Official Protocol Title:	A Single-Dose Clinical Trial to Study the Safety, Tolerability, Pharmacokinetics, and Anti-Retroviral Activity of MK-8583 Monotherapy in Anti-Retroviral Therapy (ART)-Naïve, HIV-1 Infected Patients
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Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
(hereafter referred to as the Sponsor or MSD)

One Merck Drive
P.O. Box 100
Whitehouse Station, New Jersey, 08889-0100, U.S.A.

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

TITLE:

A Single-Dose Clinical Trial to Study the Safety, Tolerability, Pharmacokinetics, and Anti-Retroviral Activity of MK-8583 Monotherapy in Anti-Retroviral Therapy (ART)-Naïve, HIV-1 Infected Patients

EudraCT NUMBER: 2017-004017-92

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1.0 TRIAL SUMMARY

Abbreviated Title	MK-8583 Single Dose Study in HIV-1 Infected Patients
Sponsor Product Identifiers	MK-8583
Trial Phase	Phase Ib
Clinical Indication	Treatment of HIV-1 Infection
Trial Type	Interventional
Type of control	Historical placebo control
Route of administration	Oral
Trial Blinding	Unblinded Open-label
Treatment Groups	Up to three panels (Panel A, B, and C) of 6 subjects each will receive a single dose of MK-8583.
Number of trial subjects	Approximately 18 subjects will be enrolled.
Estimated duration of trial	The Sponsor estimates that the trial will require approximately 7 months from the time the first subject signs the informed consent until the last subject's last study-related phone call or visit.
Duration of Participation	Each subject will participate in the trial for approximately 8 weeks from the time the subject signs the Informed Consent Form (ICF) through the final contact. After a screening phase of approximately 4 weeks, each subject will be receiving assigned treatment for 1 day. After the end of treatment each subject will be followed for approximately 28 days. Subjects choosing to forgo follow-on combination anti-retroviral therapy (ART) may also be asked if they wish to continue to participate in observational monitoring beyond 28 days.

A list of abbreviations used in this document can be found in Section 12.5.

2.0 TRIAL DESIGN

2.1 Trial Design

This is an open-label, single-dose, multiple panel trial to evaluate the safety, tolerability, pharmacokinetics (PK), and anti-retroviral therapy (ART) activity of MK-8583 monotherapy in ART-naïve, Human Immunodeficiency Virus type 1 (HIV-1) infected subjects. The primary study endpoints are the safety and tolerability of MK-8583 and the change in plasma HIV-1 RNA (log10 copies/mL) compared with historical placebo data. This study will be conducted in conformance with Good Clinical Practices.

Up to three panels of 6 subjects each will be enrolled in a sequential manner. All doses of study drug will be administered following at least an 8-hour fast. In each panel, subjects will receive a single dose of MK-8583. Safety procedures and biological specimen collections will occur at designated time points. Subjects in Panel A will receive a single oral dose of MK-8583 100 mg. The exact dose administered in Panels B and C will be selected following review of all available safety, PK and viral dynamic data from prior panel(s); the dose will not exceed 150 mg. There will be an interval of time between dosing of panels to allow for

review of safety, PK, and viral dynamic data to inform dose selection in the following panel. It is estimated that this review will take approximately 30-40 days.

Initiation of ART: At a designated time following administration of study drug, subjects will be encouraged to initiate an ART regimen. The exact timing and regimen will be decided by the subject in consultation with his/her physician, but ART initiation will not occur before Day 10 post-dose (see Section 5.5). Once initiated, the duration of suppressive ART is recommended to be at least ~25 days, or approximately 5 half-lives of tenofovir diphosphate (TFV-DP) in peripheral blood mononuclear cells (PBMCs). To lessen the chance of HIV resistance mutations, the Sponsor recommends that ART initiation occurs on or before Day 14 post-dose. The Sponsor will not provide this therapy.

The initiation of follow-on ART is not a requirement for participation in the study. All subjects will be followed for safety monitoring for a maximum of approximately 28 days after dosing of MK-8583. If subjects start ART as planned, on Day 10 through 14 after dosing, the final blood draw for viral load (VL), viral resistance, or PK will occur on the day of ART initiation (prior to receiving the first dose of ART).

If subjects do not initiate ART, the Investigator may ask to continue regular blood draws for PK assessments, VL changes, and viral resistance for up to ~28 days post-dose. Subjects choosing to forgo follow-on ART may also be asked if they wish to continue to participate in observational monitoring of VL and viral resistance beyond 28 days. The timing of these blood draws beyond Day 28 will first be discussed with the Sponsor.

If subjects initiate an ART regimen that does not include tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide fumarate (TAF), the Investigator may ask to continue regular blood draws for PK assessments for up to ~28 days post-dose. The timing of these blood draws beyond Day 28 will first be discussed with the Sponsor.

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart - Section 6.0. Details of each procedure are provided in Section 7.0 – Trial Procedures.

Because this is a Phase I assessment of MK-8583 in humans, the pharmacokinetic, pharmacodynamic and safety profiles of the compound are still being elucidated. This protocol is therefore written with some flexibility to accommodate the inherent dynamic nature of Phase I clinical trials. Please refer to Section 7.1.5 – Visit Requirements for examples of modifications permitted within the protocol parameters.

2.2 Trial Diagram

The trial design is depicted in Figure 1 and Table 1.

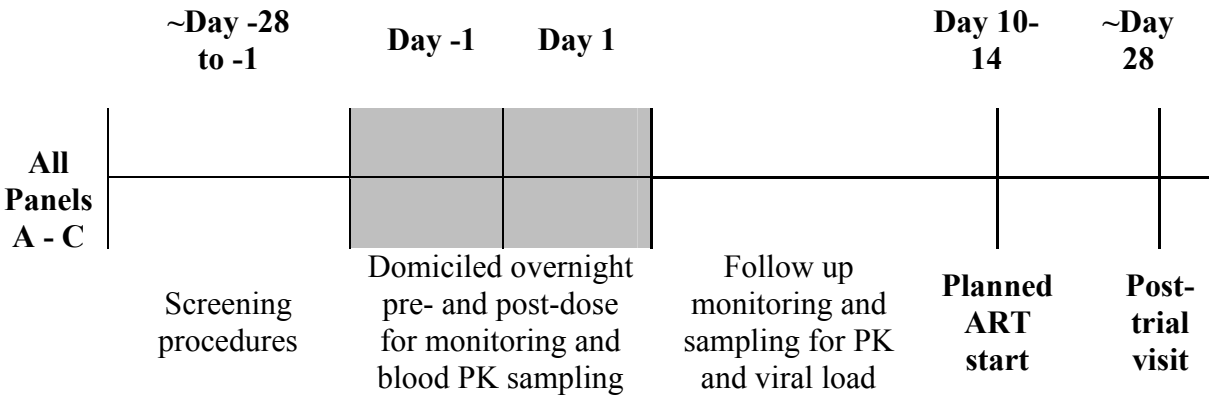

Figure 1 Trial Design Diagram

Table 1 Dose Plan

Panel[a]	Dose[b]
Panel A	100 mg
Panel B	≤ 150 mg
Panel C[c]	≤ 150 mg

[a] In each panel, 6 subjects will receive a single dose of MK-8583.

[b] The dose administered in Panels B and C will be determined following review of safety, PK, and viral load data from the previous panel(s) and will not exceed 150 mg. At least approximately 30-40 days will separate the administration of doses between panels to allow time for review of the previous panel safety, PK and viral load data.

[c] A decision to enroll Panel C will be made upon completion of the previous panels and review of safety, PK, and viral load data.

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

1) **Objective**: To evaluate the anti-retroviral activity of MK-8583 in HIV-1 infected subjects relative to historical subjects receiving placebo.

   Hypothesis: At a dose that is sufficiently safe and generally well tolerated, MK-8583 has superior anti-retroviral activity compared to placebo, as measured by change from baseline in plasma HIV-1 RNA (log10 copies/mL) at 168 hours post-dose. That is, the true mean difference in the plasma HIV -1 RNA reduction from baseline between MK-8583 and placebo is at least 0.5 log10 copies/mL.

2) **Objective:** To evaluate the safety and tolerability of MK-8583 in HIV-1 infected subjects.

3.2 Secondary Objective(s) & Hypothesis(es)

1) **Objective:** To evaluate the intracellular PK profile of TFV-DP and to determine PK parameter values (including AUC0-168hr, Tmax, Cmax, C168hr, and apparent terminal t1/2) in PBMCs after administration of single oral doses of MK-8583 to HIV-1 infected subjects.

   Hypothesis: The true geometric mean (GM) TFV-DP PBMC C168hr is ≥ 0.1 μM for at least one dose level that also exhibits an acceptable safety and tolerability profile.

2) **Objective:** To characterize the single dose plasma PK profile of MK-8583 and to determine the PK parameter values (including AUC0-last, AUC0-inf, Tmax, Cmax, apparent terminal t1/2, CL/F and Vz/F) after administration of MK-8583 to HIV-1 infected subjects.

3) **Objective**: To obtain the single dose plasma PK profile of TFV and to determine the PK parameter values (including AUC0-last, AUC0-inf, Tmax, Cmax, and apparent terminal t1/2) after administration of MK-8583 to HIV-1 infected subjects.

4) **Objective**: To evaluate the PK-PD association of TFV-DP with viral load reduction.

3.3 Exploratory Objectives

1) **Objective:** To evaluate the relationship between dose and anti-retroviral activity of MK-8583.

2) **Objective:** To quantify PBMC levels of tenofovir monophosphate (TFV-MP).

3) **Objective:** To explore the relationship between genetic variation and response to the treatment(s) administered and mechanisms of disease. Variation across the human genome may be analyzed for association with clinical data collected in this study.

4.0 BACKGROUND & RATIONALE

4.1 Background

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on MK-8583.

4.1.1 Pharmaceutical and Therapeutic Background

As treatment for HIV-1 has improved, HIV-1 infection has shifted from being an acute disease to being a chronic, manageable condition. There is now a clear medical need for new treatment regimens and dosing strategies that are both highly effective and very well tolerated. In particular, increased tolerability and ease of administration are expected to improve long-term adherence. A highly-potent nucleoside reverse transcriptase inhibitor (NRTI) with superior tolerability and ease of administration would be a valuable addition to the HIV-1 armamentarium.

MK-8583 is a novel, potent tenofovir prodrug (TFV PD) that belongs to the class of HIV-1 NRTIs. Marketed NRTIs include lamivudine, emtricitabine, abacavir, didanosine, stavudine, and zidovudine, as well as 2 TFV PDs, TDF and TAF.

TFV PDs have an acyclic nucleoside phosphonate on an adenine base. The phosphorylated moiety, TFV-DP competes with the natural substrate, deoxyadenosine, for incorporation by reverse transcriptase into newly synthesized cDNA strands. Once incorporated, TFV-DP terminates strand elongation, inhibiting viral replication.

TDF (VIREAD®) is a TFV PD, currently marketed by Gilead Sciences, Inc., that has been available since 2001. Following absorption, TDF is rapidly converted to TFV, which is then taken up by cells and converted intracellularly to the active anabolite, TFV-DP. After over 15 years in clinical use, TDF has been associated with small but significant decreases in kidney function (mean decrease in eGFR of 3.9 mL/ min, 95% confidence interval 2.1 - 5.7) [1] [2]and mild decreases in bone marrow density (BMD) [3], (approximate 2% loss in BMD in the spine and hip) in chronically treated patients. These effects are directly associated with high levels of TFV in circulation. TAF (VEMLIDY®), a more recently approved TFV PD, exhibits greater stability than TDF and is more efficiently taken up by target cells (i.e. PBMCs) thereby rendering lower levels of TFV in systemic circulation and lower levels of TFV available to cause toxicity to non-target cells (i.e. renal tubule cells and bone). The lower concentration of circulating TFV is believed to contribute to TAF's improved safety profile compared to TDF, although both compounds display similar efficacy in longer term clinical studies when administered as part of a complete treatment regimen.

