administration to determine if any adverse events have occurred since the last study visit.

Abbreviations: C-I = Check-in, CRU = Clinical research unit, DNA = deoxyribonucleic acid, FBR = Future Biomedical Research, FSH = Follicle-stimulating hormone, FU = Follow-Up, HD = Hemodialysis, HIV = Human immunodeficiency virus, IRB/IEC = Institutional review board/independent ethics committee, P = Predose, PK = Pharmacokinetic.

# 7 BACKGROUND AND RATIONALE

## 7.1 Background

P2X3 receptors are ligand-gated ion channels that respond to adenosine triphosphate (ATP) and are almost exclusively localized on C-fiber sensory neurons, including those that innervate the upper and lower airways. ATP is released by damaged, stressed, and inflamed tissues. ATP and P2X3 containing receptors have been shown to be involved in airways sensitization and their involvement provides a rationale for P2X3 antagonism in the treatment of chronic cough.

MK-7264, a selective P2X3 receptor antagonist, is the first clinical agent targeting this receptor, and is being evaluated for treatment of cough. Additionally, MK-7264 has been evaluated in asthma, interstitial cystitis/bladder pain syndrome, and osteoarthritis pain. P2X3 antagonists may address the unmet medical needs for any of these indications.

Refer to the Confidential Clinical Investigator's Brochure (IB) for detailed background information on MK-7264 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

Preliminary data indicate that MK-7264 is eliminated primarily through renal elimination with metabolism playing a secondary role in its elimination. Following multiple dose administration, approximately 60% of a 50 mg dose was excreted at steady state in healthy subjects. Thus, it is anticipated that the in the setting of renal impairment, alterations in the pharmacokinetics of MK-7264 are likely and dose adjustments may be indicated. The need for dose adjustment is a clinically significant issue as the incidence of renal impairment is associated with increasing age, and the patient population in MK-7264-012, a Phase 2b chronic cough efficacy study, had a median age of approximately 60, though there was a wide range of ages from 22 to 79.

The potential impact of mild renal impairment was assessed in a previous Phase 1 multiple dose study in healthy and elderly adult male and female subjects, MK-7264-007, which included subjects with mild renal impairment. A non-population based preliminary pharmacokinetic analysis of this study investigated the impact of eGFR on exposures (AUC and Cmax) in elderly and non-elderly subjects using a linear fixed effect model. In this analysis, a subject with mild renal impairment (eGFR = 60 mL/min) in comparison to a subject with normal renal function (eGFR = 90 mL/min) would be predicted to have an increase of AUC0-t and Cmax of 19% and 11%, respectively, with a

300 mg dose at steady state. Age and gender did not appear to have an effect on the pharmacokinetics of MK-7264 independent of eGFR in this analysis.

Since MK-7264 is eliminated primarily through renal excretion, the impact of renal function on pharmacokinetics of MK-7264 will be extended beyond the previous experience in subjects with mild impairment to subjects with moderate and severe renal impairment as well as subjects with ESRD. The relationship between renal function (as measured by eGFR) and exposure (as measured by AUC) will be explored by comparing the pharmacokinetics in within-study control subjects with normal renal function to those with varying degrees of renal impairment. The study will also examine the degree to which MK-7264 is removed from plasma by hemodialysis. The safety and tolerability of MK-7264 when administered in subjects with renal impairment will also be assessed. The control subjects will be matched by age (mean within ± 10 years) and body weight (mean ± 10 kg) to the mean age and body weight of pooled moderate and severe renal impairment subjects, as recommended by the draft FDA Guidance (Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function Study Design, Data Analysis, and Impact on Dosing and Labeling; issued March 2010)[1].

### 7.2.2 Rationale for the Dose Selection and Dose Regimen

A single dose administration regimen has been chosen for this study. Pharmacokinetic data from multiple dose administration at doses between 7.5 and 50 mg twice daily (BID) of MK-7264 demonstrate accumulation of 1.4 to 1.5-fold. This accumulation was well predicted by the single-dose data, with no observed time-dependent non-linearities. Thus the characterization of the single dose pharmacokinetics of MK-7264 in subjects with renal impairment should be sufficient to define appropriate adjustments in dosing with chronic administration of MK-7264 in this patient population.

Single and multiple doses of MK-7264 up to 1800 mg BID have been generally well tolerated in healthy subjects, with the most common dose-related AEs associated with taste disturbance (dysgeusia, ageusia, hypogeusia). In the rising single dose study MK-7264-001, taste disturbance related AEs were observed at doses of 200 mg or greater, and not at doses of 100 mg or lower. In the multiple dose studies, the incidence of taste related AEs at 50 mg BID of MK-7264 ranged from 58% to 81% of subjects. A recently completed Phase 2b study in patients with chronic cough indicated that a 50 mg BID dose of MK-7264 was the dose where maximum efficacy in reducing the frequency of awake cough was reached.

Therefore, the dose proposed in this study will be 50 mg, which will be the highest potential dose in the Phase 3 program, in order to provide information regarding the effect of RI on the pharmacokinetics of a therapeutic dose of MK-7264.

Given the margin between the single dose of 50 mg and the 1800 mg dose that has been generally well tolerated, subjects with severe and moderate renal impairment may be administered a single oral 50 mg dose of MK-7264 in parallel in this study.

### 7.2.3 Rationale for Endpoints

The primary objective of this study is to evaluate the pharmacokinetic profile of MK-7264 in subjects with impaired renal function. This study will compare the overall pharmacokinetic profile of MK-7264 in subjects with impaired renal function to that of healthy subjects, and this will be assessed by overall exposure (AUC0-∞), Cmax, CL/F and CLr.

