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Celerion Project No.: CA21806

Merck Protocol No.: MK-8591-010-01

US IND No.: 134,036

A Study to Evaluate the Potential Interaction of MK-8591 with MK-1439 (Doravirine) in Healthy Adult Subjects

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
16-Jun-2017 by PPD	Final Protocol, Amendment 1 **Purpose of Amendment** The protocol is amended to add additional serum pregnancy tests to the study events schedule, address inconsistencies in safety laboratory blood draw windows, and denote a change to the Principal Investigator (PI) for the study. **Rationale for Amendment** The final protocol event schedule included serum pregnancy tests for Screening and for the first check-in but were omitted for subsequent check-in procedures. Serum pregnancy tests are to be conducted at all succeeding study check-ins. The amendment also includes a change to PI. **<u>Changes to the Study Protocol</u>** **Section 2 – Principal Investigator and Sponsor - Signatories** The PI has been changed. **From:** James Carraher, MD 621 Rose Street Lincoln, Nebraska 68502, USA Tel.: PPD Fax: PPD E-mail: PPD **To:** Charles Tomek, MD 621 Rose Street Lincoln, Nebraska 68502, USA Tel.: PPD Fax: PPD E-mail: PPD **Section 6 – Study Events Flowchart** The flowchart has been updated to include additional serum pregnancy tests for check-in procedures on Day 4 of Period 1, predose procedures on Days 14 and 19 of Period 2, and at the Follow-up visit on Day 33.

	Addtionally footnote "i" has been applied to predose safety laboratory samples and serum pregnancy tests scheduled on Days 14 and 19 allowing these samples to be drawn within 24 hours prior to dosing on these days. It has also been applied to serum pregnancy tests on check-in Days -1 and 4 of Period 1 indicating these samples are to be performed within 24 hours of the next scheduled dose. Footnote "e" has been corrected to footnote "f" for Day 1 (Period 2) denoting procedures taken on Day 6 of Period 1 and on Day 1 of Period 2 are to be taken only once. **Section 10.1.5 – Laboratory tests (First paragraph)** In Section 6 (Study Events Flowchart) of the final protocol, footnote i states that the predose laboratory test in Period 1 scheduled on Day -1 will be performed within 24 hours of dosing. Initially, in Section 10.1.5 (Laboratory Tests), the predose laboratory tests in Period 1 and Period 2 were allowed with a variance of 30 minutes. Text in Section 10.1.5 has been modified as follows: **From:** The following variance in laboratory safety tests will be allowed: • 30 mins (for Period 1 predose on Days 1 and 5, and Period 2 predose on Days 1, 14, and 19) • 48 hours (for Day 33) **To:** The following variance in laboratory safety tests will be allowed: • 48 hours (for Day 33) **Section 10.5 - Blood Volume Drawn for Study Assessments** Table 2 has been updated to include a blood volume of 4 mL to be drawn at check-in on Day 4 for the serum pregnancy test. The total blood volume was changed from 315.5 mL to 319.5 mL. Serum pregnancy tests performed on Days 14, 19, and 33 will be conducted from the serum chemistry blood volume drawn at these times and therefore an additional blood volume is not required for these 3 additional pregnancy tests.
14-Mar-2017 by PPD	Final Protocol

2 PRINCIPAL INVESTIGATOR AND SPONSOR – SIGNATORIES

A Study to Evaluate the Potential Interaction of MK-8591 with MK-1439 (Doravirine) in Healthy Adult Subjects

SPONSOR:

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5 SYNOPSIS

Compound:	MK-8591
Clinical Indication:	Treatment of human immunodeficiency virus type 1 (HIV-1) infection
Study Phase and Type:	Phase 1 - Interventional
Study Objectives, Hypothesis, and Estimation:	**Primary:** Objective 1: To assess the effect of MK-8591 following multiple dose administration on the pharmacokinetics of plasma MK-1439 (e.g., AUC0-24, C24, Cavg, Cmax, Tmax, and apparent terminal t½). Hypothesis: There is no clinically meaningful effect of MK-8591 on the AUC0-24, C24, and Cmax of plasma MK-1439. That is, the true geometric mean ratios [(MK-8591 + MK-1439)/(MK-1439)] for AUC0-24, C24, and Cmax of MK-1439 are contained within the preliminary bounds of [0.5, 2.0]. Objective 2: To assess the effect of steady-state levels of plasma MK-1439 on the pharmacokinetics of plasma MK-8591 following multiple dose administration (e.g., AUC0-24, C24, Cavg, Cmax, Tmax, and apparent terminal t½). Estimation: The AUC0-24 and Cmax of plasma MK-8591 after multiple oral daily doses of MK-8591 coadministered with multiple doses of MK-1439 will be estimated and compared to the values observed after multiple dose administration of MK-8591 alone. **Secondary:** Objective: To evaluate the safety and tolerability of multiple doses of MK-8591 alone, of multiple doses of MK-1439 alone, and of multiple doses of MK-8591 coadministered with multiple doses of MK-1439. **Planned Exploratory Biomarker:** Objective: To explore the relationship between genetic variation and response to the treatments administered, and mechanisms of disease. Variation across the human genome may be analyzed for association with clinical data collected in this study.
Summary of Study Design:	This is a double-blind, placebo-controlled, randomized, fixed-sequence, 2-period, drug-drug interaction (DDI) study. On Days 1 through 5 of Period 1, an oral dose of 100 mg MK-1439 or placebo will be administered once daily (QD). Serial blood samples will be collected for the pharmacokinetic assessment of MK-1439 for 24 hours following MK-1439 dosing on Day 5 and trough blood samples will be collected at specified times.

	On Days 1 through 19 of Period 2, an oral dose of 2.25 mg MK-8591 or placebo will be administered QD with an oral dose of 100 mg MK-1439 or placebo coadministered QD for 5 days on Days 15 through 19. Serial blood samples will be collected for the pharmacokinetic assessment of MK-8591 for 24 hours following MK-8591 dosing on Days 14 and 19 and will be collected for the pharmacokinetic assessment of MK-1439 for 24 hours following MK-1439 dosing on Day 19. Blood samples for pharmacokinetic assessments of MK-8591 and MK-1439 will continue through Day 33 of Period 2. Trough blood samples will be collected at specified times. Subjects who receive placebo in Period 1 will also receive placebo in Period 2. There will be no washout period between last dose in Period 1 and first dose in Period 2. All subjects (including subjects who terminate early) will return to the clinical research unit (CRU) 14 days after the last study drug administration for follow-up procedures and to determine if any adverse events have occurred since the previous study visit.
Number of Subjects:	Fourteen (14), healthy, adult, male and female subjects between 19 and 55 years of age (inclusive) will be enrolled.
Dosage, Dosage Form, Route, and Dose Regimen:	Treatments are described as follows: Treatment A: (Period 1) 100 mg MK-1439 (1 x 100 mg tablet) or placebo administered QD on Days 1 to 5. Treatment B: (Period 2) 2.25 mg MK-8591 (2 x 1 mg capsules and 1 x 0.25 mg capsule) or placebo administered QD at Hour 0 on Days 1 to 19 with QD doses of 100 mg MK-1439 (1 x 100 mg tablet) or placebo coadministered at Hour 0 on Days 15 to 19. Subjects will be randomized in Period 1 to receive either the active drug (MK-8591 and MK-1439) or the placebo in 5:2 ratio. Subjects who received placebo in Period 1 will also receive placebo in Period 2. All study drugs will be administered orally, with approximately 240 mL of water.

Key Assessments:	**Pharmacokinetics:** Values of the following steady-state plasma pharmacokinetic parameters will be calculated for MK-1439 on Day 5 of Period 1 and Day 19 of Period 2 and for MK-8591 on Day 14 and Day 19 of Period 2, as appropriate: AUC0-24, C24, Cavg, Cmax, Tmax, and apparent terminal t½. A linear mixed-effects model will be used for the analysis of the natural log (ln)-transformed AUC0-24, C24, and Cmax of MK-1439 and AUC0-24 and Cmax of MK-8591, using the appropriate statistical procedures. **Safety:** Safety will be monitored via physical examination and collection of 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 be computed and provided, as deemed clinically appropriate.