Currently recommended first-line treatment of HIV infection in naïve patients calls for 3 agents and generally includes 2 NRTI agents in combination with either an integrase strand transfer inhibitor, a protease inhibitor, or a non-nucleoside reverse transcriptase inhibitor. While the currently approved NRTIs represent a cornerstone of modern ART, 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, highly potent NRTIs, like MK-8583, with improved safety and tolerability. Furthermore, reducing the frequency that patients need to take anti-retroviral therapy from daily to weekly would remove a significant barrier to adherence and thereby improve health outcomes.

4.1.2 MK-8583

MK-8583 is a TFV PD that inhibits HIV-1 reverse transcriptase (RT). In vitro, MK-8583 demonstrated potent inhibition of HIV-1 R8 virus in PBMCs. TFV PDs are taken up by target cells and converted into TFV, which is then phosphorylated to the active antiviral TFV-DP. Extracellular TFV is also generated through prodrug metabolism and leakage out of target cells and must be renally cleared. Plasma TFV levels correlate with renal accumulation and toxicity. Therefore, prodrugs that are transported into leukocytes and converted to TFV-DP more readily will generate less plasma TFV and will have lower toxicity potential. In vitro, MK-8583 generates approximately 3-fold higher concentrations of intracellular TFV-DP than TAF. The more efficient conversion of MK-8583 into the active

metabolite leads to lower circulating levels of TFV, the metabolite responsible for toxicity, and therefore MK-8583 is expected to have a more favorable safety profile than TAF.

MK-8583 was evaluated in genetic toxicity assays, safety pharmacology models, and in repeat dose oral toxicity and toxicokinetic studies of up to 3 months in duration in rats and dogs. In both species, TFV was the major metabolite in plasma and excreta, which is consistent with in vitro studies that indicate hydrolysis to TFV is the primary elimination pathway of MK-8583.

MK-8583 is not expected to be a victim of CYP-mediated drug interactions. MK-8583 is a substrate of human P-gp and could be a victim of P-gp-mediated drug interactions. TFV is eliminated by renal excretion and is a substrate of OAT1, OAT3 and MRP4 in vitro. Therefore, TFV may be affected by drugs that reduce renal transport. In vitro, MK-8583 is an inhibitor of CYP3A, OATP1B1, and OATP1B3, and therefore MK-8583 has the potential to perpetrate drug interactions on substrates of these enzymes.

In preclinical safety studies, the primary toxicological effects of MK-8583 were noted in the gastrointestinal tract and in the kidneys. These changes were similar to those reported for other TFV PDs (TDF and TAF) at similar systemic exposures of the TFV metabolite. Based on the consistency of preclinical findings with MK-8583, TDF, and TAF, no specific preclinical findings were attributed to the novel prodrug, MK-8583.

MK-8583 was assessed in a single rising-dose study in healthy subjects. Following oral administration, MK-8583 was rapidly absorbed (time to maximum plasma concentration [Tmax] ~ 0.5 hour) and rapidly eliminated from the plasma (terminal half-life [t1/2] of 0.2 to 0.4 hours). Prodrug exposure was dose-proportional at doses ≥ 40 mg. Plasma TFV exposure was also dose-proportional, with a Tmax of 1 to 4 hours and a t1/2 in the range of 19 to 30 hours. TFV-DP in PBMCs exhibited a median Tmax of 4 to 24 hr and a terminal t1/2 ranging from 65 to 136 hours. The PBMC TFV-DP AUC increased approximately dose-proportionally, and the Cmax increased somewhat more than dose-proportionally. Food somewhat lowered peak and extent of exposure of PBMC TFV-DP (GM fed/fasted ratio of 0.83 for AUC0-inf, 0.32 for maximum concentration [Cmax], 0.47 for C168hr). Elimination of plasma MK-8583 was monophasic, while elimination of plasma TFV was biphasic. PBMC TFV-DP presented monophasic elimination, but showed signs of biphasic elimination at higher doses.

Single oral doses of MK-8583 up to 150 mg were generally well tolerated. No SAEs, events of clinical interest (ECIs), or deaths were reported. A total of 24 subjects enrolled in the trial. No trends were observed between AE incidence and increasing dose levels, and there were no AE findings consistent with renal or bone toxicity. No clinically meaningful trends were observed for changes in clinical laboratory values, vital signs (VS), or ECGs as a function of dose or treatment.

Please refer to the Investigator's Brochure (IB) for more detailed information on MK-8583.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

MK-8583 has a promising preclinical and clinical profile and has potential to be an effective long acting TFV PD. This study is being conducted to assess the short-term anti-retroviral activity of MK-8583 monotherapy. Proof-of-concept trials demonstrate that agents that robustly suppress the VL as short-term monotherapy can be expected to deliver long-term efficacy as combination therapy [4]. This study's design and objectives conform to the EMA Guideline describing appropriate clinical development for anti-retroviral agents as monotherapy [5]. As described in this Guideline, the purpose of a monotherapy study is to characterize the relationship between dose, plasma concentration, and the short-term in vivo anti-retroviral activity.

Infected subjects who are therapy naïve will be enrolled in this study in order to decrease the presence of TFV resistant mutations. Prior to enrollment, subjects will be screened for the presence of common NRTI resistance mutations (International AIDS Society - USA (IASUSA) [6] to set a baseline standard for MK-8583-sensitivity to the viral variants present in each subject. Subjects identified with common mutations known to affect susceptibility to TFV (e.g., K65R, K70E, M184V/I, or combinations of three or more thymidine analog mutations (TAMs) including M41L, L210W, T215Y, D67N, K70R, K219Q/E/N) will be excluded from the study. Should unanticipated non-responders or viral breakthrough be observed despite this pre-screening process, a portion of the screening blood sample will be archived for phenotyping and/or genotyping of any previously unidentified clinically meaningful resistance variants.

4.2.2 Rationale for Dose Selection/Regimen/Modification

As this is a Phase I assessment of MK-8583 in humans, and the PK, PD and safety profiles of the compound are still being evaluated, modifications to the dose or dosing regimen may be required to achieve the scientific goals of the trial objectives and/or to ensure appropriate safety monitoring of the trial subjects. Details of allowed modifications are provided in Section 7.1.5.5 - Trial Design/Dosing/Procedures Modifications Permitted within Protocol Parameters.

The doses tested in this study will evaluate the effectiveness of MK-8583 in suppressing viral replication and will allow for assessment of potential differentiation in tolerability and efficacy. The study is specifically designed with an emphasis on collecting single dose viral dynamic data. Since only a single dose of MK-8583 will be administered to each subject, risk of resistant strain emergence is minimal.

Doses selected for this study are projected to fall within the expected clinical dose range. A dose that achieves a TFV-DP C168h in PBMCs of 100 nM is projected to be efficacious. This is approximately the Day 7 PBMC Ctrough achieved with daily dosing of TDF 300 mg (the therapeutic dose) for one week, which results in a 0.5 log10 reduction in VL [4]. In the single-rising dose study of MK-8583 in healthy subjects, a PBMC TFV-DP C168h target of 100 nM was achieved at doses ≥ 40 mg of MK-8583.

To maximize the chances of efficacy and minimize the impact of inter-subject PK variability, a 100 mg dose of MK-8583 will be administered to subjects in Panel A. This dose is expected to achieve PBMC TFV-DP concentrations well above that of the projected minimum effective dose of 40 mg (see above) while maintaining a plasma concentration of the TFV metabolite (the relevant correlate of toxicity) at ≤ ½ the exposure seen at the preclinical no-observed-adverse-effect level (NOAEL).

There will be a break between dosing of panels to allow for review of all available safety, PK, and viral dynamic data to inform dose selection in the following panel. It is estimated that this review will take approximately 30-40 days. Because plasma MK-8583, plasma TFV, and PBMC TFV-DP PK data from healthy subjects are expected to be similar to that of HIV-1 infected subjects, PK data from single doses administered to healthy subjects in Protocol 001 will also be used to aid in the selection of doses for the present study to ensure that plasma MK-8583 levels do not exceed the exposure cap.

The specific dose selected for Panel B will depend on data from Panel A. Assuming PK data indicate that higher exposures maintain safety margins, a higher dose may be tested to see if it delivers greater efficacy. Alternatively, if 100 mg generates exposures in HIV-infected subjects that are higher than what was seen in healthy subjects, or if safety concerns arise, a lower dose may be tested. After Panel B, the Sponsor will assess the utility of testing a third dose in Panel C to further explore PK, PD, and the safety profile of the compound.

Additionally, safety data through at least 168 hours post-dose, including AEs, standard laboratory safety tests, VS, and 12-lead ECGs, physical examinations (PEs) will be reviewed by the Sponsor and the investigator prior to dose escalation, and the decision to proceed to a new dose level will be based upon acceptable safety of MK-8583 at the previous dose. The doses selected for Panels B and C in this study will not exceed the maximum dose of 150 mg previously administered to healthy subjects.

The reduction in VL for each dose level will be compared to historical placebo data from clinical trials previously conducted by the Sponsor. Given the overall favorable safety profile of MK-8583 in preclinical and clinical testing to date, a placebo control to minimize investigator and subject bias with respect to adverse experiences is not deemed necessary.

4.2.2.1 Starting Dose for This Trial

The proposed starting dose in Panel A is 100 mg as noted above. Prior clinical evaluation up to 150 mg demonstrated that MK-8583 was generally well tolerated.

The toxicity studies (summarized below) indicated that the no-observed-adverse-effect level (NOAEL) in the more sensitive preclinical species was 3 mg/kg/day in the dog. Previous studies indicate TFV PDs exhibit generally similar PK in healthy subjects and HIV-infected subjects [7]**.** Assuming the same correlation holds for MK-8583, a dose of 100 mg is expected to yield an AUC0-inf (approximately equivalent to AUC0-168hr) for plasma TFV and plasma MK-8583 of 2,380 nM*hr and 430 nM*hr, respectively. The dog NOAEL yielded an AUC0-168hr (calculated by multiplying the AUC0-24hr x 7 days) for TFV and MK-8583 of 17,850 nM*hr and 620 nM*hr, respectively. Therefore, relative to the predicted exposures at 100 mg, the safety data provide a 7.5-fold (for TFV) and 1.4-fold (for MK-8583) safety margin (see Table 2).

Table 2 Exposure predictions for the starting dose of 100 mg

	Preclinical NOAEL AUC0-168hr (nM*hr) [a]	Clinical Dose	Clinical AUC0-inf (nM*hr)	Exposure Multiple
Plasma TFV	17,850	100 mg	2,380 [b]	7.5
		150 mg	3,840 [c]	4.7
Plasma MK-8583	620	100 mg	430 [b]	1.4
		150 mg	684 [c]	0.9

[a] AUC0-168hr (AUC0-24 x 7 days) observed at the dog NOAEL (3 mg/kg/day)
[b] AUC0-inf interpolated from Protocol 001, assuming dose-proportionality
[c] AUC0-inf calculated from Protocol 001, predicted to be similar to AUC0-168hr

4.2.2.2 Maximum Dose/Exposure for This Trial

The maximum allowable clinical exposure for this study is defined by the safety findings from 3-month Good Laboratory Practice (GLP) oral toxicity studies in rat and canine models.

In rats, the 3-month oral toxicity study identified no test article related toxicology findings at the highest dose tested, 150 mg/kg/day, and this was set as the rodent no-observed-adverse-effect level (NOAEL).