For ESRD subjects only, CLD,plasma, CLD,dialysate, AD, and AD,total will provide a measure of the extent of MK-7264 removal by HD.

### 7.2.4 Rationale for Planned Exploratory Biomarker Research

**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.

### 7.2.5 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, ESTIMATION, AND ENDPOINTS

## 8.1 Objectives and Estimation

### 8.1.1 Primary

**Both Parts:**

Objective: To evaluate the plasma pharmacokinetics of MK-7264 administered to subjects with varying degrees of RI compared to healthy matched control subjects.

Estimation: In subjects with moderate and severe RI, and subjects with ESRD, pharmacokinetic parameters (AUC0-∞, AUC0-last, Cmax, CL/F, and CLr, as appropriate) of MK-7264 following administration of a single 50 mg dose will be estimated and compared to those observed in healthy matched control subjects.

**Part 2 Only:**

Objective: To investigate the extent of MK-7264 removal by hemodialysis.

Estimation: The extent to which MK-7264 is removed from plasma by hemodialysis will be estimated following administration of a single 50 mg dose of MK-7264 in subjects with ESRD requiring hemodialysis.

### 8.1.2 Secondary (Both Parts)

Objective: To evaluate the safety and tolerability of MK-7264 in subjects with moderate and severe RI (Part 1) and in subjects with ESRD on hemodialysis (Part 2).

### 8.1.3 Exploratory

Objective 1 (both parts): To estimate and compare the pharmacokinetic parameters (AUC0-12, AUC0-24, AUC0-48, Ae0-24, Ae0-48, Tmax, Vz/F, apparent terminal t½, and Fe, as applicable) between subjects with various degrees of RI and healthy matched control subjects.

Objective 2 (both parts): Analyze the potential relationship between appropriate MK-7264 pharmacokinetic parameters and renal function.

Objective 3 (Part 2 only): To estimate pharmacokinetic parameters (AUCD, AUC[2.5-6]Ca, AUC[2.5-6]Cv, CLD,plasma, CLD,dialysate, AD, AD,total) for MK-7264 in subjects with ESRD following dosing, as appropriate.

### 8.1.4 Planned Exploratory Biomarker (Both Parts)

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**

The primary pharmacokinetic endpoints will include AUC0-∞, AUC0-last, Cmax, and CL/F in plasma and CLr in urine, as appropriate, for MK-7264 in subjects with RI versus healthy matched subjects.

The pharmacokinetic parameters AUC0-12, AUC0-24, AUC0-48, Tmax, apparent terminal t½, and Vz/F in plasma, and Ae0-24, Ae0-48, and Fe in urine, as appropriate, for MK-7264 will also be computed.

**Part 2**

The primary pharmacokinetic endpoints will include AUC0-∞, AUC0-last, Cmax, CL/F, AUCD, AUC(2.5-6)Ca, and AUC(2.5-6)Cv, as appropriate, for MK-7264 in subjects with ESRD in plasma following the HD dosing versus non-HD dosing.

The following pharmacokinetic parameters will also be calculated for MK-7264 in plasma following the HD and non-HD dosing, as appropriate: AUC0-12, AUC0-24, AUC0-48, Tmax, apparent terminal t½, Vz/F, CLD,plasma, CLD,dialysate, AD, and AD,total.

**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 Part 1, the pharmacokinetics of MK-7264 will be evaluated in subjects with moderate and severe RI compared to healthy matched control subjects. In Part 2, the pharmacokinetics of MK-7264 will be evaluated in subjects with ESRD requiring HD under dialysis and non-dialysis conditions. Parts 1 and 2 of the study may be conducted concurrently.

Twenty-four (24), adult, male and female subjects between 18 and 80 years of age (inclusive) will be enrolled; 6 subjects with ESRD requiring HD, 6 subjects with severe RI, 6 subjects with moderate RI, and 6 healthy matched control subjects.

Once subjects with ESRD and subjects with severe and moderate RI are enrolled, the healthy matched control subjects will be enrolled. Each healthy control subject will be matched to the mean age (±10 years) and weight (±10 kg, where the weight is rounded to the nearest kg) of subjects with RI.

Screening of subjects will occur within 28 days prior to the first dose.

Assignment to a renal function group will be as follows:

| Group | N | eGFR (mL/min/1.73m$^2$)* |
|---|---|---|
| Part 1 | | |
| Severe Insufficiency | 6 | <30 **, not on dialysis |
| Moderate Insufficiency | 6 | 30 – 59 *** |
| Healthy Matched Control | 6 | ≥90**** |
| Part 2 | | |
| ESRD requiring HD | 6 | requiring HD |

* eGFR based on MDRD equation at screening. Baseline eGFR will be obtained twice during the screening period, 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 < 20 mL/min/1.73m$^2$

*** Reasonable efforts will be made to enroll at least 2 subjects with eGFR values of 30 - 45 mL/min/1.73m$^2$

**** Healthy control subjects are within ±10 years of the mean age and within ± 10 kg (where the weight is rounded to the nearest kg) of the mean weight for the pooled severe RI, moderate RI, and ESRD groups. For healthy subjects a creatinine clearance computed over a 24 hour urine collection for subjects that do not qualify with ≥90 eGFR may be done for confirmation purposes.