6 STUDY EVENTS FLOW CHART

Study Procedures[a]	Screening [b]	Study Days in Period 1 [c]																				
Days →		-1	1		2	3		4		5											6	
Hours →		(C-I) [d]	P	0	0	P	0	0	C-I [d]	P	0	0.5	1	2	3	4	8	12	16 [e]	20	0 [f]
Administrative Procedures																						
Informed Consent	X																					
Informed Consent for Future Biomedical Research	X																					
Inclusion/Exclusion Criteria	X	X [g]																				
Medical History	X																					
Safety Evaluations																						
Full Physical Examination [h]	X	X																				
Height	X																					
Weight	X	X																				
12-Lead Electrocardiogram	X	X [i]								X												X [f]
Vital Signs (heart rate & blood pressure)	X	X [i]	X							X												X [f]
Vital Signs (respiratory rate & temperature)	X	X [i]	X							X												X [f]
Hem, Serum Chemistry [j], and Urinalysis	X	X [i]																				X [f]
Serum Pregnancy Test (female subjects only)	X	X [i]							X [i]													
Serum FSH (postmenopausal females only)	X																					
Urine Drug and Alcohol Screen	X	X							X													
Urine Cotinine Screen	X	X							X													
HIV/Hepatitis Screen	X																					
Adverse Events Monitoring	X	X																				
Concomitant Medication Monitoring	X																					

Study Procedures[a]	**Screening** [b]	**Study Days in Period 1** [c]																				
Days →		**-1**	**1**		**2**	**3**		**4**		**5**											**6**	
Hours →		**(C-I)** [d]	**P**	**0**	**0**	**P**	**0**	**0**	**C-I** [d]	**P**	**0**	**0.5**	**1**	**2**	**3**	**4**	**8**	**12**	**16** [e]	**20**	**0** [f]
Study Drug Administration / Pharmacokinetics																						
MK-1439 Administration				X	X		X	X			X											
Blood for MK-1439 Pharmacokinetics			X			X				X		X	X	X	X	X	X	X	X	X	X	X [f]
Blood for MK-8591 Pharmacokinetics																						X [f]
Other Procedures																						
Blood for Genetic Analysis [k]			X																			
Confinement in the CRU			X							X												
Visit and Return Visits	X				X	X		X														

Study Procedures [a]	**Study Days in Period 2** [c]																												
Days →	**1** [f]		**2**	**3**	**4**	**5**		**6**	**7**	**8**	**9**		**10**	**11**	**12**	**13**		**14**								**15**		
Hours →	**P**	**0**	**0**	**0**	**0**	**P**	**0**	**0**	**0**	**0**	**P**	**0**	**0**	**0**	**0**	**0**	**C-I** [d]	**P**	**0**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**20**	**P**	**0**
12-Lead Electrocardiogram	X [f]																	X			X	X	X						
Vital Signs (heart rate & blood pressure)	X [f]					X					X							X		X	X	X	X	X	X		X		
Vital Signs (respiratory rate & temperature)	X [f]																	X											
Hem, Serum Chemistry [j], and Urinalysis	X [f]																	X [i]											
Serum Pregnancy Test (female subjects only)																		X [i]											
Urine Drug and Alcohol Screen																	X												
Urine Cotinine Screen																	X												
Adverse Events Monitoring	X																												
Concomitant Medication Monitoring	X																												
Study Drug Administration / Pharmacokinetics																													
MK-1439 Administration																													X
MK-8591 Administration		X	X	X	X		X	X	X	X		X	X	X	X	X			X										X
Blood for MK-1439 Pharmacokinetics	X																										X		
Blood for MK-8591 Pharmacokinetics	X					X					X							X		X	X	X	X	X	X	X	X		
Other Procedures																													
Confinement in the CRU	X	X															X												
Return Visits			X	X	X	X		X	X	X	X		X	X	X	X													

Study Procedures [a]	Study Days in Period 2 [c]																						FU / ET [l]
Days →	16		17		18			19											20		24	27	33
Hours →	P	0	P	0	P	0	C-I [d]	P	0	0.25	0.5	1	2	3	4	8	12	16 [e]	20	0	0	0	0
Safety Evaluations																							
Full Physical Examination																							X [m]
12-Lead Electrocardiogram								X			X	X	X										X [m]
Vital Signs (heart rate & blood pressure)	X		X		X			X		X	X	X	X	X	X	X	X	X		X			X [m]
Vital Signs (respiratory rate & temperature)								X															X [m]
Hematology, Serum Chemistry [j], and Urinalysis								X [i]															X [m]
Serum Pregnancy Test (female subjects only)								X [i]															X [m]
Urine Drug and Alcohol Screen							X																
Urine Cotinine Screen							X																
Adverse Events Monitoring	X																						
Concomitant Medication Monitoring	X																						
Study Drug Administration / Pharmacokinetics																							
MK-1439 Administration		X		X		X			X														
MK-8591 Administration		X		X		X			X														
Blood for MK-1439 Pharmacokinetics	X		X		X			X			X	X	X	X	X	X	X	X	X	X	X	X	X [m]
Blood for MK-8591 Pharmacokinetics	X		X		X			X		X	X	X	X		X	X			X	X	X	X	X [m]
Other Procedures																							
Confinement in the CRU							X						X										
Return Visits		X		X		X															X	X	X

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 is no washout period between the last dose in Period 1 and the first dose of Period 2. Day 6 of Period 1 equates to Day 1 of Period 2.

d. Subjects will be admitted to the CRU on Days -1 and Day 4 of Period 1 and Days 13 and 18 of Period 2, at the time indicated by the CRU.

e. The 16-hour time point following dosing of MK-1439 on Day 5 of Period 1 and Day 19 of Period 2 will occur either on Day 5 or Day 6 of Period 1 and Day 19 or Day 20 of Period 2, respectively, depending on the time of dosing on Day 5 (Period 1) and Day 19 (Period 2), respectively

f. Procedures taken on Day 6 of Period 1 and on Day 1 of Period 2 are to be taken only once. Safety assessments at this time (ECG, vital signs, and safety laboratory sample) and pharmacokinetic sampling for MK-1439 (24 hours post Day 5 sample) and predose MK-8591 sample will be performed prior to MK-8591 administration.

g. To be performed in Period 1 only.

h. A directed physical examination may be performed at other times not listed on the flow chart, at the investigator's discretion.

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

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

k. 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.

l. All subjects (including subjects who terminate early) will return to the CRU 14 days after the last study drug administration for follow-up procedures and to determine if any adverse events have occurred since the last study visit.

m. To be performed at the end of Period 2 or prior to early termination from the study.

Abbreviations: C-I = Check-in, CRU = Clinical research unit, DNA = deoxyribonucleic acid, ECG = Electrocardiogram, ET = End of Study or Early Termination, FBR = Future biomedical research, FSH = Follicle-stimulating hormone, FU = Follow-Up, Hem = Hematology, HIV = Human immunodeficiency virus, IRB/IEC = Institutional Review Board/Independent Ethics Committee, P = predose.

7 BACKGROUND AND RATIONALE

7.1 Background – MK-8591

MK-8591 is a novel, potent human immunodeficiency virus type 1 (HIV-1) nucleoside reverse transcriptase inhibitor (NRTI). MK-8591 is an inactive nucleoside prodrug that is converted to the pharmacologically active triphosphate form (MK-8591-TP) via endogenous intracellular kinases. MK-8591-TP is a highly potent and specific inhibitor of HIV-1 reverse transcriptase (RT) activity *in vitro*, with a novel mechanism of action. MK-8591 acts as a chain terminator by preventing translocation of the primer:template in the RT active site, and prevents binding of incoming deoxyribonucleotide triphosphate molecules (dNTPs). MK-8591 demonstrates a high barrier to resistance *in vitro*.