Dogs were administered MK-8583 at 3, 10, and 30 mg/kg/day in 3-month oral toxicity studies. All animals in the 30 mg/kg/day dose group were terminated early in Study Week 7 or 8 due to severe body weight losses, associated with decreased food consumption, decreased activity, and decreased heart rate. Increased incidences of emesis and salivation, and hematological and serum biochemical changes were also observed, including laboratory and histomorphologic indicators of significant kidney toxicity. In the 10 mg/kg/day dose group, observed test article-related clinical pathology findings included mild increases in creatinine associated with histomorphologic changes in the kidneys and slight increases in aspartate aminotransferase (AST) and alkaline phosphatase. The increases in AST and alkaline phosphatase were not associated with histomorphologic changes and were therefore not toxicologically significant. The maximum tolerated dose for the dog was therefore set at 10 mg/kg/day.

Test article-related postmortem changes were observed in the stomachs of dogs receiving the 3 mg/kg/day dose. Specifically, these were large vacuolated cells in the gastric mucosal pyloric mucosa. Although these changes were of unknown toxicological significance, the NOAEL for the dog was set at 3 mg/kg/day.

There are significant differences in the protein binding of MK-8583 in rat (71-82%, depending on concentration) vs. human and dog (93% and 95%, respectively), whereas TFV protein binding is minimal across all species. For these reasons, exposure to total TFV and exposure to unbound MK-8583 were used to select the more sensitive species for the NOAEL exposure margins.

The AUC0-168hr was selected as the relevant exposure parameter, instead of Cmax, because the preclinical toxicity of MK-8583 was associated with chronic dosing and was similar to clinical toxicity observed with chronic dosing of marketed TFV prodrugs. (The mean TFV Cmax at the preclinical NOAEL and at the maximum clinical dose of 150 mg were 102 nM and 175 nM, respectively. The mean MK-8583 Cmax at the preclinical NOAEL and at the maximum clinical dose of 150 mg were 168 nM and 1,074 nM, respectively.)

TFV Exposure Multiple: Comparing the TFV AUC0-168hr at the dog NOAEL (17,850 nM*hr at 3 mg/kg/day) to that of the rat (446,000 nM*hr at 150 mg/kg/day), the dog represents the more sensitive species. Therefore, the maximum allowable exposure is based on the TFV AUC0-168hr at the NOAEL of the dog, in this case 17,850 nM*hr. In healthy subjects, the maximum dose of 150 mg yielded a TFV AUC0-inf (approximately equal to the AUC0-168hr) of 3836 nM*hr; the preclinical safety data provide a 4.7-fold exposure margin (EM) (see Table 2).

MK-8583 Exposure Multiple: Whereas the plasma protein binding of TFV is minimal across all species, there are significant inter-species differences in the protein binding of MK-8583 (~70-80% in rat, ~93-95% in human and dog). The total MK-8583 AUC0-168hr at the dog NOAEL (620 nM*hr at 3 mg/kg/day) and at the rat NOAEL (540 nM*hr at 150 mg/kg/day) are similar. But comparing the unbound MK-8583 AUC0-168hr at the dog NOAEL (29.8 nM*hr at 3 mg/kg/day) to that of the rat (96.6 nM*hr) identifies the dog as the more sensitive species. In healthy subjects, the maximum dose of 150 mg yielded an MK-8583 AUC0-inf (approximately equal to the AUC0-168hr) of 684 nM*hr, which is 0.9-fold that of the MK-8583 AUC at the dog NOAEL (620 nM*hr, see Table 2).

All changes observed in the toxicology studies were similar to those reported for other TFV prodrugs (TDF and TAF) at similar systemic exposures of the TFV metabolite [8] and [9]. Based on the consistency of preclinical findings with MK-8583, TDF, and TAF, no specific preclinical findings were attributed to the novel prodrug, MK-8583. Therefore, although the MK-8583 prodrug exposure at 150 mg slightly exceeds that at the preclinical NOAEL, the 150 mg dose is an appropriate maximum for this single-dose trial because the observed preclinical toxicity is attributable to TFV, not to the MK-8583 prodrug, and because 150 mg was generally well-tolerated by healthy subjects in Protocol 001.

While plasma MK-8583, plasma TFV, and PBMC TFV-DP PK data from healthy subjects are expected to be similar to that of HIV-1 infected subjects, the PK and safety data from each panel in this study will also be reviewed and compared with data from Protocol 001 prior to dose selection for the next panel.

4.2.2.3 Rationale for Dose Interval

MK-8583, a prodrug of tenofovir, which inhibits HIV-1 reverse transcriptase, is not considered a compound with a high degree of uncertainty related to the potential risk of harm to participants, according to the publication "Guideline on Strategies to Identify and Mitigate Risks for First-in-Human and Early Clinical Trials with Investigational Medicinal Products" (European Medicine Agency [EMA] guidance released July 2017). The degree of uncertainty was determined by careful evaluation of the following: mode of action of MK-8583, presence or absence of biomarkers, the nature of the target, the relevance of available animal models and/or findings in non-clinical safety studies, single dose safety/PK data in

healthy volunteers, and the study population. Furthermore, it acts via a well-established mechanism (inhibition of HIV-1 reverse transcriptase), for which multiple marketed agents act similarly (TDF, TAF, and others). Safety assessment toxicity studies, ancillary pharmacology studies, and the first in human data with MK-8583 provide no contraindications to the initiation of clinical studies in subjects with this compound via the oral route. No dose-limiting toxicities were observed in 3-month rat and dog toxicity studies.

The trial design includes three sequential panels of 6 subjects each. For each panel in each period, subjects that receive MK-8583 on the same day will be spaced apart by time intervals according to Phase I Clinical Research standards for compounds not considered to be of high risk. There will be a break of at least approximately 30 to 40 days between dosing of MK-8583 in consecutive panels to allow for review of safety data and potential AEs as well as PK and viral dynamic data to inform dose selection. There will also be frequent, careful assessments of adverse events throughout the post-dose period. This recommendation is in keeping with the projected safety profile and the ability of the Phase I unit to monitor each subject closely.

4.2.3 Rationale for Endpoints

4.2.3.1 Safety Endpoints

The safety and tolerability of MK-8583 will be monitored by standard clinical assessments, which will adequately assess for preclinical safety findings in the rodent and canine models.

4.2.3.2 Pharmacokinetic Endpoints

Antiviral efficacy of TFV PDs is believed to be related to the concentration of the active moiety (TFV-DP) in PBMCs, rather than to concentrations in plasma. Considering that this is a weekly compound, the C168h in PBMCs is expected to be associated with efficacy. Based on a combined meta-analysis of in vitro and published clinical exposure response data, the target PBMC TFV-DP Ctrough concentration will be 100 nM. This target is hypothesized to achieve a reduction in HIV viral load of $\geq$ 0.5 log10 copies, relative to historical placebo, which is predictive of longer term efficacy (see below and Section 4.2). This is the Ctrough and associated VL reduction seen with the clinical dose of TDF.

The PK of MK-8583 and its anabolites in HIV subjects will be evaluated to refine the PBMC TFV-DP target concentrations associated with efficacy. In addition, information regarding PK and safety will be evaluated by means of assessment of plasma concentrations of MK-8583 and TFV.

4.2.3.3 Pharmacodynamic Endpoints

A PD endpoint of $\geq$ 0.5 log10 suppression of HIV-1 RNA from baseline on Day 7, relative to historical placebo data, will be used. This target is consistent with prior monotherapy proof-of-concept studies of NRTIs, including TDF 300 mg daily, which has proven long-term efficacy both as treatment and prevention of HIV infection [4] [10]. An endpoint at 7 days was set based on these published results with daily TDF monotherapy, but also with the expectation that a weekly drug will need to deliver persistent VL suppression throughout the duration between doses.

A posterior probability threshold P%=80% is chosen. A favorable posterior probability threshold is defined when the true mean HIV-1 reduction > 0.5 log [relative to Placebo] is >P%; there is relatively low probability of a favorable outcome when the true mean reduction is < 0.5 log10 copies/mL (about 20% or less) and relatively high probability for favorability when the true mean reduction is > 0.7 log10 copies/mL (about 80% or more), assuming a true SD = 25%.

Based on the long half-life of the active moiety TFV-DP, changes in VL may be assessed through 28 days for subjects who do not initiate follow-on ART. Additionally, the kinetics of VL reduction versus dose and exposure will also be determined.

4.2.3.4 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.

4.2.3.5 Future Biomedical Research

The Sponsor will conduct Future Biomedical Research on specimens consented for future biomedical research during this clinical trial. This research may include genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma) and/or the measurement of other analytes, depending on which specimens are consented for future biomedical research.

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 Section 12.2 – Collection and Management of Specimens for Future Biomedical Research.

The Sponsor will also be collecting baseline stool samples for future HIV research. Analysis of these samples may include, but will not be limited to, measurement of host inflammatory markers, microbiome composition, gene expression, metabolites, and viral load dynamics. Detailed instructions for stool sample collection are included in the Study Operations Manual.

4.3 Benefit/Risk

It cannot be guaranteed that subjects in clinical trials will directly benefit from treatment during participation as clinical trials are designed to provide information about the safety and effectiveness of an investigational medicine.

Additional details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying Investigators Brochure (IB) and Informed Consent documents.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male/Female subjects with HIV-1 infection who are naïve to ART between the ages of 18 and 60 years (inclusive) will be enrolled in this trial.

5.1.2 Subject Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

1. Provide written informed consent. The subject may also provide consent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.
2. Be a male or non-pregnant and non-breast feeding female, 18 to 60 years of age at the pretrial (screening) visit; further:
    a. if male with female partner(s) of child-bearing potential: see Section 5.7.3.1 for required methods of birth control.
    b. if female with reproductive potential: subject must demonstrate a serum β-human chorionic gonadotropin (β–hCG) level consistent with the nongravid state at the pretrial (screening) visit and agree to use acceptable methods of birth control beginning at the pretrial (screening) visit, throughout the trial and until 30 days following cessation of treatment. Acceptable methods of birth control are defined in Section 5.7.3.1.
    c. if postmenopausal female: subject is without menses for at least 1 year and have a documented follicle stimulating hormone (FSH) level in the postmenopausal range at pretrial (screening),

AND/OR

d. If surgically sterile female: subject is status post hysterectomy or oophorectomy.

NOTE: These procedures must be confirmed with medical records. In the absence of documentation, hysterectomy may be confirmed by pelvic exam or if necessary by ultrasound; oophorectomy may be confirmed by hormone levels, particularly FSH in the post-menopausal range. Information must be captured appropriately within the site's source documents

3. Have a Body Mass Index (BMI) ≤35 kg/m^2. BMI = weight (kg)/height (m) ^{2}.
4. Other than HIV infection, have baseline health judged to be stable based on medical history, physical examination, vital sign measurements, and laboratory safety tests (see Section 7.1.3) performed at the prestudy (screening) visit and/or prior to administration of the initial dose of study drug.
5. Be documented HIV-1 positive as determined by a positive ELISA or QT-PCR with confirmation (e.g., Western Blot).
6. Be diagnosed with HIV-1 infection ≥ 3 months prior to screening or perform the French 2008 HAS Algorithm to confirm chronic HIV.
7. Have a screening plasma CD4+ T-cell count of ≥ 200/mm^3.
8. Have a screening plasma HIV-1 RNA ≥ 5,000 copies/mL within 30 days prior to the treatment phase of this study.
9. Be ART-naïve, which is defined as having never received any anti-retroviral agent OR the following:

   ≤ 30 consecutive days of an investigational anti-retroviral agent, excluding an NRTI,

   OR

   ≤ 60 consecutive days of combination ART not including an NRTI
10. Have no evidence at screening for mutations affecting susceptibility to tenofovir [including K65R, K70E, M184V/I, or combinations of three or more thymidine analog mutations (TAMs) including M41L, L210W, T215Y, D67N, K70R, K219Q/E/N] as previously defined in Section 4.2.1.
11. Have the following laboratory values at screening: direct bilirubin ≤ 1.0 mg/dL, AST (SGOT) and ALT (SGPT) ≤ 2 x upper limit of normal.