**Part 1**

On Day 1, a single oral dose of MK-7264 will be administered followed by pharmacokinetic sampling for 72 hours. Urine samples will be collected for 48 hours postdose, if possible.

**Part 2:**

Subjects with ESRD requiring HD will receive a single dose of MK-7264 on two occasions.

On Day 1 of Period 1, subjects with ESRD requiring HD will receive a single oral dose of MK-7264 immediately following their scheduled HD, followed by pharmacokinetic sampling for 72 hours. Subjects will initiate the next HD immediately following the 72-hour blood draw on Day 4. If the next scheduled HD must be initiated before 72 hours postdose, a sample for MK-7264 analysis will be collected prior to HD. Urine samples will be collected for 48 hours postdose, if possible.

On Day 1 of Period 2, subjects with ESRD requiring HD will receive a single oral dose of MK-7264 approximately 2 hours prior to their scheduled HD followed by pharmacokinetic sampling for 72 hours. The HD session will initiate immediately following the 2-hour blood draw. During this dialysis session, pre- and post-dialyzer plasma samples will be collected every 30 minutes during HD and dialysate samples will be collected pre-dialysis, post-dialysis, and for 1 minute every 30 minutes during HD for MK-7264 analysis. Urine samples will be collected for 48 hours postdose, if possible.

There will be a washout period of approximately 7 days (with 3 dialysis sessions) between MK-7264 dosing in Periods 1 and 2.

**Both Parts:**

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

Subjects may be replaced at the discretion of the Sponsor.

### 9.1.1 Confinement, Return Visit, and Follow-up

In each part and in each period, subjects will be housed from Day -2 or Day – 1 at the time indicated by the CRU, until after the 72-hour blood draw. At all times, a subject may be required to remain at the CRU for longer at the discretion of the Investigator.

The clinic will contact all subjects (including those who terminate the study early) approximately 14 days after the last study drug administration 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 Subjects with Moderate or Severe Renal Insufficiency or with ESRD

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 subject, 18-80 years of age, inclusive, at screening.

2. Subject is a non-smoker or moderate smoker (≤ 20 cigarettes/day or the equivalent). Subject must agree to consume no more than 10 cigarettes or equivalent/day from the time of screening and throughout the period of sample collection.

3. Subject has a body mass index (BMI) ≥ 18.5 and ≤ 40.0 kg/$m^2$, at screening.

4. Females be non-pregnant, non-breast feeding and:

   a. If with reproductive potential: subject must demonstrate a serum β-human chorionic gonadotropin (β –hCG) level consistent with the nongravid state at screening and agree to use (and/or have their partner use) two (2) acceptable methods of birth control beginning at screening, throughout the study and until 2 weeks after the last dosing of study drug. Combination method (requires use of two of the following):

      - diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide and contraceptive sponge)
      - cervical cap with spermicide (nulliparous women only)
      - contraceptive sponge (nulliparous women only)
      - male condom or female condom (cannot be used together)

   b. If postmenopausal: subject is without menses for at least 1 year and have a documented follicle stimulating hormone (FSH) level in the postmenopausal range at screening,

   c. If surgically sterile: subject is status post hysterectomy, oophorectomy, or tubal ligation.

      NOTE: These procedures must be confirmed with medical records. In the absence of documentation, hysterectomy may be confirmed by pelvic exam or if necessary by ultrasound; 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.

5. A subject understands the study procedures in the informed consent forms (ICFs), is willing and able to comply with the protocol, and provides written informed consent for the trial. Future Biomedical Research participation is voluntary and is not required in order to participate in the trial.

#### 9.2.1.2 Subjects with Moderate or Severe Renal Insufficiency Only

6. With the exception of RI, subject is judged to be in good health based on medical history, physical examination, vital signs, and laboratory safety tests. Subject has no clinically significant ECG abnormality, as deemed by the Investigator. Subjects who do not qualify based on a reversible condition or mild intercurrent illness may be re-screened after the underlying condition is resolved.

7. Subject has baseline eGFR <30 mL/min/1.73m$^2$ and is not on dialysis (severe RI) or 30 – 59 mL/min/1.73m$^2$ (moderate RI) based on eGFR equation from MDRD at screening as 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 twice (at least 72 hours apart as part of subject screening) and the mean of the two values will be used. The second baseline eGFR sample may be obtained at the time of check-in.

   Reasonable efforts will be made to enroll at least 2 subjects with eGFR values of < 20 mL/min/1.73m$^2$ (severe RI group) and at least 2 subjects with eGFR values of 30 - 45 mL/min/1.73m$^2$ (moderate RI group).

#### 9.2.1.3 Subjects with ESRD Requiring Hemodialysis Only

6. Baseline health is judged to be stable based on medical history, laboratory profiles, vital signs, or ECGs at screening, as deemed by the Investigator.

7. Subject has ESRD maintained on stable regiment of thrice-weekly HD for at least 3 months prior to first dosing.

#### 9.2.1.4 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 subjects, 18-80 years of age, inclusive, at screening. Age must be within ± 10 years of the mean age of subjects with RI.

2. Subject is a non-smoker or moderate smoker (≤ 20 cigarettes/day or the equivalent). Subjects must agree to consume no more than 10 cigarettes or equivalent/day from the time of screening and throughout the period of sample collection.

3. Subject has a BMI ≥ 18.5 and ≤ 40.0 kg/m$^2$, at screening. Subject must be within ± 10 kg of the mean weight (where the weight is rounded to the nearest kg) of the mean weight of subjects with RI.