Currently marketed NRTIs include tenofovir disoproxil fumarate (TDF), lamivudine, emtricitabine, abacavir, didanosine, stavudine, and zidovudine. The standard of care for the treatment of HIV infection in naïve patients calls for 3 agents, with 2 NRTIs in combination with either an integrase strand transfer inhibitor, a protease inhibitor, or a non-nucleoside reverse transcriptase inhibitor (NNRTI). [1] While the currently approved NRTIs represent a cornerstone of modern anti–retroviral therapy, there are significant class associated toxicities including loss of bone mineral density, new or worsening renal impairment, severe lactic acidosis, and serious hypersensitivity reactions. Because tolerability issues are one of the most common reasons for lack of adherence and subsequent viral failure, a need exists for new NRTIs like MK-8591 that possess a high barrier to resistance with an improved safety and tolerability profile.

Refer to the Confidential Clinical Investigator's Brochure (IB) for detailed background information on MK-8591 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

7.1.1 Summary of Clinical Experience

As of 13-January-2017 five clinical studies (PN 001, 002, 003, 005, and 006) have been conducted with MK-8591. PN 001 was a double-blind, single-rising dose trial to evaluate the safety, tolerability, and pharmacokinetics of MK-8591 in healthy subjects. PN 002 was a double-blind, multiple-rising dose trial to evaluate the safety, tolerability, and pharmacokinetics of MK-8591 in healthy subjects. PN 003 is an ongoing unblinded, open-label, single dose trial to evaluate the safety, tolerability, pharmacokinetics, and anti-retroviral activity of MK-8591 in HIV-1 infected patients. PN 005 assessed the two-way interaction of MK-8591 and dolutegravir (DTG)/TDF. PN 006 assessed the pharmacokinetics of levonorgestrel/ethinyl estradiol (LNG/EE), following a single dose of LNG/EE when given alone and when given with multiple doses of MK-8591. As of 13-January-2017, MK-8591 has been administered to 68 healthy subjects and 24 HIV-1 infected patients. Unblinded safety data from PN 001, 002, and 005, and preliminary safety data from PN 003 and 006 indicate

that single and multiple doses of MK-8591 have been generally well tolerated. There have been no serious adverse experiences and no trial participants discontinued due to an adverse experience in any study.

Plasma pharmacokinetic data indicate that MK-8591 was rapidly absorbed with a median Tmax of 0.5 hour. Plasma concentrations decreased in a bi-phasic manner with an initial rapid phase and a slow terminal phase with an apparent terminal t½ of approximately 50-60 hours. Intracellular MK-8591-TP levels reached Cmax between 6 and 24 hours and declined with an apparent terminal t½ of approximately 120 to 210 hours. MK-8591 plasma exposure appeared to increase in an approximately dose-proportional manner between 5 mg and 400 mg. Following administration of 30 mg MK-8591 with a high-fat meal, MK-8591 had a slightly delayed absorption with a median plasma Tmax of 1.25 hours, compared to the Tmax of 0.5 hours under fasted conditions. Administration of a high-fat meal resulted in 49% decrease in Cmax and 10% increase in AUC0-∞ of plasma MK-8591. Intracellular MK-8591-TP pharmacokinetics was largely unaffected by a high-fat meal and observed geometric mean ratios (GMRs)(Fed/Fasted) for MK-8591-TP AUC0-∞, Cmax, and C168 were 0.96, 0.96, and 0.98, respectively. Following administration of multiple doses of MK-8591 once weekly, there appeared to be a modest degree of accumulation of intracellular MK-8591-TP based on AUC0-168 and Cmax, while there was little to no accumulation of intracellular MK-8591 TP based on C168. Pharmacokinetic data in HIV-1 infected subjects generally agree with the data in healthy subjects.

MK-8591 has been administered to treatment-naïve HIV-positive subjects at doses of 1 mg, 2 mg, 10 mg, and 30 mg. Preliminary viral load reduction data show greater than 1.0 log drop on average at all doses tested.

7.1.2 Metabolism – MK-8591

MK-8591 is anabolized to the active triphosphate in peripheral blood mononuclear cells (PBMCs). Elimination of MK-8591 is anticipated to be balanced between renal excretion of unchanged parent drug and adenosine deaminase mediated metabolism, a non-CYP mediated pathway. In addition, MK-8591 is not a substrate of P-glycoprotein (P-gp), organic anion transporter 1 (OAT1), OAT3, and organic cation transporter 2 (OCT2). Thus, MK-8591 is not likely to be a victim of CYP- or transport-mediated DDI.

MK-8591 is also not a CYP inhibitor or inducer *in vitro*, and is not an inhibitor of P-gp, OAT1, OAT3, OCT2, organic anion transporting polypeptide 1B1 (OATP1B1), bile salt export pump (BSEP), multidrug resistance protein 2 (MRP2), multidrug resistance protein 3 (MRP3), and multidrug resistance protein 4 (MRP4). Thus, MK-8591 is also not likely to be a perpetrator of DDI.

MK-8591 has been evaluated in two DDI studies to date, examining potential DDIs with DTG, TDF, and oral contraceptives (levonorgestrel/ethinyl estradiol). No DDIs were observed between MK-8591 and DTG/TDF or between MK-8591 and LNG/EE as expected.

7.2 Background – MK-1439

MK-1439 (doravirine) is a NNRTI in development for the treatment of HIV-1 infection. MK-1439 is a potent inhibitor of HIV-1 replication *in vitro* and is active against both wild type (WT) virus and most common NNRTI resistant variants at concentrations achieved with QD dosing. The antiviral activity of MK-1439 was tested in cell culture. MK-1439 displays 95% effective concentration (EC_{95}) of 20, 42, and 27 nM against WT, K103N, and Y181C mutant viruses, respectively, in the presence of

50% human serum [2]. MK-1439 has a favorable preclinical profile and clinical pharmacology studies indicate that MK-1439 may be dosed QD, without regard to food.

Refer to the Confidential Clinical Investigator's Brochures (IB) for detailed background information on MK-1439 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

7.2.1 Summary of Clinical Experience – MK-1439

Safety

Approximately 1106 adult subjects have been administered one or more doses of MK-1439. As of 27-Jan-2017, Phase 1 studies have included 622 subjects, including 12 HIV-1 infected subjects. MK-1439 has been generally well tolerated when administered as a single dose up to 1200 mg, as multiple doses up to 200 mg administered QD for up to 48 weeks in combination with background antiretroviral therapy, and as 750 mg administered QD for 10 days.

In a Phase 2 investigation, MK-1439 was dosed up to 200 mg QD in combination with Truvada® in over 200 HIV-1 infected subjects; MK-1439 was generally well-tolerated for up to 96 weeks. In Phase 3, 100 mg MK-1439 QD (N=385) or 800-mg darunavir QD plus 100 mg ritonavir QD (N=384) were administered each in combination with Truvada® or EPZICOM®/KIVEXA® for up to 48 weeks. The most frequently reported adverse events (≥ 5% of subjects in either treatment group) were diarrhea (MK-1439: 14.1%; DRV/r: 22.5%), headache (13.8%, 10.7%), nausea (10.7%, 12.0%), nasopharyngitis (7.8%, 10.2%), upper respiratory tract infection (9.4%, 6.0%), fatigue (8.1%, 5.2%), dizziness (5.0%, 3.9%), upper abdominal pain (5.0%, 2.6%), back pain (5.5%, 2.1%), and cough (5.0%, 1.6%). Forty-two (5.5%) of the 766 treated subjects experienced ≥ 1 serious adverse events during this period, with the serious adverse event incidence being similar between subjects in both treatment groups. Two subjects (1 in each treatment group) experienced serious adverse events that were considered by the investigator to be related to blinded study drug: 1 subject in the MK-1439 group experienced nausea and vomiting, and 1 subject in the DRV/r group experienced peripheral edema. One subject died on-study, but this was not considered by the investigator to be drug-related. Eighteen (2.3%) subjects experienced adverse events that resulted in discontinuation of study drug (MK-1439: 6 subjects [1.6%]; DRV/r: 12 subjects [3.1%]) during the analysis period. Of these 18 subjects, 12 (1.6%) individuals discontinued study drug due to serious adverse events that were considered drug-related by the investigator. Three subjects discontinued study drug in response to the onset of serious adverse events.