5.1.3 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

1. Is under the age of legal consent.
2. Is mentally or legally institutionalized / incapacitated, has significant emotional problems at the time of pretrial (screening) visit or expected during the conduct of the trial or has a history of clinically significant psychiatric disorder of the last 5 years. Subjects who have had situational depression may be enrolled in the trial at the discretion of the investigator.

3. Has a history of clinically significant endocrine, gastrointestinal, cardiovascular, hematological, hepatic, immunological (outside of HIV-1 infection), renal, respiratory, genitourinary or major neurological (including stroke and chronic seizures) abnormalities or diseases. Subjects with a history of a minor medical event (e.g., uncomplicated kidney stones, as defined as spontaneous passage and no recurrence in the last 5 years, or childhood asthma) may be enrolled in the trial at the discretion of the investigator.
4. Has a history of cancer (malignancy). Subjects who have a remote cancer history who, in the opinion of the trial Investigator, are highly unlikely to sustain a recurrence for the duration of the trial may be included.
5. Has a history of significant multiple and/or severe allergies (e.g. food, drug, latex allergy), or has had an anaphylactic reaction or significant intolerability (i.e. systemic allergic reaction) to prescription or non-prescription drugs or food.
6. Is positive for Hepatitis B surface antigen.
7. Subject has a history of chronic Hepatitis C unless there has been documented cure and/or patient with a positive serologic test for HCV has a negative HCV viral load, in which case may be enrolled in the trial at the discretion of the investigator.
8. Had major surgery, donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks prior to the pretrial (screening) visit.
9. Has participated in another investigational trial within 4 weeks or 5 half-lives, whichever is greater, prior to the pretrial (screening) visit. The 4-week or 5-half-lives window will be derived from the date of the last visit in a previous trial.
10. Is unable to refrain from or anticipates the use of any medication, including prescription and non-prescription drugs or herbal remedies beginning approximately 2 weeks (or 5 half-lives) prior to administration of the initial dose of trial drug, throughout the trial, until the post-trial visit. There may be certain medications that are permitted, see Section 5.5.
11. Consumes greater than 3 glasses of alcoholic beverages (1 glass is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce]) per day. Subjects who consume 4 glasses of alcoholic beverages per day may be enrolled at the discretion of the investigator.
12. Consumes excessive amounts, defined as greater than 6 servings (1 serving is approximately equivalent to 120 mg of caffeine) of coffee, tea, cola, energy -drinks, or other caffeinated beverages per day.
13. Is an excessive smoker (i.e., more than 10 cigarettes/day) and is unwilling to restrict smoking to ≤10 cigarettes per day or is unwilling to follow the smoking restrictions defined by the CRU.
14. Has a clinically significant abnormality on the electrocardiogram (ECG) performed at the prestudy (screening) visit and/or prior to administration of the initial dose of study drug.
15. Has QTcF interval ≥ 470 msec (for males) or ≥ 480 msec (for females).

16. Has a positive urine drug screen (except for cannabis) at screening and/or pre-dose; rechecks are allowed.
17. Has received any investigational agent or any anti-retroviral agent within 60 days of study drug administration.
18. Intends to receive any ART during the treatment phase of this study.
19. Is any concern to the investigator regarding the safe participation of the subject in the trial or if, for any other reason; the investigator considers the subject inappropriate for participation in the trial (e.g. prior NRTI exposure).
20. Is unwilling to comply with additional the trial restrictions (see Section 5.7 for a complete summary of trial restrictions).
21. Is or has an immediate family member (e.g., spouse, parent/legal guardian, sibling or child) who is investigational site or Sponsor staff directly involved with this trial.

5.2 Trial Treatment(s)

The treatment to be used in this trial is outlined below in Table 3.

Table 3 Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Panel	Use
MK-8583	100 mg	1	Oral	Single Dose/Panel A	Experimental
MK-8583	≤150 mg	1	Oral	Single Dose/Panel B	Experimental
MK-8583	≤150 mg	1	Oral	Single Dose/Panel C	Experimental

Trial treatment should begin on the day of treatment allocation/randomization or as close as possible to the date on which the subject is allocated/assigned.

Study medication should be administered in the fasted state, with approximately 240 mL of water. Additional water may be offered during the capsule administration in increments of 50 mL, as needed. On all treatment days, subjects will fast from all food and drink except water for at least 8 hours prior to trial drug administration. Water will be restricted from 1 hour prior to and after trial drug administration.

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

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection (Preparation)

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background & Rationale. There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each subject.

5.2.1.2 Dose Modification (Escalation/Titration/Other)

All dose modification decisions will be made jointly by the investigator and the Sponsor. Each dose modification decision will occur after at least 6 subjects have completed the previous dose level.

Before proceeding to Panel B, PK data will be reviewed from Panel A to determine whether or not PK from HIV-infected subjects is similar to that observed in healthy subjects from Protocol 001. Dose modification decisions will be based on key safety data including: vital signs, 12-lead ECG, laboratory safety tests, adverse events and review of viral dynamic data from the previous dose levels up to at least 168 hours. Pharmacokinetic and pharmacodynamic data may be included in the dose modification decisions. See Background & Rationale - Section 4.0.

If, as judged by the Sponsor and investigator, the safety and tolerability data do not justify dose modification, the dose will not be modified as planned. Instead, subjects may:

- receive the same dose level to further explore safety and tolerability at that level;
- receive a lower dose of the trial drug;
- receive the same or lower dose as a divided dose; or
- receive a lower dose with or without food.

Or, dosing may be stopped. Subject discontinuation criteria are outlined in Section 5.8.

Prior to each treatment, the clinical and laboratory safety data from the previous dose level will be reviewed by the investigator and discussed with the Sponsor to permit a decision on whether to advance to the next dose level. No dose modification will occur without the joint agreement of the investigator and the Sponsor.

5.2.2 Timing of Dose Administration

All doses of MK-8583 will be given at approximately the same time in the morning.

5.2.3 Trial Blinding

This is an open-label trial; therefore, the Sponsor, investigator and subject will know the treatment administered.

5.3 Randomization or Treatment Allocation

Subjects will be assigned randomly according to a computer-generated allocation schedule.

A sample allocation schedule is shown below in Table 4.

Table 4 Sample Allocation Schedule

Subjects [a]	Panel A	Panel B [b]	Panel C [b]
N=6 (per panel)	100 mg	≤ 150 mg	≤ 150 mg

[a] Subjects will participate in only one panel.

[b] Doses may be adjusted based on viral load data and review of key safety variables (including vital signs, 12-lead ECGs, laboratory safety tests, and adverse events).

5.4 Stratification

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

5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

If a subject does not discontinue all prior medications within 14 days or 5 half-lives of starting the trial, he/she may be included in the study if the investigator can rationalize that the specific use of a prior medication is not clinically relevant within the context of the trial.

Concurrent use of any prescription or non-prescription medication, or concurrent vaccination, during the course of the trial (i.e., after randomization or treatment allocation) must first be discussed between the investigator and Sponsor prior to administration, unless appropriate medical care necessitates that therapy or vaccination should begin before the investigator and Sponsor can consult. The subject will be allowed to continue in the trial if both the Sponsor and the investigator agree.

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

Initiation of ART: All subjects will be encouraged to initiate ART some interval after their dose of MK-8583. The exact timing and regimen will be decided by the subject in consultation with his/her physician, but ART initiation will not occur before Day 10 (240 hours post-dose). This timing is required to gather full efficacy data for this novel long-acting anti-retroviral compound and is consistent with prior anti-retroviral monotherapy proof-of-concept trials, in which low-dose anti-retroviral monotherapy has been administered for as long as 28 days [10] and with European Medicines Agency (EMA) guidance [5]. If the physician and/or Investigator believe there is a strong indication to start ART before Day 10, this should be discussed with the Sponsor prior to starting, as with other concomitant medications (see above).

To lessen the chance of HIV resistance mutations developing, the Sponsor recommends that ART initiation occurs before PBMC TFV-DP concentrations fall below 100 nM. (100 nM is set as the lower limit because this is the steady-state Ctrough of TDF.) In Panel A (100 mg dose), the PBMC TFV-DP concentration is expected to fall below 0.1 μM after 4 half-lives, or ≥ 14 days, and therefore it is recommended that ART is initiated on or before Day 14. In subsequent panels, the Sponsor will provide the site with written guidance, prior to the start of dosing, as to the time when PBMC TFV-DP concentrations are expected to fall below the 100 nM lower limit.

For subjects who choose to initiate ART following the treatment phase of the study, the specific ART regimen selected will be a decision of the subject in consultation with the Investigator and/or the subject's physician.

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

5.6 Rescue Medications & Supportive Care

No rescue or supportive medications are specified to be used in this trial.

5.7 Diet/Activity/Other Considerations

5.7.1 Diet and Fruit Juice Restrictions

5.7.1.1 Diet

Fasting requirements for trial procedures, such as but not limited to laboratory safety evaluations are specified in Section 7.0.

Subjects will fast from all food and drinks, except water, for at least 8 hours prior to trial drug administration (and laboratory safety tests). Subjects will fast from all food and drinks except water between trial drug administration and the first scheduled meal. Meals and snack(s) will be provided by the investigator at time points indicated in the trial flowchart. Subjects will fast from all food and drinks except water between meals and snacks. The caloric content and composition of meals will be the same in each treatment period. After the 24-hour post-dose procedures have been completed, subsequent meals and snacks will be unrestricted in caloric content, composition and timing.

Water will be provided during trial drug administration. Water will be restricted 1 hour prior to and 1 hour after trial drug administration.

Instructions on whether to take MK-8583 with or without food and/or drink may be modified during the trial based on newly available data.

5.7.1.2 Fruit Juice Restrictions

Subjects will refrain from the consumption of grapefruit juice, grapefruits and grapefruit products beginning approximately 2 weeks prior to administration of the initial dose of trial drug, throughout the trial and until the post-trial visit.

On the dosing day, subjects will also refrain from the consumption of all fruit juices 24 hours prior to and after trial drug administration. All other days during the trial, consumption of fruits and fruit juices (except for grapefruit, grapefruit juices, and grapefruit products) is allowed.

5.7.2 Alcohol, Caffeine, Tobacco, Activity

5.7.2.1 Alcohol Restrictions

Subjects will refrain from consumption of alcohol 24 hours prior to the pre- and post-trial visits and from 24 hours prior to and after trial drug administration. At all other times, alcohol consumption is limited to no more than approximately 3 alcoholic beverages or equivalent (1 glass is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce]) per day.

5.7.2.2 Caffeine Restrictions

Subjects will refrain from consumption of caffeinated beverages from 12 hours prior to the pre- and post-trial visits and from 12 hours prior to and after trial drug administration. At all other times, caffeinated beverages or xanthine-containing products will be limited to no more than 6 servings per day amounts (>6 servings: 1 serving=120 mg of caffeine).

5.7.2.3 Smoking Restrictions

Smoking should be limited to ≤ 10 cigarettes per day and follow the smoking restrictions defined by the CRU while on site.

5.7.2.4 Activity Restrictions

Subjects will avoid unaccustomed strenuous physical activity (i.e., weight lifting, running, bicycling, etc.) from the pre-trial (screening) visit until the post-trial visit.