4. Subject is medically healthy with no clinically significant medical history, physical examination, laboratory profiles, vital signs, or ECGs, as deemed by the Investigator.

5. Females must be non-pregnant, non-breastfeeding and:

   a. If with reproductive potential: subject must demonstrate a serum β –hCG level consistent with the nongravid state at screening and agree to use (and/or have their partner use) two (2) acceptable methods of birth control beginning at screening, throughout the study and until 2 weeks after dosing of study drug. Combination method (requires use of two of the following):

      - diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide and contraceptive sponge)
      - cervical cap with spermicide (nulliparous women only)
      - contraceptive sponge (nulliparous women only)
      - male condom or female condom (cannot be used together)

   b. If postmenopausal: subject is without menses for at least 1 year and have a documented follicle stimulating hormone (FSH) level in the postmenopausal range at screening,

   c. If surgically sterile: subject is status post hysterectomy, oophorectomy, or tubal ligation.

      NOTE: These procedures must be confirmed with medical records. In the absence of documentation, hysterectomy may be confirmed by pelvic exam or if necessary by ultrasound; 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. Subject has baseline eGFR ≥ 90 mL/min/1.73 $m^2$ based on eGFR equation from MDRD at screening, defined as follows (for females multiply result by 0.742, if African American multiply result by 1.212)*:

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

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

   Baseline eGFR will be obtained twice (at least 72 hours apart as part of subject screening), and the mean of the two values will be used. The second baseline eGFR sample may be obtained at the time of check-in. A creatinine clearance computed over a 24-hour urine collection for subjects that do not qualify with ≥ 90 eGFR may be done for confirmation purposes.

7. Subject understands the study procedures in the ICFs, is willing and able to comply with the protocol, and provides written informed consent for the trial. Future Biomedical Research participation is voluntary and is not required in order to participate in the trial.

### 9.2.2 Exclusion Criteria

#### 9.2.2.1 Subjects with Moderate or Severe Renal Insufficiency or with ESRD

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

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

2. Subject has a history or presence of clinically significant medical or psychiatric condition or disease in the opinion of the Investigator.

3. Subject 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.

4. Subject has a history or presence of alcoholism or drug abuse within the past 6 months prior to first dosing.

5. Subject has a history or presence of hypersensitivity or idiosyncratic reaction to the study drug or related compounds (including sulfonamides).

6. Subject has a history or presence of:

   - renal artery stenosis;
   - major risk factors for renal/urinary calculi, as judged by Investigator.

7. Subject (with exception of subject with ESRD) has rapidly fluctuating renal function as determined by historical measurements. Rapidly fluctuating renal function is defined as > 20% difference between two measurements of eGFR taken at least 72 hour apart as part of subject screening may be enrolled after consultation with Sponsor if additional evidence can be provided to support stable renal function.

8. Subject with ESRD has required frequent emergent HD (≥3) within a year prior to first dosing.

9. A female subject who is pregnant, or who is lactating.

10. Subject has positive results for the urine or saliva drug 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.

11. Subject has positive results at screening for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C virus (HCV).

12. Subject has positive macroscopic hematuria or crystalluria at screening or check-in, as deemed clinically significant by Investigator.

13. Subject 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.

14. Subject has been on a diet incompatible with the on-study diet, in the opinion of the Investigator, within the 28 days prior to first dosing, and throughout the study.

15. Subject has donated blood or had significant blood loss within 56 days prior to first dosing.

16. Subject has donated plasma within 7 days prior to the first dosing.

17. Subject is or has an immediate family member (e.g., spouse, parent/legal guardian, sibling or child) who is a member of the investigational site or sponsor staff member directly involved with this trial.

18. Subject has taken MK-7264 at any time prior to first dosing on the current study.

19. Subject participated in another clinical trial within 28 days prior to first dosing. The 4-week window will be derived from the date of dosing in the previous study to Day 1 of the current study. All visits and procedures from any previous study must be completed before screening for any given subject.

#### 9.2.2.2 Healthy Subjects

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

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

2. Subject has a history or presence of clinically significant medical or psychiatric condition or disease in the opinion of the Investigator.

3. Subject 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.

4. Subject has a history or presence of alcoholism or drug abuse within the past 2 years prior to dosing.

5. Subject has a history or presence of hypersensitivity or idiosyncratic reaction to the study drug or related compounds (including sulfonamides).

6. Subject has a history or presence of:

   - renal artery stenosis;
   - major risk factors for renal/urinary calculi (current or history within the past 5 years of renal/urinary calculi or conditions, which predispose to renal/urinary calculi);

7. A female subject who is pregnant, or who is lactating.

8. Subject has positive results for the urine or saliva drug 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.

9. Subject has positive results at screening for HIV, HBsAg, or HCV.

10. Subject has positive macroscopic hematuria or crystalluria at screening or check-in, as deemed clinically significant by Investigator.

11. Subject 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.

12. Subject has been on a diet incompatible with the on-study diet, in the opinion of the Investigator, within the 28 days prior to dosing, and throughout the study.

13. Subject has donated blood or had significant blood loss within 56 days prior to dosing.

14. Subject has donated plasma within 7 days prior to the dosing.

15. Subject is or has an immediate family member (e.g., spouse, parent/legal guardian, sibling or child) who is a member of the investigational site or sponsor staff member directly involved with this study.

16. Subject has taken MK-7264 at any time prior to dosing on the current study.

17. Subject participated in another clinical trial within 28 days prior to dosing. The 4 week window will be derived from the date of dosing in the previous study to Day 1 of the current study. All visits and procedures from any previous study must be completed before screening for any given subject.