Pharmacokinetics

Preliminary pharmacokinetic data for single dose administration up to 1200 mg MK-1439 indicate that with oral administration to healthy male subjects, MK-1439 was rapidly absorbed with median peak plasma concentration values of 1 to 5 hours postdose. MK-1439 plasma concentrations declined

in a monoexponential manner, with mean terminal elimination half-life values ranging from 11 to 18 hours. In single dose administration over the range 6 to 150 mg, MK-1439 AUC0-∞ and Cmax values increased approximately dose proportionally, with slightly less than dose proportional increases beyond 150 mg. Renal excretion represents a minor route of elimination with only 6% of the dose excreted unchanged in urine following a 50 mg single dose.

The multiple-dose data were consistent with single-dose data and support QD administration of MK-1439. The median Tmax values on Days 1 and 10 or 14 ranged from 1 to 4 hours following 30 mg to 750 mg QD doses. Following 10-14 days of QD dosing, MK-1439 plasma concentrations declined in a monoexponential manner, with mean apparent terminal elimination t½ values ranging from 12 to 19 hours, consistent with single dose data. After multiple days of QD dosing, steady state was achieved by Day 4 or 5. At steady state, the mean AUC0-24, Cmax, and C24 accumulation ratios based on Day 10 or Day 14/ Day 1 GMRs were 1.2-1.5, consistent with predictions from single-dose data. Administration of MK-1439 with a high-fat meal increased AUC0-∞ by 16%, while the Cmax remained essentially unchanged.

7.2.2 Metabolism – MK-1439

MK-1439 is eliminated primarily by CYP3A-mediated metabolism. MK-1439 is a substrate for P-gp *in vitro* but P-gp does not play a significant role in its disposition. MK-1439 is not a substrate of OATP1B1 or 1B3.

MK-1439 was not an inhibitor of CYP enzymes *in vitro*, and inhibited OATP1B1, OATP1B3, OAT1, OAT3, OCT2, and BCRP with high IC50 values (ranging from 16-75µM) relative to its anticipated unbound Cmax at the 100 mg dose (0.7 µM). Furthermore, MK-1439 is not an inducer of CYP1A2 or CY2B6 and only a weak inducer of CYP3A4; a DDI study with midazolam demonstrated that MK-1439 did not have a clinically meaningful effect on the PK of midazolam. These findings suggest that MK-1439 is not likely to act as a perpetrator of DDI at clinically relevant MK-1439 concentrations.

In the DDI studies of MK-1439 performed to date, clinically meaningful interactions were observed after CYP3A4 induction and inhibition. Strong induction of CYP3A4 (rifampin) led to an 88% reduction in exposure and 97% reduction of Cmin, while moderate induction (efavirenz) led to a 50-60% reduction in exposure and 70-85% reduction of Cmin. Inhibition of CYP3A4 activity (ritonavir, ketoconazole) led to a 3-fold increase in MK-1439 AUC and no meaningful effect (20-30% increase) on Cmax. Additional DDI studies to examine MK-1439 as a potential victim did not demonstrate clinically meaningful DDI with pantoprazole, antacid suspension, tenofovir, and DTG.

The DDI evaluation of MK-1439 as a perpetrator demonstrated no clinically meaningful DDI after dosing with midazolam, oral contraceptives, metformin, atorvastatin, and DTG. Additional DDI studies, with sofosbuvir/ledipasvir, elbasivir/grazoprevir, and methadone, also demonstrated no clinically meaningful DDI.

7.2.3 Predicted MK-8591/MK-1439 DDI

The extensive DDI analysis of MK-1439 has demonstrated only the interaction with CYP3A4 inhibitors and inducers, which was predicted based on the *in vitro* studies. As MK-8591 was not observed to inhibit or induce CYP3A4, it is not anticipated to affect the pharmacokinetics of MK-1439.

The elimination of MK-8591 is anticipated to be balanced between by renal filtration and adenosine deaminase mediated metabolism. MK-1439 has not been tested as an inhibitor of adenosine deaminase and thus the potential for an interaction with MK-8591 through this pathway is unknown. However, the involvement of two clearance pathways for MK-8591 reduces the likelihood of MK-1439 having a significant effect on the PK of MK-8591. Therefore, MK-1439 is not anticipated to be a perpetrator of DDI against MK-8591.

7.3 Rationale

7.3.1 Rationale for this Study and Study Design

MK-8591 and MK-1439 belong to distinct classes of antiretroviral therapy, and are being developed for the treatment of HIV-1 infection. Potential treatment regimens that include MK-8591 and MK-1439 are to be evaluated in upcoming clinical trials. The current recommendation for first-line treatment of HIV infection in naïve patients calls for 3 agents and typically includes 2 NRTIs in combination with an integrase strand transfer inhibitor, a protease inhibitor, or NNRTI. This study is being performed to determine whether there is an effect on pharmacokinetics and/or safety when multiple doses of MK-8591 and MK-1439 are co-administered.

7.3.2 Rationale for the Dose Selection and Regimen

Single QD doses of 100 mg MK-1439 were selected as this dose is projected therapeutic dose. Single doses of MK-1439 up to 1200 mg and multiple doses up to 750 mg for 10 days have been evaluated and found to be generally well tolerated. The administration of 1200 mg single dose of MK-1439 resulted in AUC0-∞ and Cmax values of 250 µM.hours and 11.2 µM, respectively, providing a clinical safety margin of approximately 6-fold for AUC0-24 and Cmax, respectively. MK-1439 is expected to reach steady-state after 5 days of dosing.

A dose of 2.25 mg MK-8591 will be administered QD for 19 days. Single doses up to 400 mg and multiple doses up to 100 mg once weekly for 3 doses have been generally well tolerated. Pharmacokinetic and viral dynamic simulations suggest that MK-8591 doses ranging from 0.25 mg to 5 mg administered once daily are projected to be efficacious. MK-8591 is expected to reach steady state after 12 days of dosing.

7.3.3 Rationale for Pharmacokinetic Endpoints

The primary pharmacokinetic endpoints will include AUC0-24, C24, and Cmax for MK-1439, and AUC0-24 and Cmax for MK-8591, as these parameters describe the exposure and bioavailability of MK-1439 and MK-8591 and are thought to be the most relevant pharmacokinetic parameters for the purpose of evaluating an interaction between these compounds.

7.3.4 Rationale for Bounds for this Trial

As clinical experience with MK-8591 is still relatively limited, no bounds will be set for this compound. Of note, monotherapy has been successful down to a one-time dose of 1.0 mg (0.44 x relative to 2.25 mg), with 0.5 mg and 0.25 mg to be examined, but efficacy bounds in a 2- or 3-drug regimen have not been set. A daily dose of 5 mg MK-8591 (2.22 x relative to 2.25 mg) will be examined in PN 009, with interim PK and safety results after 3 weeks of dosing being assessed prior

to the initiation of this trial. Thus, although the potential effect of MK-1439 on MK-8591 will only be estimated in this trial, approximate bounds of [0.5, 2.0] appear an adequate range.

The preliminary comparability bounds of [0.5, 2.0] for MK-1439 are based on the clinical experience from Phase 2b and Phase 3, and are defined relative to the mean steady state C24 (for the lower bound) and mean steady state AUC0-24 (for the upper bound) achieved at the 100 mg QD dose in HIV-1 infected subjects. The lower bound also corresponds to the median C24 value from the 50 mg QD dose, which was studied in the Phase 2b trial and had efficacy similar to 100 mg QD. The upper bound of 2.0 for MK-1439 steady state AUC0-24 is based on the median steady state AUC0-24 value achieved at the 200 mg QD dose, the highest dose examined in the Phase 2b trial. In the Phase 2b trial, there was no evidence of exposure or dose-related toxicities across the range of 25 mg to 200 mg doses evaluated.