5.7.3 Contraception and Pregnancy Testing

5.7.3.1 Contraception

Women of childbearing potential can be enrolled. However, a highly effective method of contraception must be used with a failure rate of < 1%. Acceptable methods of birth control (to be used during the period as specified in Section 5.1.2) are the following: intrauterine device (IUD without local hormone release), vasectomy of partner having occurred >3 months prior to screening with a confirmatory negative sperm count. Surgical sterilization of the male partner or the female subject (hysterectomy or oophorectomy) must be documented with medical records.

Oral contraceptives are not allowed as a method of birth control in this trial.

Subjects must be completely informed of the unknown risks of pregnancy and agree not to become pregnant during the time they are participating in this trial.

If there is any question that a subject will not be reliable in the use of appropriate contraceptive methods, they should not be entered into the trial.

Male subjects with female partner(s) of child-bearing potential must agree to use a medically acceptable method of contraception during the trial and for 90 days after the last dose of trial drug. Males should use a condom. Female partners must additionally use one of the

following methods if they are not pregnant: hormonal contraception, intra-uterine device, diaphragm, or cervical cap. If their partner is pregnant, males must agree to use a condom and no additional method of contraception is required for the pregnant partner. Male subjects must also agree to not donate sperm during the study and for a period of 90 days after the last dose of study drug.

If there is any question that a subject will not be reliable in the use of appropriate contraceptive methods, he/she should not be entered into the trial

5.7.3.1.1 Pregnancy Testing

Female subjects of childbearing potential will be tested for serum β-human chorionic gonadotropin (hCG) at pretrial. Serum or urine β-hCG will be tested at pre-dose and at the last trial visit. In the case of a positive or borderline serum β-hCG pregnancy test at the pretrial visit, the subject must not enter the trial; in the case of a positive or borderline serum or urine β-hCG pregnancy test during the trial, the pregnancy test should be repeated and confirmed positive. If the pregnancy has been confirmed the subject must be discontinued from the trial immediately and the pregnancy must be reported the Sponsor as outlined in Section 7.2.2.

5.8 Subject Withdrawal/Discontinuation Criteria

5.8.1 Discontinuation

For subjects who are discontinued from treatment, all applicable discontinuation activities will be performed according to Section 7.1.4.1 – Withdrawal/Discontinuation, or if available, Protocol Clarification Letter.

Discontinuation from treatment is "permanent." Once a subject is discontinued, he/she shall not be allowed to restart treatment.

5.8.2 Withdrawal from the Trial

A subject must be withdrawn from the trial if the subject withdraws consent from the trial.

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

Specific details regarding procedures to be performed at the time of withdrawal from the trial including the procedures to be performed should a subject repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the subject, as well as specific details regarding withdrawal from Future Biomedical Research are outlined in Section 7.1.4 – Other Procedures.

5.9 Subject Replacement Strategy

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

5.10 Beginning and End of the Trial

The overall trial begins when the first subject signs the informed consent form. The overall trial ends when the last subject completes the last study-related phone-call or visit, withdraws from the trial or is lost to follow-up (i.e. the subject is unable to be contacted by the investigator).

A trial may be paused during review of newly available preclinical/clinical safety, pharmacokinetic, pharmacodynamic, efficacy or biologic data or other items of interest, prior to a final decision on continuation or termination of the trial. It may be necessary to keep the trial open for gathering/reviewing of additional supportive data to optimally complete the objective(s) of the trial. If necessary, the appropriate amendment(s) to the protocol and/or appropriate communication(s) will be generated. The overall trial end will then not be identified until the Sponsor has made the decision to end the trial following this review period. The Competent Authority(ies) and Institutional Review Board(s)/Independent Ethics Committee(s) [IRB(s)/IEC(s)] will be apprised of the maximum duration of the trial beyond the last subject out and the justification for keeping the trial open.

5.11 Clinical Criteria for Early Trial Termination

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

A primary objective of this early Phase I trial is to identify a safe and well-tolerated dose and/or dosing regimen that achieve pharmacokinetic, pharmacodynamic and/or biologic targets in humans based on preclinical or early clinical data. Therefore, it is possible that trial subjects may not receive all doses specified in the protocol if this objective is achieved at lesser dose levels in this trial. This would not be defined as early termination of the trial, but rather an earlier than anticipated achievement of the trial objective(s). If a finding (e.g., pharmacokinetic, pharmacodynamic, efficacy, biologic targets, etc.) from another preclinical or clinical trial using the trial treatment(s), comparator(s), drug(s) of the same class, or methodology(ies) used in this trial, results in the trial(s) or program being stopped for non-safety reasons, this also does not meet the definition of early trial termination.

Early trial termination is defined as a permanent discontinuation of the trial due to unanticipated concerns of safety to the trial subjects arising from clinical or preclinical trials with the trial treatment(s), comparator(s), drug(s) of the same class or methodology(ies) used in this trial.

Enrollment of the trial will be halted in the following circumstances:

1. One subject reports a serious adverse event with a potential causal relationship to the study drug or two (2) subjects per panel report severe adverse events with a potential causal relationship to study drug.
2. Three (3) or more of the enrolled subjects experience the same adverse event requiring withdrawal from the study, or the same severe adverse event assessed as having a potential causal relationship to study drug.
3. Two (2) subjects experience severe but not life threatening adverse experiences or severe clinically significant laboratory abnormalities that are similar in nature.

4. One (1) serious adverse experience/laboratory abnormality is reported that is life threatening, results in persistent or significant disability/incapacity, results in or prolongs an existing inpatient hospitalization, or is another important medical event OR participant death thought to be potentially related to the investigational product.
5. Two (2) or more of the enrolled subjects experience confirmed QTcF > 500 ms or QTcF change from baseline > 60 ms in a given panel with a potential causal relationship to study drug.

If one of the above circumstances occurs, enrollment and dosing will be halted, and an internal safety review will be conducted prior to making a decision about terminating the study. The safety of subjects will be assessed on an ongoing basis, and while conditions that could warrant early trial termination are not limited to those noted above, these criteria are meant to pre-specify circumstances under which the trial may be terminated early. In the event that the trial is interrupted or safety data suggest that the benefit-to-risk assessment has been meaningfully altered and must be reassessed, the Regulatory Authority will be notified. Following the internal safety review, if the Sponsor deems it appropriate to restart enrollment and dosing, if required, the Sponsor will submit an amendment to the competent authority prior to restart. If approved, enrollment and dosing may restart at that time.

6.0 TRIAL FLOW CHART

	Panels A, B, and C																		
	Scheduled Time																		
				Hours Post-dose															
	Prestudy	Pre-dose	0	0.25	0.5	1	2	4	6	12	24	36	48	72	96	168	240	312	672/Post-trial [a]
Administrative Procedures																			
Informed Consent	X																		
Informed Consent for Future Biomedical Research	X																		
Inclusion/Exclusion Criteria	X	X																	
Subject Identification Card	X																		
Medical History	X																		
Assignment of Screening Number	X																		
Assignment of Randomization Number [c]		X																	
Prior/Concomitant Medication Review	X	X----------																	----------X
Subject domiciling in the clinical research unit		X----------									----------X								
Clinic Procedures/Assessments																			
Full Physical Examination (PE)	X	X[d]														X			X
Height	X																		
Weight	X																		
12-Lead Electrocardiogram [e]	X	X				X					X					X			X
Vital Signs (heart rate, blood pressure, respiratory rate, body temperature) [f]	X	X				X					X					X			X
Orthostatic Vital Signs (heart rate, blood pressure) [f]	X	X				X					X					X			X
Standard Meals [g]								X----------			----------X								
MK-8583 Administration			X																
Adverse Events Monitoring	X ----------																		----------X
Laboratory Procedures/Assessments																			
Laboratory Safety Tests (hematology, chemistry, urinalysis)	X	X[d]									X					X			X
Urine /Serum β-Human Chorionic Gonadotropin (β-hCG) [h]	X	X[d]																	X
Serum FSH [i]	X																		
Urine/Blood Drug Screen [j]	X	X[d]																	
HIV/Hepatitis Screen	X																		
Blood for Genetic Analysis [b]		X																	

	Panels A, B, and C																	
	Scheduled Time																	
				Hours Post-dose														
	Prestudy	Pre-dose	0	0.25	0.5	1	2	4	6	12	24	36	48	72	96	168	240	312	672/Post-trial [a]
Stool for Future Biomedical Research [o]		X																	
Pharmacokinetic/Pharmacodynamic Evaluations																			
Blood for Plasma MK-8583 and TFV Assay [k]		X		X	X	X	X	X	X	X	X	X	X	X					
Blood for MK-8583 PBMC Assay [l, n]		X						X		X	X		X	X	X	X	X	X	X
Blood for HIV RNA, Viral Resistance [m, n]	X	X						X		X	X		X	X	X	X	X	X	X
CD4-positive cell count	X																		

	Panels A, B, and C																		
	Scheduled Time																		
				Hours Post-dose															
	Prestudy	Pre-dose	0	0.25	0.5	1	2	4	6	12	24	36	48	72	96	168	240	312	672/Post-trial [a]

a. The post-trial visit will occur approximately 28 days following administration of the study drug. Follow up for any clinical or laboratory adverse experiences should occur by phone or in person if the post-trial visit occurs prior to 28 days following the last dose of study drug. For confirmation of viral load return to baseline, additional data from viral load samples collected during routine follow-up visits may be transmitted to the sponsor for those patients who do not begin ART and who provide appropriate informed consent. Subjects may be asked to participate in observational monitoring beyond the 672 hour post-trial visit.
b. 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. This sample, to be collected on randomized subjects only, should be obtained one time only, pre-dose, on Day 1.
c. On Day 1, the randomization number is assigned after the completion of all pre-dose procedures prior to trial drug administration.
d. The pre-dose PE, laboratory assessments, and urine/blood drug screen may be performed within 24 hours prior to dosing.
e. Pre-dose ECGs will be obtained in triplicate, at least 1-2 minutes apart, and will be obtained within 3 hours prior to dosing of the trial drug. Pre-study and post-dose ECGs will be single measurements. Subjects should be resting in a semi-recumbent position for at least 10 minutes prior to obtaining ECG. See Section 7.1.2 for additional details.
f. Pre-dose semi-recumbent HR and BP will be triplicate measurements obtained at least 1-2 minutes apart within 3 hours prior to study administration. Subjects should be resting in the semi-recumbent position for at least 10 minutes prior to obtaining HR and BP. Following each semi-recumbent HR and BP measurement, subjects assume a standing position for at least ~2 minutes and then orthostatic HR and BP will be obtained. Pre-study and post-dose vital sign measurements will be single measurements. See Section 7.1.2 for additional details.
g. Standardized meals will be provided at ~4 and ~10 hours post-dose. A snack will be offered at ~ 7 and 13 hours post-dose. After the 24 hour post-dose procedures have been completed, subsequent meal and snacks will be unrestricted in terms of caloric content, composition and timing.
h. For female subjects of childbearing potential only. Urine pregnancy test may be performed instead of serum at pre-dose.
i. For postmenopausal woman only.
j. Additional urine drug screen tests may be performed at the discretion of the Investigator.
k. Leftover main study plasma will be stored for future biomedical research, if the subject consents to Future Biomedical Research consent.
l. For all panels, PBMC samples may be collected up to the post-trial visit regardless of initiation of ART.
m. For all panels, blood for HIV-1 viral RNA (also called viral load, VL) and viral resistance may be collected up to and including the day of ART initiation. Subjects choosing to forgo follow-on ART may also be asked if they wish to continue to participate in observational monitoring of VL and viral resistance testing beyond 28 days.
n. The 672 hour sample may be collected at the post-trial visit. Leftover main study PBMC will be stored for future biomedical research if the subject consents to Future Biomedical Research consent.
o. Informed consent for future biomedical research samples must be obtained to collect the stool samples. Stool samples will be collected at any time before dosing, according to the instructions in the Study Operations Manual. But if a sample cannot be obtained prior to dosing, this subject will be omitted from stool collection, the dosing will still proceed as scheduled and this will not be considered a protocol deviation.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The investigator or qualified designee must obtain documented consent from each potential subject prior to participating in a clinical trial or Future Biomedical Research. If there are changes to the subject's status during the trial (e.g., health or age of majority requirements), the investigator or qualified designee must ensure the appropriate consent is in place.