### 9.2.3 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped 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 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).
- If a subject vomits within 3 hours after dosing, i.e., a period of time equal to two times the Tmax of MK-7264, he/she may be withdrawn from the study. The clinical report will include reasons for subject withdrawals as well as details relevant to the subject's withdrawal.

#### 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 clinic will contact all subjects (including those who terminate the study early) approximately 14 days after the last study drug administration to determine if any adverse events have occurred since 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 PPD 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 Therapy

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

- Xanthines/Caffeine: 24 hours before dosing in Part 1 and each period in Part2 until the last pharmacokinetic sample collection;

- Alcohol: 48 hours before dosing in Part 1 and each period in Part2 until the last pharmacokinetic sample collection;
- Grapefruit/Seville orange: 14 days before dosing in Part 1 and first dose in Part2 until the last pharmacokinetic sample collection.

Subjects who are taking medications for stable diseases for ~2 weeks for subjects with RI (including ESRD) and ~1 month for healthy subjects prior to first dosing will be allowed to participate in the study at the discretion of the Investigator and following consultation with the Sponsor Clinical Monitor. 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.

Concurrent therapy with any 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, unless appropriate medical care necessitates that therapy should begin before the Investigator and Sponsor Clinical Monitor can be consulted. During the study, 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 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 P-gp transporters will be prohibited. These 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. Medications of particular concern include, but are not limited to azole antifungals (ketoconazole, itraconazole), macrolide antibiotics (erythromycin, clarithromycin), HIV protease inhibitors, nefazodone, rifampin, dexamethasone, troglitazone, barbiturates, and any drug or supplement (e.g., St. John's wort) that inhibits or induces P-gp transporters. Weak P-gp 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) will be allowed to participate in the study at the discretion of the Investigator and following consultation with the Sponsor Clinical Monitor. Subjects must be on a stable regimen for at least 2 weeks (or 5 half-lives of the study drug, whichever is longer) prior to first study drug administration and is able to withhold the use within 4 hours prior to administration of the study drug.

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 first dosing of study drug.

Phosphate binders containing aluminum, calcium, or lanthanum salts; iron supplements or other metal cations;H2-receptor antagonists (H2RAs [except cimetidine]); or multivitamins containing iron or zinc must be withheld at least 8 hours prior to dosing and at least 4 hours post dosing.

**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 P-gp transporters will be prohibited for at least 14 days and 28 days respectively prior to dosing and throughout the study. Certain medications may be deemed acceptable following consultation with the Sponsor Clinical Monitor and the Investigator. Appropriate sources will be consulted by the Investigator or designee to confirm lack of potential pharmacokinetic/pharmacodynamic interaction with study drug.

### 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 overnight for at least 10 hours prior to study drug administration. Subjects will continue the fast for at least 4 hours postdose.

On all days that subjects are confined in the CRU, standard meals will be provided at approximately 4 and 9 hours postdose, and at appropriate times thereafter. Snacks will be offered 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.

Depending on the CRU rules and regulations, subjects may be prohibited from smoking during their confinement or during portions of their confinement.

## 9.4 Treatments

### 9.4.1 Treatments Administered

**Part 1:**

Subjects will receive a single oral dose of 50 mg MK-7264 (1 x 50 mg tablet) at Hour 0 on Day 1.

**Part 2:**

Period 1: Subjects will receive a single oral dose of 50 mg MK-7264 (1 x 50 mg tablet) at Hour 0 on Day 1 immediately following their scheduled HD.

Period 2: Subjects will receive a single oral dose of 50 mg MK-7264 (1 x 50 mg tablet) at Hour 0 on Day 1, approximately 2 hours prior to their scheduled HD.

**Both Parts:**

MK-7264 will be administered following an overnight fast, with approximately 240 mL of water.

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

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

The exact clock time of dosing will be recorded.

### 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 the dose of MK-7264.

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

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

### 9.4.5 Study Design or Procedure Modifications Permitted within Protocol Parameters

The dose and administration of the trial study drug to any subject may not be modified. If necessary a subject must be discontinued for the reasons described in Section 9.2.3

# 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-7264 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), and BMI ($kg/m^2$) 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 physical examination will be performed as per 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.

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 10 minutes of the scheduled time point.

### 10.1.4 ECG Monitoring

Single 12-lead ECGs will be performed as outlined in the Study Events Flow Chart (Section 6).

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.

ECGs will be measured within 24 hours prior to Day 1 dosing for the predose time point. When scheduled postdose, ECGs will be performed within approximately 20 minutes of the scheduled time point.

A subject will be withdrawn from the study by the Study Physician or his/her designee 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 only will receive HD as per their regular schedule. Dosing in Period 1 will occur immediately following completion of a normally scheduled HD and dosing in Period 2 will occur approximately 2 hours prior to the normally scheduled HD as per the Study Events Flow Chart (Section 6).

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 per 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)
- Alkaline phosphatase
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (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
- 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 dropout or rechecks, subjects may not have fasted for 8 hours before the serum chemistry sample is taken.

** At screening, eGFR will be calculated based on MDRD for renal classification assignment. Baseline eGFR will be obtained twice and the mean of the two values will be used for group assignment in Part 1 of the study.