If N=10 and the Type I error level of alpha=0.05, overall there is at least 91% probability that all three 90% CIs of the true GMR [(MK-8591 + MK-1439)/(MK-1439)] of AUC0-24, C24 and Cmax fall within the target interval [0.5, 2.0] simultaneously, assuming a nonnegative correlation among the three test statistics of AUC0-24, C24 and Cmax of MK-1439, and true GMRs of 1 for all three parameters. The above power calculations are based on assumed true within-subject standard deviations of 0.266, 0.410, and 0.198, respectively, for ln-AUC0-24, ln-C24, and ln-Cmax.

7.3.5 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.

7.3.6 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, HYPOTHESIS AND ENDPOINTS

8.1 Objectives, Hypothesis, and Estimation

8.1.1 Primary

Objective 1: To assess the effect of MK-8591 following multiple dose administration on the pharmacokinetics of plasma MK-1439 (e.g., AUC0-24, C24, Cavg, Cmax, Tmax, and apparent terminal t½).

Hypothesis: There is no clinically meaningful effect of MK-8591 on the AUC0-24, C24, and Cmax of plasma MK-1439. That is, the true geometric mean ratios [(MK-8591 + MK-1439)/(MK-1439)] for AUC0-24, C24, and Cmax of MK-1439 are contained within the preliminary bounds of [0.5, 2.0].

Objective 2: To assess the effect of steady-state levels of plasma MK-1439 on the pharmacokinetics of plasma MK-8591 following multiple dose administration (e.g., AUC0-24, C24, Cavg, Cmax, Tmax, and apparent terminal t½).

Estimation: The AUC0-24 and Cmax of plasma MK-8591 after multiple oral daily doses of MK-8591 coadministered with multiple doses of MK-1439 will be estimated and compared to the values observed after multiple dose administration of MK-8591 alone.

8.1.2 Secondary

Objective: To evaluate the safety and tolerability of multiple doses of MK-8591 alone, of multiple doses of MK-1439 alone, and of multiple doses of MK-8591 coadministered with multiple doses of MK-1439.

8.1.3 Planned Exploratory Biomarker

Objective: To explore the relationship between genetic variation and response to the treatments 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:

The primary plasma pharmacokinetic endpoints will include AUC0-24, C24, and Cmax for MK-1439, and AUC0-24 and Cmax for MK-8591.

The plasma pharmacokinetic Cavg, Tmax, and apparent terminal t½ for MK-1439 and MK-8591 will also be computed, as appropriate.

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 a double-blind, placebo-controlled, randomized, fixed-sequence, 2-period, DDI study.

Fourteen (14), healthy, adult, male and female subjects will be enrolled. Subjects will be randomized to receive either the active drugs (MK-8591 and MK-1439) or the placebo in 5:2 ratio.

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

On Day 1 of Period 1, subjects will be randomized to receive either the study drugs or placebo. Subjects will receive study drug/placebo in a fixed sequence (AB). Subjects who receive placebo in Period 1 will also receive placebo in Period 2.

On Days 1 through 5 of Period 1, an oral dose of 100 mg MK-1439 or placebo will be administered QD. Serial blood samples will be collected for the pharmacokinetic assessment of MK-1439 for 24 hours following MK-1439 dosing on Day 5. Trough blood samples will be collected at specified times.

On Days 1 through 19 of Period 2, an oral dose of 2.25 mg MK-8591 or placebo will be administered QD with an oral dose of 100 mg MK-1439 or placebo coadministered QD for 5 days on Days 15 through 19. Serial blood samples will be collected for the pharmacokinetic assessment of MK-8591 for 24 hours following MK-8591 dosing on Days 14 and 19 and will be collected for the pharmacokinetic assessment of MK-1439 for 24 hours following MK-1439 dosing on Day 19. Blood samples for pharmacokinetic assessments of MK-8591 and MK-1439 will continue through Day 33 of Period 2. Trough blood samples will be collected at specified times.

There will be no washout period between last dose in Period 1 and first dose in Period 2.

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

Subjects may be replaced at the discretion of the Sponsor, as outlined in Section 9.2.3.

9.1.1 Confinement, Return Visits, and Follow-up

In Period 1, subjects will be housed on Day -1 and on Day 4, at the time indicated by the CRU, until Day 1 (after first dose) and Day 6 (after MK-8591/placebo dosing and/or study procedures), respectively. Subjects will return for the subsequent study procedures as indicated in the Study Events Flow Chart (Section 6).

In Period 2, subjects will be housed on Day 13 and on Day 18, at the time indicated by the CRU, until Day 15 (after dosing and/or study procedures) and Day 20 (after the 24-hour blood draw), respectively. Subjects will return for the subsequent study procedures as indicated in the Study Events Flow Chart (Section 6).

A subject may be required to remain at the CRU for longer at the discretion of the Investigator.

All subjects (including subjects who terminate early) will return to the CRU 14 days after the last study drug administration for follow-up procedures and to determine if any adverse events have occurred since the last study visit.

9.1.2 Study Duration

The duration of the study from screening to Day 33 (includes the follow-up visit) of Period 2 is approximately 9.5 weeks.

9.2 Selection of Study Population

9.2.1 Inclusion Criteria

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

1. Subject is a healthy adult male or female (non-childbearing potential only) subject, 19-55 years of age, inclusive, at screening.

2. Subject has a body mass index (BMI) $\geq$ 19 and $\leq$ 32.0 kg/m^2, at screening.

3. Subject appears healthy with no clinically significant medical history or findings at screening physical examination, laboratory profile, vital signs, or ECG, as deemed by the Investigator.

4. Female subjects must be of non-childbearing potential and must have undergone one of the following sterilization procedures at least 6 months prior to the first dose and have official documentation:

   - hysteroscopic sterilization;
   - bilateral tubal ligation or bilateral salpingectomy;
   - hysterectomy;
   - bilateral oophorectomy;

   or be postmenopausal with amenorrhea for at least 1 year prior to the first dose and have follicle-stimulating hormone (FSH) serum levels consistent with postmenopausal status.

   Female subjects of non-childbearing potential who has undergone one of the sterilization procedures mentioned above, but could not provide official documentation, must be sexually inactive and remain inactive throughout the study, or must agree to use a physical (e.g., condom, diaphragm, or other) and a chemical (e.g., spermicide) barrier method from the time of screening and for at least 14 days following the last dose.

5. Non-vasectomized male subjects must agree to use a condom with spermicide or abstain from sexual intercourse from the first dose until 90 days after the last dose. No restrictions are required for vasectomized males provided their vasectomy has been performed 4 months or more prior to study start. Male subjects who have been vasectomized less than 4 months prior to study start must follow the same restrictions as a non-vasectomized male.

6. Male subjects must agree not to donate sperm from the first dose until 90 days after the last dose of study drug.

7. Subjects must be able to swallow multiple capsules/tablets.

8. Subject understands the study procedures in the informed consent forms (ICFs), be willing and able to comply with the protocol, and provides written informed consent for the trial, including for Future Biomedical Research. Future Biomedical Research will be conducted as a required part of the trial.

9.2.2 Exclusion Criteria

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 used nicotine-containing products within 3 months prior to dosing.

5. Subject has a history or presence of alcoholism or drug abuse within the past 2 years prior to the first dose.

6. Subject has a history or presence of hypersensitivity or idiosyncratic reaction to the study drugs or related compounds.

7. Subject has a history or presence of drug-induced rash.

8. Subject is a female subject of childbearing potential.

9. Subject is a female subject who is pregnant or lactating.

10. Subject has positive results for the urine drug and alcohol screen at screening or first check-in.

11. Subject has a positive urine cotinine at screening or first check-in.

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

13. Subject has a seated blood pressure less than 90/40 mmHg or greater than 140/90 mmHg at screening (subjects need to be in range for both systolic and diastolic measurements to be eligible.).

14. Subject has a seated heart rate lower than 40 bpm or higher than 99 bpm at screening.

15. Subject has a QTcF interval is >450 msec (males) or >470 msec (females) or the subject has ECG findings deemed abnormal with clinical significance by the principal investigator (PI) or designee at screening.