7.1.1.1.1 General Informed Consent

Consent must be documented by the subject's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's 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.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/IEC requirements, applicable laws and regulations and Sponsor requirements.

7.1.1.1.2 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.

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

7.1.1.3 Subject Identification Card

All subjects will be given a Subject Identification Card identifying them as participants in a research trial. The card will contain trial site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will provide the subject with a Subject Identification Card immediately after the subject provides written informed consent. At the time of treatment allocation/randomization, site personnel will add the treatment/randomization number to the Subject Identification Card.

The subject identification card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about trial medication/vaccination in emergency situations where the investigator is not available.

7.1.1.4 Medical History

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

7.1.1.5 Prior and Concomitant Medications Review

7.1.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 28 days before starting the trial.

7.1.1.5.2 Concomitant Medications

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

7.1.1.6 Assignment of Screening Number

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur prior to randomization or treatment allocation. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects.

Specific details on the screening visit requirements (screening/rescreening) are provided in Section 7.1.5.1.

7.1.1.7 Assignment of Treatment/Randomization Number

All eligible subjects will be randomly allocated and will receive a treatment/randomization number. The treatment/randomization number identifies the subject for all procedures

occurring after randomization. Once a treatment/randomization number is assigned to a subject, it can never be re-assigned to another subject.

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

7.1.1.8 Trial Compliance (Medication/Diet/Activity/Other)

Administration of trial medication will be witnessed by the investigator and/or trial staff.

7.1.2 Clinical Procedures/Assessments

Physical Exam:

The physical exam assessments will be defined and conducted per the site SOP.

Body Weight and Height

Body weight and height will be obtained with the subjects shoes off, jacket or coat removed.

Body Mass Index (BMI)

BMI equals a person's weight in kilograms divided by height in meters squared. (BMI=kg/m2).

12-Lead ECG

Special care must be taken for proper lead placement by qualified personnel. Skin should be clean and dry prior to lead placement. Subjects may need to be shaved to ensure proper lead placement. Female subjects may need to remove interfering undergarments.

Subjects should be resting in the semi-recumbent for at least 10 minutes prior to each ECG measurement.

The correction formula to be used for QTc is Fridericia.

For repeat ECGs, the clinical site will decide whether to leave the electrodes in place or mark the position of the electrodes for subsequent ECGs. To mark the position of the electrodes, 12-lead electrode sites will be marked on the skin of each subject with an ECG skin marker pen to ensure reproducible electrode placement.

Pre-dose ECGs will be obtained in triplicate at least 1-2 minutes apart, and the pre-dose ECG will be obtained within 3 hours prior to dosing MK-8583. The average of triplicate pre-dose measurements will be used for the baseline ECG. Pre-study screening and post-dose ECG measurements will be single measurements.

If a subject demonstrates an increase in QTcF interval ≥60 msec compared with mean pre-dose baseline measurement, the ECG will be repeated twice within 5 minutes. The average value of the QTcF interval from the 3 ECGs will represent the value at that time point. If the average QTcF interval increase from baseline for any post-dose time point is ≥60 msec, the subject will continue to be monitored by repeat 12-lead ECGs every 15 minutes for at least 1 hour or until the QTcF is within 60 msec of baseline. If prolongation of the QTcF interval

≥60 msec persists, a consultation with a study cardiologist may be appropriate and the Sponsor should be notified.

If the QTcF interval is ≥500 msec (confirmed upon recheck and manual measurement), the Sponsor should be notified and the ECGs should be reviewed by a cardiologist. The subject should be telemetry-monitored (until the QTcF is <500 msec) or should be considered for transfer to a location where closer monitoring and definitive care (e.g., a Cardiac or Intensive Care Unit) is available.

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

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

A study cardiologist should be arranged by the Principal Investigator to be available as needed to review ECG tracings with abnormalities.

Body Temperature

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

Vital Sign Measurements (Heart Rate and Blood Pressure)

Subjects should be resting in a semi-recumbent position for at least 10 minutes prior to having vital sign measurements obtained. Semi-recumbent vital signs will include heart rate (HR) and blood pressure (BP). The correct size of the blood pressure cuff and the correct positioning on the subjects' arm is essential to increase the accuracy of blood pressure measurements. The same method (e.g., manual or automated) must be used for all measurements for each individual subject and should be the same for all subjects.

Pre-dose HR and BP will be triplicate measurements obtained at least 1-2 minutes apart, and the pre-dose measurements will be obtained within 3 hours of dosing MK-8583. The average of these measurements will be used as the baseline. Pre-study screening and post-dose vital sign measurements will be single measurements.

Orthostatic vital signs (HR and BP) will also be obtained. Subjects should be semi-recumbent for at least 10 minutes and then stand upright for 2 minutes prior to measurement of orthostatic vital signs.

Subjects will continue to rest semi-recumbent from dosing until 4 hours post-dose except to stand for the measurement of orthostatic vital signs or other trial related procedure. Pre-dose vital signs may be obtained up to 3 hours prior to dosing.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. The total amount of blood/tissue to be drawn/collected over the course of the trial (from pre-trial to post-trial visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per subject can be found in Section 12.3.

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry and urinalysis are specified in Table 5.

Table 5 Laboratory Tests

Hematology	**Chemistry**	**Urinalysis**	**Other**
Hematocrit	Albumin	Red blood Cell & white blood cell	Follicle Stimulating Hormone (FSH) - for postmenopausal females only*
Hemoglobin	Alkaline phosphatase	Glucose	Urine/Serum β-human chorionic gonadotropin (β-hCG) – for females of childbearing potential only**
Platelet count	Alanine aminotransferase (ALT)	Protein	Hepatitis B surface antigen and HCV antibodies
WBC (total and differential) including: Absolute neutrophils Absolute lymphocytes Absolute monocytes Absolute eosinophils Absolute basophils	Aspartate aminotransferase (AST)	Specific gravity	HIV (including HIV-RNA, resistance mutations (per inclusion criterion 10))
CD4+ T cell count (screening)	Bicarbonate	Microscopic exam, if abnormal results are noted	Urine/Blood Drug Screen
	Calcium	pH	
	Chloride		
	Creatinine		
	Glucose		
	Phosphorus		

Hematology	Chemistry	Urinalysis	Other
	Potassium		
	Sodium		
	Total Bilirubin		
	Direct Bilirubin		
	Total protein		
	Urea		

*Only collected at prestudy.

**Serum pregnancy test to be performed at prestudy; serum or urine pregnancy test will be performed at pre-dose.

Laboratory safety tests will be performed after at least an 8-hour fast. Pre-dose laboratory procedures can be conducted up to 24 hours prior to dosing.

7.1.3.2 Pharmacokinetic/Pharmacodynamic Evaluations

The decision as to which plasma and/or urine samples collected will be assayed for evaluation of PK/PD will be collaboratively determined by the Department of Quantitative Pharmacology and Pharmacometrics (QP2) and the appropriate department within Translational Pharmacology, (e.g., samples at lower doses may not be assayed if samples at higher doses reveal undetectable drug concentrations). If indicated, these samples may also be assayed and/or pooled for assay in an exploratory manner for metabolites and/or additional PD markers.

7.1.3.2.1 Blood Collection for Plasma TFV and MK-8583

Sample collection, storage and shipment instructions for plasma MK-8583 and TFV samples will be provided in a Study Operations Manual.

7.1.3.2.2 Blood Collection for PBMC

Sample collection, processing, storage and shipment instructions for PBMC samples will be provided in the Study Operations Manual.

7.1.3.2.3 Blood Collection for HIV-1 Viral RNA and Viral Resistance

Sample collection, storage and shipment instructions for these blood samples will be provided by the site's local laboratory.

7.1.3.3 Planned Genetic Analysis Sample Collection

Sample collection, storage and shipment instructions for Planned Genetic Analysis samples will be provided in the Study Operations Manual.

7.1.3.4 Future Biomedical Research Samples

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

- DNA for future research
- Stool for future research
- Leftover main study PBMC stored for future research
- Leftover main study plasma from MK-8583 and TFV assays stored for future research

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

The investigator or trial coordinator must notify the Sponsor when a subject has been discontinued/withdrawn from the trial. If a subject discontinues for any reason at any time during the course of the trial, the subject may be asked to return to the clinic (or be contacted) for a post-trial visit (approximately 28 days after the last dose of trial drug is given) to have the applicable procedures conducted. However, the investigator may decide to perform the post-trial procedures at the time of discontinuation or as soon as possible after discontinuation. If the post-trial visit occurs prior to 28 days after the last dose of trial drug is given, the investigator should perform a follow-up phone call 28 days after the last dose of trial drug to determine if any adverse events have occurred since the post-trial clinic 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 7.2 - Assessing and Recording Adverse Events.

7.1.4.1.1 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.

7.1.4.1.2 Lost to Follow-up

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

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

7.1.4.2 Subject Blinding/Unblinding

This is an open label trial; there is no blinding for this trial.

7.1.4.3 Domiciling

Subjects will report to the clinical research unit (CRU) the evening prior to the scheduled day of trial drug administration in each treatment period and remain in the unit until 24 hours post-dose. At the discretion of the investigator, subjects may be requested to remain in the CRU longer.

7.1.4.4 Calibration of Critical Equipment

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

Critical Equipment for this trial includes:

- Vital signs, ECG and centrifuge equipment
- Equipment and specified supplies necessary for PBMC sample collection and processing:
    - Equipment such as, but not limited to, centrifuges with refrigeration function, microscope, and pipettes
    - Freezers for the assay samples

7.1.5 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.5.1 Screening

Approximately 4 weeks prior to treatment allocation/randomization, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1.

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

7.1.5.2 Treatment Period

7.1.5.2.1 Pre-dose Procedures (All Panels)

Prior to each treatment panel, the clinical and laboratory safety data from the previous dose level and previous treatment panel will be reviewed by the Investigator and the Clinical Team and a mutual decision on whether to advance to the next higher dose level will be made. No dose modification will occur without agreement of the Investigator and the Sponsor.

Subjects will report to the CRU the day prior to the scheduled day of administration of the study drug or time specified by the investigator. Subjects will fast from all food and drink, except for water, for a minimum of 8 hours prior to study drug administration and prior to obtaining samples for laboratory safety tests (refer to Section 7.1.3.1).

After the Day 1 pre-dose procedures have been completed, subjects will be assigned a unique randomization number associated with a specific treatment sequence as defined by a computer-generated allocation schedule. For details on procedures, please refer to the Study Flow chart (Section 6.0), Procedures (Section 7.1.2) and/or corresponding appendices.

7.1.5.2.2 Treatment Procedures (All Panels)

Procedures for study drug administration and post-dose procedures are listed in the Study Flow Chart, Section 6.0 of this protocol.

Subjects will be administered a single dose of MK-8583 in the morning. The exact clock time of dosing should be recorded.

7.1.5.3 Post-Trial

Post-trial procedures are listed in the Study Flow Chart, Section 6.0 of this protocol.

Subjects will be required to return to clinic approximately 28 days after the last dose of trial drug for the post-trial visit. If the post-trial visit occurs less than 28 days after the last dose of trial drug, a subsequent follow-up phone call should be made at 28 days post the last dose of trial drug to determine if any adverse events have occurred since the post-trial clinic visit.