*** 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?<br>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?<br>If yes, did the adverse event resolve or improve?<br>If yes, this is a positive dechallenge. If no, this is a negative dechallenge.<br>(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?<br>If yes, did the adverse event recur or worsen?<br>If yes, this is a positive rechallenge. If no, this is a negative rechallenge.<br>(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.)<br>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>
<tr><td colspan="2">Related (there is a reasonable possibility of Sponsor's product relationship)</td><td>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.</td></tr>
</table>

| | |
|---|---|
| **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-7264 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-7264 will be provided separately.

Blood collections outside the following windows will be considered deviations:

| Hour | Deviation window |
|---|---|
| 0.0 to 0.5 hour | ± 2 minutes |
| > 0.5 to 2.0 hour | ± 2 minutes |
| > 2.0 to 8.0 hour | ± 2 minutes |
| > 8.0 to 24 hour | ± 5 minutes |
| > 24.0 hour | ± 10 minutes |

#### 10.2.2 Urine Collection (Part 1 only)

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

Urine samples for determination of MK-7264 concentrations will be collected at selected intervals as delineated in the Study Events Flow Chart (Section 6). For subjects with moderate and severe RI, and subjects with ESRD, urine samples will be collected whenever possible, as they may not be able to produce urine at 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-7264, during the entire postdose in-house observation 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 do 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.

### 10.2.3 Dialysate Collection

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-7264 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 in the Appendix 3.

## 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 (this includes serum pregnancy for female subjects only when scheduled at the same time) | 3 | 12.5 | 37.5 |
| Blood for MK-7264 | 15 | 3 | 45 |
| | | Total Blood Volume (mL)→ | 103.5[§] |

* 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 (this includes serum pregnancy for female subjects only when scheduled at the same time) | 6 | 12.5 | 75 |
| Blood for MK-7264 | 58 | 3 | 174 |
| | | Total Blood Volume (mL)→ | 270[§] |

* 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, pharmacokinetic parameters for plasma MK-7264 will be calculated as follows:

| | |
|---|---|
| AUC0-last: | Area under the concentration versus time curve, from 0 to the time of the last quantifiable (above LLOQ) sample. |
| AUC0-∞: | Area under the concentration versus time curve from 0 to infinity after dosing. |
| AUC0-12: | Area under the concentration versus time curve, from 0 to 12 hours after dosing. |
| AUC0-24: | Area under the concentration versus time curve, from 0 to 24 hours after dosing. |
| AUC0-48: | Area under the concentration versus time curve, from 0 to 48 hours after dosing. |
| CL/F: | Apparent clearance after extravascular administration. |
| Cmax: | Maximum observed plasma concentration after the administration of a given dose. |
| Tmax: | Time to maximum observed plasma drug concentration. |
| t½: | (Apparent) terminal half-life. |
| Vz/F: | Apparent volume of distribution during the terminal phase |

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

No pharmacokinetic parameters will be calculated 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 (Part 1 and Part 2)

For subjects with moderate or severe renal impairment, subjects with ESRD, and for matched healthy subjects, pharmacokinetic parameters for urine MK-7264 will be calculated as follows:

| | |
|---|---|
| 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. |

Ae0-48: Total amount of drug excreted unchanged in the urine over the period of 48 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-7264 excretion during each collection interval. Obtained by dividing the amount of MK-7264 excreted in each collection interval by the dose.

### 11.1.3 Hemodialysis: Dialysate and Plasma

For subjects with ESRD only, pharmacokinetic parameters for plasma MK-7264 will be calculated as follows based on concentration in plasma samples from the pre-dialyzer line during the dialysis period (Ca) and on concentration in plasma samples from the post-dialyzer line during the dialysis period (Cv):

AUCD: Plasma AUC values determined from Ca versus time profile during the dialysis period (2-6 hours) using 'linear up, log down' calculation method option in WinNonlin.

AUC(2.5-6)Ca: Plasma AUC values determined from Ca versus time profile during the dialysis period from 2.5 hour to 6 hours using 'linear up, log down' calculation method option in WinNonlin.

AUC(2.5-6)Cv: Plasma AUC values determined from Cv versus time profile during the dialysis period from 2.5 hour to 6 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(2.5-6)Ca – AUC(2.5-6)Cv)/ AUC(2.5-6)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 with ESRD only, pharmacokinetic parameters for dialysate MK-7264 will be calculated as follows:

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 renal impairment on the PK of MK-7264 was not chosen to satisfy any a priori statistical requirement. This sample size (N= 6 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 estimated ratios of geometric means (severe renal impairment / normal renal function) of pharmacokinetic parameters 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 between-subject geometric coefficient of variation (GCV) for MK-7264 AUC0-12, after administration of 50 mg MK-7264 observed in healthy subjects in a previous study (PN 022) is 15%. Since the between subject variability in severe renal subjects has historically been seen to be 2-3 folds higher in many studies, the geometric CV obtained from healthy were inflated by a factor of 2 for severe renal subjects and was used for the following calculations. Assuming a sample size of 6 subjects per population and observed pooled between-subject standard deviation of 0.21 for AUC0-12 on the natural log scale, then the half width of the 90% confidence intervals of GMRs for MK-7264 AUC0-12 on the log scale will be 0.22 The lower and upper 90% confidence limits for the true GMRs will be given by OBS/1.25 and OBS*1.25 for AUC0-12, respectively, where OBS is the observed GMR. Thus, for example, if the observed GMR for AUC0-12 was 1.50, then the 90% confidence intervals for the GMR would be 1.20 to 1.87.