16. Subject has an estimated creatinine clearance < 90 mL/min based on the Cockcroft-Gault equation at the screening visit. An actual creatinine clearance, as determined by a 24-hour urine collection, may be used in place of, or in conjunction with, the Cockcroft-Gault equation; subjects who have an actual or estimated creatinine clearance up to 10% below 90 mL/min may be enrolled in the study at the discretion of the Investigator.

17. Subject is unable to refrain from or anticipates the use of:

    - Any drug, including prescription and non-prescription medications, herbal remedies, or vitamin supplements beginning 14 days prior to the first dose of study drug and throughout the study. Hormone replacement therapy will not be excluded.
    - Any drugs known to be significant inducers or inhibitors of CYP enzymes and/or P-gp, including St. John's wort, for 28 days prior to the first dose of study drug and throughout the study. Appropriate sources will be consulted by the Investigator or designee to confirm lack of pharmacokinetic/pharmacodynamic interaction with the study drug.

18. Subject has been on a diet incompatible with the on-study diet within 28 days prior to the first dose.

19. Subject donated blood or had significant blood loss within 56 days prior to the first dose.

20. Subject donated plasma within 7 days prior to the first dose.

21. 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 directly involved with this trial.

22. Subject has participated in another clinical trial within 28 days prior to the first dose. The 4-week window will be derived from the date of the last blood collection or dosing, whichever is later, in the previous study to Day 1 of Period 1 of the current study.

23. A subject is any concern by the investigator regarding the safe participation of the subject in the trial or for any other reason the investigator considers the subject inappropriate for participation in the trial.

9.2.3 Subject Withdrawal/Discontinuation Criteria

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

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

Subjects may be replaced at the discretion of the Sponsor. The replacement subject will generally receive the same treatment as the subject being replaced, in a manner that maintains blinding of individual subjects. The replacement subject will be assigned a unique treatment/randomization

number. The replacement subject should begin dosing from Period 1, Day 1, based on investigator and Sponsor review and decision.

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.
- Subject has positive results for the urine drug, urine cotinine and/or alcohol tests at check-in.
- 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.
- If the subject vomits within 8 hours after dosing on Day 5 of Period 1 or Day 14 or Day 19 of Period 2 i.e., a period of time equal to 2 times the median Tmax of MK-1439 and > 10 times the median Tmax of MK-8591 and there is no longer a valid comparison of interest, 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.
- The subject interrupts trial study drug administration for more than 1 dose of MK-1439 within Period 1 or 2, or more than 2 doses of MK-8591 during Period 2 on Days 1-13, or a dose of MK-8591during Period 2 on Day 14 or Day 19.

9.2.3.1 Withdrawal/Discontinuation

The Investigator or designee must notify the Sponsor when a subject has been discontinued/withdrawn from the study. If a subject discontinues for any reason at any time during the course of the study, the procedures scheduled at early termination (as outlined in Section 6) will be performed. Furthermore, the subject will be asked to return to the clinic or be contacted, if the Investigator deems necessary, for a follow-up (14 days after the last dose of study drug), to determine if any adverse events have occurred since the last visit. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 10.1.6.

9.2.3.1.1 Withdrawal from Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research. Subjects may withdraw consent at any time by contacting the Principal Investigator for the main trial. If medical records for the main trial are still available, the Investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the subject's consent for Future Biomedical Research will be withdrawn. A letter will be sent from the Sponsor to the Investigator confirming the withdrawal. It is the responsibility of the Investigator to inform the subject of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already

performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

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

9.3 Study Restrictions

9.3.1 Prohibitions and Concomitant Therapy

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

- Xanthines/Caffeine: 24 hours before the first dose in Period 1 until the last pharmacokinetic sample collection in Period 2. On Days 1-4 (Period 1), Days 6-13, Day 16, and Days 21-33 (Period 2), i.e., non-pharmacokinetic days, small amounts of caffeine derived from normal food products or beverages e.g., 250 mL/8 oz/1 cup decaffeinated coffee or other decaffeinated beverage, per day, with the exception of espresso; 45 g/1.5 oz chocolate bar, per day, would be allowed;
- Alcohol: 48 hours before the first dose in Period 1 until the last pharmacokinetic sample collection in Period 2;
- Grapefruit/Seville orange: 14 days before the first dose in Period 1 until the last pharmacokinetic sample collection in Period 2;
- Fruit Juice: 72 hours before the first dose in Period 1 until the last pharmacokinetic sample collection in Period 2;
- Vegetables from the mustard green family (e.g., kale, broccoli, watercress, collard greens, kohlrabi, Brussels sprouts, mustard), and charbroiled meats: 7 days before the first dose in Period 1 until the last pharmacokinetic sample collection in Period 2.

No subject may take drug (including over-the-counter products), herbal products or vitamin supplements for 14 days (or 5 half-lives) prior to the first dose and throughout the study. No subject may take drugs known to be significant inducers/inhibitors of CYP enzymes and/or P-gp, including St. John's wort, for 28 days prior to the first dose of study drug and throughout the study. Medications used to treat AEs that occur during the study may be allowed at the discretion of the PI, in consultation with the Sponsor, if the medication is not expected to interfere with study drug and affect study results.

During the study, acetaminophen (up to 2 g per 24 hours) may be administered at the discretion of the Investigator. Hormone replacement therapy will not be excluded.

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.

9.3.2 Meals

Water (except water provided with dosing) will be restricted 1 hour prior to and 1 hour after each 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 dosing on Day 5 of Period 1 and prior to dosing on Day 14 and Day 19 of Period 2. On these days, subjects will continue the fast for at least 4 hours postdose. On all other dosing days, subjects will be instructed to fast for at least 1 hour prior to dosing and will remain fasted for at least 2 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 also be provided at appropriate times. When confined in the CRU, subjects will fast from all food and drink except water between meals and snacks.

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

9.3.3 Activity

On Day 5 of Period 1 and Day 14 and Day 19 of Period 2, subjects will remain ambulatory or seated upright for the first 4 hours following study drug administration, except when they are supine or semi-reclined for study procedures.

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

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

9.4 Treatments

9.4.1 Treatments Administered

MK-8591 will be supplied as 0.25 mg and 1 mg capsules.

MK-1439 will be supplied as 100 mg tablets.

All study drugs will be administered orally with approximately 240 mL of water, according to the randomization scheme (subjects are randomized in Period 1 to either active or placebo).

Treatments A and B are described as follows:

Treatment A: (Period 1)	100 mg MK-1439 (1 x 100 mg tablet) or placebo administered QD at Hour 0 on Days 1 to 5.
Treatment B: (Period 2)	2.25 mg MK-8591 (2 x 1 mg capsules and 1 x 0.25 capsule) or placebo administered QD at Hour 0 on Days 1 to 19 with QD doses of 100 mg MK-1439 (1 x 100 mg tablet) or placebo coadministered at Hour 0 on Days 15 to 19.

The pharmacy at the CRU will provide each dose in individual unit dose containers for each subject and for each study period, as per the randomization scheme.

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

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 predose eligibility criteria will be assigned a unique randomization number (in the order they become eligible for the study) prior to the first dose on Day 1 of Period 1, different from the screening number, and will receive the corresponding product, according to a randomization scheme generated at Merck.

Subjects will be randomized on Day 1 to receive active treatments (MK-1439 and MK-8591) or placebo in a 5:2 ratio. Subjects who receive placebo in Period 1 will also receive placebo in Period 2. Subjects are considered enrolled when the randomization number is assigned.

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 a double-blind, placebo-controlled study.

9.4.3.1 Maintenance of Randomization

A computerized randomization scheme will be created by a Merck statistician and shall be considered blinded (per the following).

The randomization is available only to the clinic pharmacy staff preparing the drug that is not involved in any other aspect of the study including administration of the drug. It will not be made available to the Sponsor, bioanalytical laboratory, subjects, or members of the staff responsible for the monitoring and evaluation of safety assessments.

9.4.3.2 Procedures for Breaking the Blind Prior to Study Completion

One set of sealed envelopes containing the randomization code will be supplied to the Investigator or designee at the start of the study.