7.1.5.4 Critical Procedures Based on Trial Objectives: Timing of Procedure

For this trial, the blood sample for viral load and the blood sample for MK-8583 PBMC are the critical procedures.

At any post-dose time point, the blood samples for viral load and MK-8583 PBMC need 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. Trial procedures can be performed prior or after the prescribed/scheduled time.

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

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

The following variance in procedure collection times will be permitted.

- PK Collection as outlined in Table 6 below

Table 6 PK (Blood)/PBMC/Viral Load Collection Windows

PK/PBMC/Viral Load collection	PK/PBMC/Viral Load Collection Window
0 to < 1 hr	5 min
1 to < 24 hr	15 min
24 hr to < 48 hr	2 hrs
48 to 168 hr	3 hrs
168 to 240 hr	24 hrs
> 240 hr	72 hrs

- Pre-dose standard safety evaluations: vital signs (including RR and body temperature) & ECG 3 hrs; laboratory safety tests (including drug screen) & physical exam 24 hrs prior to dosing
- Post-dose standard safety evaluations (vital signs, ECG, laboratory safety tests, physical exam) as outlined in Table 7 below:

Table 7 Post-dose Standard Safety Evaluations Collection Windows

Scheduled Time	Data Collection Window
0 to < 24 hr	30 min
24 to < 48 hr	2 hrs
48 to 168 hr	3 hrs
168 to 240 hr	24 hrs
> 240 hr	72 hrs

7.1.5.5 Trial Design/Dosing/Procedures Modifications Permitted within Protocol Parameters

This is a Phase I assessment of MK-8583 in humans, and the PK, PD and safety profiles of the compound is still being elucidated. This protocol is written with some flexibility to accommodate the inherent dynamic nature of Phase I clinical trials. Modifications to the dose, dosing regimen and/or clinical or laboratory procedures currently outlined below may be required to achieve the scientific goals of the trial objectives and/or to ensure appropriate safety monitoring of the trial subjects.

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

- Repeat of or decrease in the dose of the trial drug administered
- Entire panel(s) may be omitted
- Instructions to take trial drug with or without food or drink may also be modified based on newly available data
- Modification of the PK/PD sample processing and shipping details based on newly available data
- Decrease in the length of post-dose PK/PD sample collection

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

Up to additional 50 mL of blood may be drawn for safety, PK, and/or PD 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 12.3).

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 or pharmacodynamic 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 letter to the Trial File and forwarded to the investigator for retention. The letter may be forwarded to the IRB/IEC at the discretion of the investigator.

If an alteration impacts subject safety, affects the scientific value of the study results, and/or significantly alters the execution of the trial, a notification will be submitted prior to proceeding with the trial. If approved, enrollment and dosing may restart at that time

7.2 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 unfavourable 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 treatment allocation/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 treatment allocation/randomization through 28 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 7.2.3.1. 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).

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

An overdose is defined when 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 non-serious adverse event, unless other serious 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).

7.2.2 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 treatment allocation/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 treatment allocation/randomization through 28 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).

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

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

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is an 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.

- Is a cancer (within 5 calendar days of learning of event);
- Is associated with an overdose.

Refer to Table 8 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation/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 allocation/randomization through 28 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.

7.2.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported to the Sponsor.

For the time period beginning when the consent form is signed until treatment allocation/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 allocation/randomization through 28 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:

1. an overdose of Sponsor's product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.

2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, 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 must trigger 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.

7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events with respect to the elements outlined in Table 8. The investigator's assessment of causality is required for each adverse event. Refer to Table 8 for instructions in evaluating adverse events.

Table 8 Evaluating Adverse Events

Maximum Intensity	**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 (AE) is any adverse event occurring at any dose or during any use of Sponsor's product that:	
	†**Results in death**; or	
	†**Is 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	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis); or	
	Is a cancer (although not serious per ICH definition, is reportable to the Sponsor within 5 calendar days to meet certain local requirements); **or**	
	Overdose, although not serious per ICH definition, whether accidental or intentional, with or without an accompanying adverse event/serious adverse event, is reportable to the Sponsor within 24 hours to meet certain local requirements.	
	Other important medical events 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	Did the adverse event cause the Sponsor's product to be discontinued?	
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 AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information **The following components are to be used to assess the relationship between the Sponsor's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the 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 AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Sponsor's Product (continued)	**The following components are to be used to assess the relationship between the Sponsor's product and the AE: (continued)**	
	Dechallenge	Was the Sponsor's product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the 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 AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the 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 SPONSOR CLINICAL DIRECTOR AND THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
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).**	
Yes, there is a reasonable possibility of Sponsor's product relationship.	There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.	
No, there is not a reasonable possibility of Sponsor's product relationship	Subject did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a subject with overdose without an associated AE.)	

7.2.5 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, i.e., per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan Summary

This section contains a brief summary of the statistical analyses for this trial. Full detail is in the Statistical Analysis Plan (SAP) (Section 8.2).

Statistical Methods

Primary Objective (Safety): Incidence of adverse experiences will be descriptively summarized. Summary statistics and plots will be generated for the change from baseline values in the vital signs, ECG parameters, and selected laboratory safety parameters for subjects, as deemed clinically appropriate. Depending on the safety parameter, the difference from baseline will either be computed on the original scale (raw change from baseline) or on the log scale and back-transformed for reporting (percent change from baseline). Summary statistics for the raw laboratory safety tests, ECGs, and/or vital signs may also be computed, as deemed clinically appropriate.

Primary Objective (Pharmacodynamics): The log10 plasma HIV-RNA (copies/mL) measurements from subjects in all panels will be pooled and analyzed based on a longitudinal data analysis model containing fixed effects for dose level, time (pre-dose, 168 hrs post-dose) and dose level by time interaction, and a random effect for patient. The change from baseline for each dose level at 168 hours post-baseline will be estimated from this model. A posterior distribution for the true mean change from baseline at 168 hours will be generated for each dose level using flat priors under a normal likelihood assumption. Historical placebo data from recent monotherapy studies in HIV-1 subjects (MK-0518 Protocol 004, MK-1439 Protocol 005, MK-6186 Protocol 007, and MK-1972 Protocol 003) will be separately analyzed based on a longitudinal data analysis model containing fixed effects for study and time (pre-dose, 168 hours post-dose), and a random effect for patient. The change from baseline for placebo at 168 hours post-baseline will be estimated from this model, and a posterior distribution for the true mean change from baseline at 168 hours will be generated using flat priors under a normal likelihood assumption. Using the posterior distributions for each dose level and placebo, the posterior distribution of the true mean difference between each dose level and placebo will be generated, and the posterior probability that the true mean difference in the log10 plasma HIV-1 RNA reduction from baseline between MK-8583 and placebo is at least 0.5 log10 copies/mL will be calculated. An 80% posterior probability for at least one dose level that also exhibits an acceptable safety and tolerability profile will satisfy the primary PD hypothesis.

Power

If the true SD of the log10 reduction from baseline in plasma HIV-RNA at 168 hours post-dose is 0.25(0.4) for MK-8583, there is ~80% power to yield at least 80% posterior probability that the true mean difference in the plasma HIV-1 RNA reduction from baseline

between MK-8583 and placebo is at least 0.5 log10 copies/mL, if the true mean log10 reduction is at least 0.7 log10 (0.8 log10) with N=6 subjects in a Panel. It assumes the historical placebo sample size of 20 with mean reduction of 0 log10 and SD = 0.25. The information of placebo data was from historical placebo data of recent monotherapy studies in HIV-1 subjects (MK-0518 Protocol 004, MK-1439 Protocol 005, MK-6186 Protocol 007, and MK-1972 Protocol 003). The SD of MK-8583 is estimated based on MK-8591 Protocol 003and MK-8507 Protocol 003 studies (SD ranges from 0.24 to 0.4).

8.2 Statistical Analysis Plan

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

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

8.2.1 Hypotheses

Primary PD Hypothesis: At a dose that is sufficiently safe and generally well tolerated, MK-8583 has superior anti-retroviral activity compared to placebo, as measured by change from baseline in plasma HIV-1 RNA (log10 copies/mL) at 168 hours post-dose. That is, the true mean difference in the plasma HIV-1 RNA reduction from baseline between MK-8583 and placebo is at least 0.5 log10 copies/mL.

Secondary Pharmacokinetics Hypothesis: The true geometric mean (GM) TFV-DP PBMC C168hr is $\geq$ 0.1 μM for at least one dose level that also exhibits an acceptable safety and tolerability profile.

8.2.2 Analysis Endpoints

Primary Endpoints

Safety: Primary safety endpoints will include adverse experiences, in addition to laboratory safety tests, ECGs, and vital signs.

Pharmacodynamics: The primary PD variable in this study is plasma HIV-1 RNA collected at pre-dose and 4, 12, 24, 48, 72, 96, 168, 240, 336 and 504 hours post-dose.

Secondary Endpoints

The secondary endpoints in this study include: TFV-DP PBMC AUC0-168hr, Cmax, Tmax, C168hr and t1/2; MK-8583 plasma AUC0-last, AUC0-inf, AUC0-168hr, Tmax, Cmax, t1/2, CL/F and Vz/F; TFV plasma AUC0-last, AUC0-inf, Tmax, Cmax and t1/2.

Exploratory Endpoints

PBMC TFV-MP concentrations at designated time points.

8.2.3 Approaches to Analyses

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

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

Per-Protocol (PP): The Per-Protocol Population consists of the subset of subjects who comply with the protocol sufficiently to ensure that generated data will be likely to exhibit the effects of treatment, according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements and absence of major protocol deviations. Major protocol deviations will be identified to the extent possible by individuals responsible for data collection/compliance, and its analysis and interpretation. 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 from at least one treatment will be included in the Per-Protocol dataset. This population will be used for the PK and PD analyses.

8.2.4 Statistical Methods

Primary (Safety)

Incidence of adverse experiences will be descriptively summarized. Summary statistics and plots will be generated for the change from baseline values in the vital signs, ECG parameters, and selected laboratory safety parameters for subjects, as deemed clinically appropriate. Depending on the safety parameter, the difference from baseline will either be computed on the original scale (raw change from baseline) or on the log scale and back-transformed for reporting (percent change from baseline). Summary statistics for the raw laboratory safety tests, ECGs, and/or vital signs may also be computed, as deemed clinically appropriate.

Primary (Pharmacodynamics)

The log10 plasma HIV-RNA (copies/mL) measurements from subjects in all panels will be pooled and analyzed based on a longitudinal data analysis (LDA) model containing fixed effects for dose level, time (pre-dose, 168 hrs post-dose) and dose level by time interaction, and a random effect for patient. The response vector consists of the baseline and 168 hours post-baseline values. Time is treated as a categorical variable so that no restriction is imposed on the trajectory of means over time. The change from baseline for each dose level at 168 hours post-baseline will be estimated from this model. A posterior distribution for the true mean change from baseline at 168 hours will be generated for each dose level using flat priors under a normal likelihood assumption. Historical placebo data from recent monotherapy studies in HIV-1 subjects (MK-0518 Protocol 004, MK-1439 Protocol 005, MK-6186 Protocol 007, and MK-1972 Protocol 003) will be separately analyzed based on a longitudinal data analysis model containing fixed effects for study and time (pre-dose, 168 hrs post-dose), and a random effect for patient. The change from baseline for placebo at 168 hours post-baseline will be estimated from this model, and a posterior distribution for the true

mean change from baseline at 168 hours will be generated using flat priors under a normal likelihood assumption. Using the posterior distributions for each dose level and placebo, the posterior distribution of the true mean difference between each dose level and placebo will be generated, and the posterior probability that the true mean difference in the log10 plasma HIV-1 RNA reduction from baseline between MK-8583 and placebo is at least 0.5 log10 copies/mL will be calculated. An 80% posterior probability for at least one dose level that also exhibits an acceptable safety and tolerability profile will satisfy the primary PD hypothesis. For each dose level, the posterior probability that the true mean log10 plasma HIV-1 RNA reduction from baseline is at least 0.5 log10 copies/mL will also be calculated. Similar exploratory analyses may be performed using viral load measurements at baseline and specified post-baseline time points.