**Table 4: Estimated Precision Calculations**

| Parameter | N (per group) | Half width (log scale) | Observed GMR | 90% confidence interval for Observed GMR |
|---|---|---|---|---|
| AUC0-12 | 6 | 0.22 | 1.50 | (1.20, 1.87) |
| Cmax | 6 | 0.24 | 1.50 | (1.18, 1.91) |

Note: GCV for AUC0-12 and Cmax on Day 1 from PN 22 for 50 mg bid dose were 15% and 16%, respectively

### 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 the appropriate department within Early-Stage

Development. 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 Primary Analysis: Regression 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 C-G equation.

Separately for each pharmacokinetic parameter, individual values of AUC0-∞, AUC0-last, Cmax, CL/F, 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 (45, and 22.5 for moderate, and severe, respectively). However, for the normal renal function group, the estimated mean and corresponding 95% confidence interval will be predicted at the median of the observed eGFR values. Sample SAS code is given below:

**Proc mixed** data=pk ;
model PK= eGFR / s cl DDFM=KR alpha=**0.05** outpm=normres ;
estimate "predicted PK in severe" int **1** eGFR 22.5/alpha=**0.1** cl e;
estimate "predicted PK in moderate" int **1** eGFR **45**/alpha=**0.1** cl e;
estimate "predicted PK in mild" int **1** eGFR **75**/alpha=**0.1** cl e;
estimate "predicted PK in normal" int **1** eGFR xx /alpha=**0.1** cl e;
xx is median eGFR for healthy matched control subject group;
**run**;

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

If the model used does not fit the data adequately, other models, such as natural log transformed 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-7264 pharmacokinetic parameter values AUC0-∞, AUC0-last, Cmax, CL/F, 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 Cmax values vs age and body weight will be provided

Individual values will be listed for each PK parameter (AUC0-∞, AUC0-last, AUC0-12, AUC0-24, AUC0-48, Cmax, Tmax, CL/F, Vz/F, apparent terminal t½, Ae0-24, Ae0-48, 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).

#### 11.2.3.2 Secondary Analysis: Categorical Analysis

Separately for each pharmacokinetic parameter, individual values of AUC0-∞, AUC0-last, Cmax, CL/F, and CLr (as appropriate) will be natural log-transformed and evaluated with a linear fixed-effects model containing a categorical effect for population (ESRD renal impairment Period 1 of Part 2, severe RI, moderate RI, and healthy matched control, based on BSA normalized eGFR). 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. Sample SAS code is given below:

```
Proc mixed =data;
CLASS Population Subject;
MODEL lnpk = Population / DDFM=KR;
REPEATED / GROUP=Population;
LSMEANS Population / CL;
run;
```

To compare subjects with RI in each of the renal categories to subjects with normal renal function, a two sided 90% confidence interval for the true difference in means (renal impairment – normal renal function) will be calculated for each PK parameters (AUC0-∞, AUC0-last, Cmax, CLr, and CL/F) 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 (renal impairment/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, Cmax, CL/F, and CLr.

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, AUC0-12, AUC0-24, AUC0-48, Cmax, Tmax, CL/F, Vz/F, apparent terminal t½, Ae0-24, Ae0-48, 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, AUC0-12, AUC0-24, AUC0-48, Cmax, Tmax, CL/F, Vz/F, apparent terminal t½, Ae0-24, Ae0-48, and Fe, as applicable).

#### 11.2.3.3 ESRD Requiring Hemodialysis (Part 2)

To evaluate the extent to which MK-7264 is removed from plasma by hemodialysis, a linear mixed effect model with population (ESRD RI Period 1, ESRD Period 2) 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/F, AUC0-∞, AUC0-last, and Cmax. For each PK 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 RI in Period 2 -ESRD RI in Period 1) will be calculated for each PK parameter (AUC0-∞, AUC0-last, Cmax, and CL/F) 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 RI in Period 2 of Part 2 / ESRD RI in Period 1 of Part 2) for each pharmacokinetic parameter.

Sample SAS code is given below:

```
proc mixed data=dataset;
class population subject;
model endpoint = population/ddfm=kr;

repeated /type=UN subject=subject group=population;
run;
```

Plots with individual ratios overlaid with GMR and corresponding 90% CI will be provided for CL/F, AUC0-∞, AUClast, and Cmax

Individual listings and descriptive statistics for AUCD, AUC(2.5-6)Ca, AUC(2.5-6)Cv, CLD,plasma, CLD,dialysate, AD, and AD,total following a single-dose administration of MK-7264 will be provided for subjects with ESRD.

Individual listings and descriptive summary statistics may be provided for CLr for ESRD subjects, if CLr could be determined in these subjects.

## 11.3 Safety Evaluation

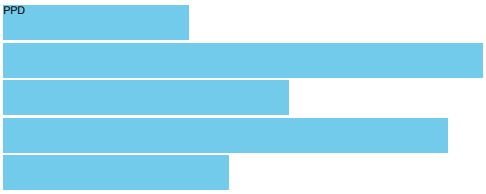
The safety and tolerability of MK-7264 will be evaluated by clinical assessment of adverse events and other safety measurements. Summary statistics for the laboratory safety tests, ECGs, and/or vital signs may also be computed and provided, as deemed clinically appropriate.

# 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:




### 12.1.2 Ethical Conduct of the Study

This research will be carried out in accordance with the protocol, US Code of Federal Regulations, Good Clinical Practices (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.

Case Report Forms (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-7264 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-7264 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.

#### 12.6.1 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label. Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site. Clinical supplies may not be used for any purpose other than that stated in the protocol.