Breaking of the blind is expressly forbidden except in the event of a medical emergency where the identity of the drug must be known in order to properly treat the subject or in the event of an interim analysis.

In the event of a medical emergency, it is requested that the Investigator make every effort to contact the Study Monitor or designee prior to breaking the blind. If breaking the blind is required because of a medical emergency, the treatment identity would be revealed by the Investigator or designee, for that subject only. In the event that the emergency is one, in which it appears that the other subjects

may be at imminent risk, the blind may be broken for all subjects dosed. The unblinding should be noted in the study file.

In all cases where the code is broken, the Investigator should record the date and reason for code breaking.

At the end of the study, envelopes will be retained or destroyed according to site procedures unless specified otherwise by the Sponsor.

9.4.3.3 Revealing of Randomization

In the absence of a medical emergency, the blinded randomization for this study will not be revealed until all data are entered in the database, edits checks are performed, queries closed, CRFs signed by the PI, and the database is officially locked.

9.4.4 Treatment Compliance

A qualified designee will be responsible for monitoring dosing. 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.

The pharmacokinetic sampling scheme currently outlined in the protocol may be modified during the trial based on newly available pharmacokinetic data (e.g., to obtain data closer to the time of peak plasma concentrations). If indicated, these collected samples may also be assayed in an exploratory manner for metabolites.

Up to additional 50 mL of blood may be drawn for safety and/or pharmacokinetic analyses. The total blood volume withdrawn from any single subject will not exceed the maximum allowable volume during his/her participation in the entire trial (Section 10.5). The timing of procedures for assessment of safety procedures (e.g., vital signs, ECG, safety laboratory tests, etc.) currently outlined in the protocol may be modified during the trial based on newly available safety, tolerability, pharmacokinetic data (e.g., to obtain data closer to the time of peak plasma concentrations). Additional laboratory safety tests may be added to blood samples previously drawn to obtain additional safety information (e.g., adding creatinine kinase to serum chemistry panel that was already drawn). These changes will not increase the number of trial procedures for a given subject during his/her participation in the entire trial.

It is understood that the current trial may employ some or none of the alterations described above. Any alteration made to this protocol to meet the trial objectives must be detailed by the Sponsor in a memo to the Trial File and forwarded to the Investigator for retention. The memo may be forwarded to the Institutional Review Board (IRB) at the discretion of the Investigator.

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-1439 and MK-8591 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 the first dose, 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 10.1.5.

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 PI 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, 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 at check-in on Day -1 of Period 1. At all predose time points, if applicable, blood pressure and heart rate will be performed within 2 hours prior to dosing. When scheduled postdose, vital signs will be performed within 10 minutes of the scheduled time point for time points up to 1 hour postdose, and within 30 minutes of the scheduled time point for time points up to 24 hours postdose.

10.1.4 ECG Monitoring

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. All ECG tracings will be reviewed by the Study Physician or his/her designee. The ECGs will be classified as normal, abnormal but not clinically significant, or having a clinically significant abnormality. In addition, ECG parameter values of ventricular rate, PR interval, QRS duration, and QT interval (corrected and uncorrected) from the automated reading will be noted on the case report form (CRF).

All clinically significant findings will be recorded as AEs for subjects enrolled in the study.

ECGs will be measured at check-in on Period 1 Day -1 and at other time points indicated in the study flow chart. When scheduled postdose, ECGs will be performed within 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 Laboratory Tests

All tests listed below will be performed as per Study Events Flow Chart (Section 6). The following variance in laboratory safety tests will be allowed:

- 48 hours (for Day 33)

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 drug screen
  - Opiates
  - Amphetamines
  - Barbiturates
  - Benzodiazepines
  - Cocaine
  - Cannabinoids
  - MDMA
- Urine alcohol screen
- Serum pregnancy test (for females only)
- FSH (for postmenopausal females only)
- Urine cotinine

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

** At screening, creatinine clearance will be calculated using Cockcroft-Gault formula.

*** 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.

10.1.6 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 (including placebo or active comparator medication) 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 randomized subjects only, all adverse events that occur after the consent form is signed but before randomization 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, placebo treatment, or a procedure. From the time of randomization 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 10.1.6.3.1. The Investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

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).

10.1.6.1 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 and 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).

10.1.6.2 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 randomization 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, placebo treatment or a procedure. Pregnancies and lactations that occur from the time of randomization 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).

10.1.6.3 Immediate Reporting of Adverse Events

10.1.6.3.1 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 randomization, 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, placebo treatment or a procedure.

For the time period beginning at treatment randomization 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.

10.1.6.3.2 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 randomization, 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, placebo treatment or a procedure.

For the time period beginning at treatment randomization 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 10.1.6.1 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.

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

10.1.6.4 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:	
	None	
	†**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 event of clinical interest 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 †).	
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	

Relationship to Sponsor's Product	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.	
Relationship to Sponsor's Product (continued)	**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:	
	Exposure	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?
	Time Course	Did the adverse event follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the adverse event compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	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
	Dechallenge	Was the Sponsor's product discontinued or dose/exposure/frequency reduced? If yes, did the adverse event resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the adverse event resulted in death or permanent disability; (2) the adverse event resolved/improved despite continuation of the Sponsor's product; (3) the trial is a single-dose drug trial; or (4) Sponsor's product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the Sponsor's product in this trial? If yes, did the adverse event recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial adverse event resulted in death or permanent disability, or (2) the trial is a single-dose drug trial; or (3) Sponsor's product(s) is/are used only one time.) NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE U.S. CLINICAL MONITOR AND THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the adverse event consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an Investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		

Record one of the following:	Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).
Related (there is a reasonable possibility of Sponsor's product relationship)	There is evidence of exposure to the Sponsor's product. The temporal sequence of the adverse event onset relative to the administration of the Sponsor's product is reasonable. The adverse event is more likely explained by the Sponsor's product than by another cause.
Not Related (there is not a reasonable possibility of Sponsor's product relationship)	Subject did not receive the Sponsor's product OR temporal sequence of the adverse event onset relative to administration of the Sponsor's product is not reasonable OR there is another obvious cause of the adverse event. (Also entered for a subject with overdose without an associated adverse event.)

10.1.6.5 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 plasma MK-1439 and plasma MK-8591 will be collected at scheduled time points as delineated in the Study Events Flow Chart (Section 6).

The following time windows will be followed for blood sample collections:

PK collection	PK Collection Window
0.0-0.5 hour	≤ ± 2 minutes
>0.5-2.0 hour	≤ ± 2 minutes
>2.0-8.0 hour	≤ ± 2 minutes
>8.0-24.0 hour	≤ ± 5 minutes

Instructions for blood sampling, collection, processing, and sample shipment for MK-1439 and MK-8591 will be provided separately.

10.3 Planned Genetic Analysis Sample Collection.

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

10.4 Future Biomedical Research Samples

.The following samples will be collected for Future Biomedical Research:

- DNA for future research

10.5 Blood Volume Drawn for Study Assessments

Table 2: Blood Volume Drawn During the Study

Sample Type	Number of Time Points	Approximate Volume per Time Point * (mL)	Approximate Sample Volume Over Course of Study (mL)
Screening laboratory safety tests (including, hematology, serum chemistry, serology), FSH (for postmenopausal female subjects only) and serum pregnancy (for female subjects only).	1	12.5*	12.5
Serum pregnancy (for female subjects only)	1	4	4
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)	5	12.5*	62.5
Blood for MK-1439	31	4	124
Blood for MK-8591	27	4	108
		Total Blood Volume (mL)→	319.5§

* 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, additional blood may be obtained (up to a maximum of 50 mL).

11 DATA ANALYSIS

11.1 Pharmacokinetic Parameters

Values of the following pharmacokinetic parameters for plasma MK-1439 and MK-8591 will be calculated as follows:

AUC0-24	Area under the concentration versus time curve, from 0 to 24 hours after dosing.
C24	Maximum observed plasma concentration at 24 hours after the administration of a given dose.
Cavg	Average steady-state concentration of drug in plasma during a dosing interval.
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.

No value for apparent terminal t½ will be reported for cases that do not exhibit a terminal log-linear phase in the concentration versus time profile.

11.2 Statistical Methods

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Pharmacology Sciences 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 following power calculations for AUC0-24, C24, and Cmax of MK-1439 are based on assumed true within-subject standard deviations of 0.266, 0.410, and 0.198, respectively, for ln-AUC0-24, ln-C24, and ln-Cmax. The above within-subject log-scale variability estimates for AUC0-24, C24, and Cmax from administration of MK-1439 were derived from MK-1439-020. The following power calculations are based on 10 subjects with available pharmacokinetic data and Type I error level of alpha=0.05.

AUC0-24: Assuming a true AUC0-24 GMR [(MK-8591 + MK-1439)/(MK-1439)] of 1, there is at least 99% probability of obtaining a 90% confidence interval for the true GMR which lies completely

within the (0.5, 2.0) target interval. If the true GMR of AUC0-24 is within 0.69 to 1.45, there is at least 80% probability that the 90% confidence interval will fall within (0.5, 2.0).

C24: Assuming a true C24 GMR [(MK-8591 + MK-1439)/(MK-1439)] of 1, there is at least 93% probability of obtaining a 90% confidence interval for the true GMR which lies completely within the (0.5, 2.0) target interval. If the true GMR of C24 is within 0.82 to 1.22, there is at least 80% probability that the 90% confidence interval will fall within (0.5, 2.0).

Cmax: Assuming a true Cmax GMR [(MK-8591 + MK-1439)/(MK-1439)] of 1, there is at least 99% probability of obtaining a 90% confidence interval for the true GMR which lies completely within the (0.5, 2.0) target interval. If the true GMR of AUC0-24 is within 0.64 to 1.58, there is at least 80% probability that the 90% confidence interval will fall within (0.5, 2.0).

OVERALL: Assuming 10 subjects with available pharmacokinetic data, nonnegative correlation among the three test statistics, and true GMRs of 1 for all three parameters, there is at least 91% probability that all three 90% CIs will satisfy their corresponding target interval simultaneously.

11.2.2 Subjects to Analyze

The decision as to which plasma samples collected will be assayed for evaluation of pharmacokinetics 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.

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

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

Per-Protocol: The population will include the subset of subjects who complied with the protocol sufficiently to ensure that generated data will likely 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 Descriptive Statistics

Individual values will be listed for each plasma pharmacokinetic parameter by treatment, 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 coefficient of variation (CV) (calculated as 100 x standard deviation/arithmetic mean), median, minimum, maximum, geometric mean, and geometric percent CV (calculated as 100 x sqrt(exp(s^2) - 1), where s^2 is the observed variance on the natural log-scale).

11.2.4 Analysis of Variance, Ratios and Confidence Intervals

Individual AUC0-24, C24, and Cmax values of MK-1439 will be natural log-transformed prior to analysis and evaluated with a linear mixed-effects model with a fixed effect for treatment. An unstructured covariance matrix will be used to allow for unequal treatment variances and to model the correlation between the 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). Sample SAS code is given below:

```
proc mixed data=dataset;
class treatment subject;
model endpoint = treatment/ddfm=kr;
repeated treatment / subject=subject type=un;
run;
```

The hypothesis will be addressed by comparing AUC0-24, C24, and Cmax values of MK-1439 from administration of MK-1439 with MK-8591 to those obtained from administration of MK-1439 alone. A two-sided ninety percent (90%) confidence interval for the true mean difference [(MK-8591 + MK-1439) minus (MK-1439) alone] for each parameter on the log scale will be computed from the above linear-mixed effect model. The 90% confidence interval will then be exponentiated to obtain the 90% confidence intervals for the true geometric mean ratio (GMR) [(MK-8591 + MK-1439)/ (MK-1439)] for AUC0-24, C24, and Cmax. If the 90% confidence intervals of the true GMR [(MK-8591 + MK-1439)/ (MK-1439)] for AUC0-24, C24, and Cmax of MK-1439 falls within the pre-specified target interval (0.5, 2.0), then the hypothesis that there is no clinically meaningful effect of MK-8591 on the AUC0-24, C24, and Cmax of MK-1439 will be supported. Plots with the individual subject treatment ratios, GMR and 90% confidence interval will be provided for AUC0-24, C24, and Cmax.

This analysis will also be conducted for AUC0-24 and Cmax of MK-8591 to assess the effect of MK-1439 on the plasma pharmacokinetic parameters of MK-8591.

11.2.5 Steady State Analysis

Plasma C24 of MK-8591 and MK-1439 will be plotted over time as appropriate to visually assess the attainment of steady state.

11.2.6 Multiplicity

No multiplicity adjustment will be performed since AUC0-24, C24, and Cmax of MK-1439 will be analyzed separately and each 90% confidence interval of GMR must be contained within their pre-specified bounds.

11.3 Safety Evaluation

The safety and tolerability of MK-8591 and MK-1439 administered alone, and in combination will be evaluated by clinical assessment of adverse events and other safety measurements.

The placebo subjects will be pooled into a single placebo group for all summaries and presentations. Safety analyses will be based on treatment actually received by the subject.

Summary statistics for the laboratory safety tests, ECGs, and/or vital signs may be computed and provided, as deemed clinically appropriate.

12 STUDY ADMINISTRATION

12.1 Ethics

12.1.1 Institutional Review Board

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

PPD

12.1.2 Ethical Conduct of the Study

This research will be carried out in accordance with the protocol, US Code of Federal Regulations, 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 signed 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 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 the study formulations (including placebos) 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-8591 or MK-1439 drugs or placebos 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.

12.7 Data Handling and Record Keeping

Celerion's Merck library CRFs will be supplied.

12.8 Report Format

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

12.9 Compliance with Law, Audit, and Debarment

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

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

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

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

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

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

The Investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation

includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, Investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. By signing this protocol, the Investigator agrees that documentation shall be retained until at least 2 years after the last approval of a marketing application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Because the clinical development and marketing application process is variable, it is anticipated that the retention period can be up to 15 years or longer after protocol database lock. The Sponsor will determine the minimum retention period and notify the Investigator when documents may be destroyed. The Sponsor 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 Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf.

2 Feng M, Wang D, Grobler JA, Hazuda DJ, Miller MD, Lai MT. *In Vitro* Resistance Selection with Doravirine (MK-1439), A Novel Nonnucleoside Reverse Transcriptase Inhibitor With Distinct Mutation Development Pathways. Antimicrob Agents Chemother. 2015; 59(1):590-8.

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 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 electronic Case Report Forms (CRFs). Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen(s)

Collection of specimens for Future Biomedical Research will be performed as outlined in the trial flow chart. In general, if additional blood specimens are being collected for Future Biomedical Research, these will usually be obtained at a time when the subject is having blood drawn for other trial purposes.

4. Confidential Subject Information for Future Biomedical Research

In order to optimize the research that can be conducted with Future Biomedical Research specimens, it is critical to link subject' clinical information with future test results. In fact little or no research can be conducted without connecting the clinical trial data to the specimen. The clinical data allow specific analyses to be conducted. Knowing subject characteristics like gender, age, medical history and treatment outcomes are critical to understanding clinical context of analytical results.

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

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

5. Biorepository Specimen Usage

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

6. Withdrawal From Future Biomedical Research

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

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

7. Retention of Specimens

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

Specimens from the trial site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not utilized in a particular trial, the trial site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

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

9. Reporting of Future Biomedical Research Data to Subjects

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

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

10. Future Biomedical Research Study Population

Every effort will be made to recruit all subjects diagnosed and treated on Sponsor clinical trials for Future Biomedical Research.

11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the subject have been minimized.

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

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

12. Questions

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

13. References

1. National Cancer Institute: http://www.cancer.gov/dictionary/?searchTxt=biomarker
2. International Conference on Harmonization: DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES - E15; http://www.ich.org/LOB/media/MEDIA3383.pdf
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/