#### 12.6.2 Discard/Destruction/Returns and Reconciliation

The Investigator is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial. For all trial sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

### 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 Harmonisation 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 will determine the minimum retention period and upon request, will provide guidance to the investigator when documents no longer need to be retained. 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 destroying 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 Principal Investigators at the different trial sites in that Member State, according to national regulations. For a single-center trial, the Protocol CI is the Principal 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 Protocol/CSR 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 before 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 PPD. 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 PPD .

## 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/

**Appendix 3: PAXgene™ Blood for DNA Analysis**

# PAXgene™ BLOOD FOR DNA ANALYSIS SPECIMEN COLLECTION PROCEDURE

## SPECIMEN COLLECTION NOTES* SCP-124-00

*__NOTE__: Refer to protocol flow chart or Specimen Collection Overview Chart for scheduled collection time points.

*__NOTE:__ Collection of specimens from vascular access devices and heparin or saline locks is not recommended due to the potential for specimen contamination. This specimen should be collected as a peripheral blood draw.

## Supplies and Materials (per patient, per time point)

### Provided to the Institution

- Requisition form/card
- "PAXgene Blood DNA" labels
- One 8.5 mL PAXgene™ Blood DNA collection tube (Cat#761115)

## Precautions

*** SAFETY PRECAUTION:** Contents of the PAXgene™ tube are irritating to skin. Wear disposable gloves, safety glasses or goggles and a laboratory coat and follow standard laboratory safety procedures while working with these tubes. If inhaled, supply fresh air; consult doctor in case of complaints. If skin contact, immediately wash with water and soap, and rinse thoroughly. If contents make eye contact, rinse opened eye for 15 minutes under running water, then consult a doctor. If swallowed, immediately call a doctor.

## Required Equipment

- Freezer for -20°C for PAXgene™ tube storage (For storage exceptions/monthly batch shipments).

## Labeling

1. Place patient-specific label on the PAXgene Blood DNA tube.

2. If required: Fill out the requisition form/card appropriately (ensure that you follow specific processing instructions per the protocol specific Laboratory Procedure Manual).

## Preparation

1. Ensure the patient has signed the appropriate IRB/ERC-approved consent for genetic specimen collection prior to collecting the specimen.

2. Ensure the PAXgene™ Blood DNA collection tubes are at room temperature prior to collecting blood.

*NOTE: Do not use tubes after the expiration date printed on the label.

3. The PAXgene™ Blood DNA collection tubes should not be the first tubes drawn during venipuncture. **It should be the last tube collected**.

## Specimen Collection

1. Collect blood into each PAXgene™ Blood DNA collection tube via your institution's recommended standard procedure for venipuncture.

   - Ensure that the blood has stopped flowing into the tube before removing the tube from the holder.
   - Each tube holds approximately 8.5 mL of blood.
   - Under-filling of the tubes could result in an incorrect blood-to-additive ratio and may lead to poor performance (e.g. poor quality or low quantity)

2. Immediately after collection, completely and gently invert the tube 10 times to mix uniformly.


***NOTE: After each tube is collected, it is CRITICAL to gently invert PAXgene™ 10 times to ensure proper mixing of blood & PAXgene™ proprietary reagent.**

## Specimen Processing & Handling

1. Within 5-10 minutes of the blood draw, place tubes upright in a wire or hard plastic rack at ambient temperature (18-25°C).

2. Tubes **must be shipped within 24 hrs of collection** to the laboratory at ambient temperature.

## Storage Exceptions (special circumstances only)

**If storing specimens for batch shipment**: Specimen tubes MUST be transferred to a -20°C freezer, in a wire or hard plastic rack in the upright position, after collection. **Specimen tubes may be stored frozen upright at -20°C for no longer than 4 weeks at -20°C.** Tubes stored at -20°C must be shipped on dry ice to the Laboratory.

*__NOTE__: Any storage time and temperature excursions must be documented and communicated upon specimen shipment within the shipment inventory documents.

***NOTE:** Frozen PAXgene™ Blood DNA collection tubes are subject to breakage on impact. To reduce the risk of breakage during handling and shipment, frozen tubes should be treated in the same manner as glass tubes. If freezing is required, a wire or hard plastic rack should be used (**NO STYROFOAM**) as the tubes may crack.

## Packaging and Shipping

1. It is the responsibility of the primary investigator to ensure that all staff personnel who will be handling, packaging, and/or shipping clinical specimens are trained and certified as required by National and International regulations and they ship materials in accordance with all current regulations relating to the handling and shipping of hazardous goods.

2. Follow packing and shipping instructions for **AMBIENT** shipments.

3. Contact shipping courier to obtain any required documentation/forms required for shipment.

4. Ship to the Laboratory **within 24 hr of the blood draw**.

5. **Shipping schedule** – Select overnight or priority delivery and ensure that shipments are received at the destination vendor Monday through Friday, except on U.S. holidays. Shipments can be received on Saturday with advanced notification. **Contact the Vendor if you are uncertain about the shipping or receiving schedule.**

   ***NOTE:** For storage exceptions where ambient shipment was not possible, and

specimens were frozen (approximately -20°C), always ship frozen specimens on DRY ICE.

**Shipping Address:**
**BioProcessing Solutions Alliance**
Attn: CommStaff
Nelson Biological Laboratories
**604 Allison Road, C120**
**Piscataway, New Jersey 08854, USA**
Tel.: PPD
Fax: PPD
Email: PPD