Secondary (Pharmacokinetics)

Separately for each PK parameter, individual values of TFV-DP in PBMC PK parameters AUC0-168hr, Cmax, and C168hr from subjects in all panels will be pooled, natural log transformed and analyzed based on a linear model containing a fixed effect for dose level. The 95% confidence intervals for the least squares means by dose level will be constructed on the natural log scale and will reference the t-distribution. Exponentiating the least-squares means and lower and upper limits of these confidence intervals will yield estimates for the population geometric means and confidence intervals about the geometric means on the original scale. The posterior probability that the true GM C168hr PBMC TFV-DP level is $\geq$ 0.1 μM will be calculated for each dose level using flat priors under a normal likelihood assumption. An 80% posterior probability for at least one dose level that also exhibits an acceptable safety and tolerability profile will satisfy the secondary PK hypothesis.

MK-8583 plasma AUC0-last, AUC0-inf, Cmax, CL/F and Vz/F, and TFV plasma AUC0-last, AUC0-inf and Cmax will be analyzed in a similar fashion.

Descriptive Statistics

Individual values will be listed for each PK parameter by dose level, and the following (non-model-based) descriptive statistics will be provided: N (number of subjects with non-missing data), arithmetic mean, standard deviation, arithmetic percent CV (calculated as 100 x standard deviation/arithmetic mean), median, minimum, maximum, geometric mean, and geometric percent CV (calculated as 100 x sqrt($\exp(s^2)$ - 1), where s^2 is the observed variance on the natural log-scale).

The above descriptive statistics, as well as a mean plot will also be provided for VL reduction by dose level and all time points.

Secondary and Exploratory (Pharmacokinetic/Pharmacodynamic)

The PK-PD and dose-PD association of MK-8583 will be explored. Graphs to visualize the association of the reduction in log10 plasma HIV-1 RNA levels with TFV-DP in PBMC by parameters and dose will be generated. Exploratory linear and/or non-linear model fits may be considered, as appropriate. Exposure levels and doses that result in various proportions of the population (e.g., 80%, 90%) that have at least 0.5 log10 reduction from baseline in plasma HIV-1 RNA levels with high confidence may be estimated.

The duration of anti-retroviral suppression after single dose MK-8583 will be evaluated with individual plots across time.

For PBMC levels of TFV-MP, descriptive statistics (similar to those of secondary PK parameters) will be provided by dose.

General

For all analyses, data will be examined for departures from the assumptions of the statistical model(s) as appropriate; e.g., heteroscedasticity, nonnormality of the error terms. Distribution-free methods may be used if a serious departure from the assumptions of the models(s) is observed, or suitable data transformations may be applied.

8.2.5 Multiplicity

Since there is only one primary PD hypothesis and it is being evaluated with Bayesian methods, no multiplicity adjustment will be made.

8.2.6 Sample Size and Power

If the true SD of the log10 reduction from baseline in plasma HIV-RNA at 168 hours post-dose is 0.25(0.4) for MK-8583, there is ~80% power to yield at least 80% posterior probability that the true mean difference in the plasma HIV-1 RNA reduction from baseline between MK-8583 and placebo is at least 0.5 log10 copies/mL, if the true mean log10 reduction is at least 0.7 log10 (0.8 log10) with N=6 subjects in a Panel. It assumes the historical placebo sample size of 20 with mean reduction of 0 log10 and SD = 0.25. The information of placebo data was from historical placebo data of recent monotherapy studies in HIV-1 subjects (MK-0518 Protocol 004, MK-1439 Protocol 005, MK-6186 Protocol 007, and MK-1972 Protocol 003). The SD of MK-8583 is estimated based on MK-8591 Protocol 003and MK-8507 Protocol 003 studies (SD ranges from 0.24 to 0.4).

A posterior probability threshold P%=80% is chosen. A favorable posterior probability threshold is defined when the true mean HIV-1 reduction > 0.5 log [relative to Placebo] is >P%; there is relatively low probability of a favorable outcome when the true mean reduction is < 0.5 log10 copies/mL (about 20% or less) and relatively high probability for favorability when the true mean reduction is > 0.7 log10 copies/mL (about 80% or more), assuming a true SD = 25%.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

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

Clinical Supplies will be provided by the Sponsor as summarized in Table 9.

Clinical supplies will be packaged to support enrollment and replacement subjects as required. When a replacement subject is required, the Sponsor or designee needs to be contacted prior to dosing the replacement supplies.

Table 9 Product Descriptions

Product Name & Potency	Dosage Form	Source/Additional Information
MK-8583 10 mg	Capsule	Provided centrally by the Sponsor
MK-8583 100 mg	Capsule	Provided centrally by the Sponsor

9.2 Packaging and Labeling Information

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

Subjects will receive open label single doses dispensed from supplies packaged in bulk open label bottles. No kitting is required.

9.3 Clinical Supplies Disclosure

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

9.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

9.5 Discard/Destruction/Returns and Reconciliation

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

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

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

10.1.2 Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/ERC, or regulatory authority representatives may consult and/or copy trial documents in order to verify worksheet/case report form data. By signing the consent form, the subject agrees to this process. If trial documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

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

10.1.3 Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and trial site personnel, may be used and disclosed for trial management purposes, as part of a regulatory submissions, and as required by law. This information may include:

1. name, address, telephone number and e-mail address;
2. hospital or clinic address and telephone number;
3. curriculum vitae or other summary of qualifications and credentials; and
4. other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, in your country and other countries, including countries that do not have laws protecting such information. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory authorities or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

If this is a multicenter trial, in order to facilitate contact between investigators, the Sponsor may share an investigator's name and contact information with other participating investigators upon request.

10.1.4 Confidentiality of IRB/IEC Information

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

10.2 Compliance with Financial Disclosure Requirements

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

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

10.3 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 Good Clinical Practice (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 Section 12.1 - Merck Code of Conduct for Clinical Trials.

The investigator also agrees to allow monitoring, audits, IRB/IEC 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 Good Clinical Practice 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 Good Clinical Practice 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 [Clinical Study Report (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.

10.4 Compliance with Trial Registration and Results Posting Requirements

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

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

10.5 Quality Management System

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (SOPs) to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, 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.

10.6 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 for this protocol will be provided separately.

10.7 Publications

This trial is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. The Sponsor will work with the authors to submit a manuscript describing trial results within 12 months after the last data become available, which may take up to several months after the last subject visit in some cases such as vaccine trials. However, manuscript submission timelines may be extended on OTC trials. For trials intended for pediatric-related regulatory filings, the investigator agrees to delay publication of the trial results until the Sponsor notifies the investigator that all relevant regulatory authority decisions on the trial drug have been made with regard to pediatric-related regulatory filings. Merck will post a synopsis of trial results for approved products on www.clinicaltrials.gov by 12 months after the last subject's last visit for the primary outcome, 12 months after the decision to discontinue development, or product marketing (dispensed, administered, delivered or promoted), whichever is later.

These timelines may be extended for products that are not yet marketed, if additional time is needed for analysis, to protect intellectual property, or to comply with confidentiality agreements with other parties. Authors of the primary results manuscript will be provided the complete results from the Clinical Study Report, subject to the confidentiality agreement. When a manuscript is submitted to a biomedical journal, the Sponsor's policy is to also include the protocol and statistical analysis plan to facilitate the peer and editorial review of the manuscript. If the manuscript is subsequently accepted for publication, the Sponsor will allow the journal, if it so desires, to post on its website the key sections of the protocol that are relevant to evaluating the trial, specifically those sections describing the trial objectives and hypotheses, the subject inclusion and exclusion criteria, the trial design and procedures, the efficacy and safety measures, the statistical analysis plan, and any amendments relating to those sections. The Sponsor reserves the right to redact proprietary information.

For multicenter trials, subsequent to the multicenter publication (or after public disclosure of the results online at www.clinicaltrials.gov if a multicenter manuscript is not planned), an investigator and his/her colleagues may publish their data independently. In most cases, publication of individual trial site data does not add value to complete multicenter results, due to statistical concerns. In rare cases, publication of single trial site data prior to the main paper may be of value. Limitations of single trial site observations in a multicenter trial should always be described in such a manuscript.

Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors must meet conditions 1, 2 and 3. Significant contributions to trial execution may also be taken into account to determine authorship, provided that contributions have also been made to all three of the preceding authorship criteria. Although publication planning may begin before conducting the trial, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to

the trial and writing, as discussed above. The first author is responsible for defending the integrity of the data, method(s) of data analysis and the scientific content of the manuscript.

The Sponsor must have the opportunity to review all proposed abstracts, manuscripts or presentations regarding this trial 45 days prior to submission for publication/presentation. Any information identified by the Sponsor as confidential must be deleted prior to submission; this confidentiality does not include efficacy and safety results. Sponsor review can be expedited to meet publication timelines.

11.0 LIST OF REFERENCES

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[2] Horberg M, Tang B, Towner W, Silverberg M, Bersoff-Matcha S, Hurley L, et al. Impact of tenofovir on renal function in HIV-infected, antiretroviral-naive patients. J Acquir Immune Defic Syndr. 2010 Jan;53(1):62-9.

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[4] Ruane PJ, DeJesus E, Berger D, Markowitz M, Bredeek UF, Callebaut C, et al. Antiviral activity, safety, and pharmacokinetics/pharmacodynamics of tenofovir alafenamide as 10-day monotherapy in HIV-1-positive adults. J Acquir Immune Defic Syndr. 2013 Aug 1;63(4):449-55.

[5] European Medicines Agency. Committee For Medicinal Products For Human Use(CHMP): guideline on the clinical development of medicinal products for the treatment of HIV infection (EMEA/CPMP/EWP/633/02), 20-Nov-2008.

[6] Yeni PG, Hammer SM, Hirsch MS, Saag MS, Schechter M, Carpenter CC, et al. Treatment for adult HIV infection: 2004 recommendations of the International AIDS Society-USA Panel. JAMA. 2004 Jul 14;292(2):251-65.

[7] Hendrix CW. The clinical pharmacology of antiretrovirals for HIV prevention. Curr Opin HIV AIDS. 2012 Nov;7(6):498-504.

[8] Wrzesinski C. Pharmacology review of NDA 207-561 for Genvoya (Elvitegravir, Cobicistat, Emtricitabine, Tenofovir Alafenamide), Gilead, 09-Jan-2015.

[9] Verma S. Pharmacology review of NDA 21-356 for Tenofovir Disoproxil Fumarate (Gilead Sciences Inc.) 16-May-2001.

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12.0 APPENDICES

12.1 Merck Code of Conduct for Clinical Trials

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."

12.2 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 7.1.3.4 – Future Biomedical Research Samples will be used in various experiments to understand:

- The biology of how drugs/vaccines work
- Biomarkers responsible for how a drug/vaccine enters and is removed by the body
- Other pathways drugs/vaccines may interact with
- The biology of disease

The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor or those working for or with the Sponsor.

3. Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

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

b. Informed Consent

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

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

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of subject consent for Future Biomedical Research will be captured in the electronic Case Report Forms (eCRFs). Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen(s)

Collection of specimens for Future Biomedical Research will be performed as outlined in the 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 participant have been minimized and are described in the future biomedical research informed consent.

The Sponsor has developed strict security, policies and procedures to address 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/products/guidelines/efficacy/efficacy-single/article/definitions-for-genomic-biomarkers-pharmacogenomics-pharmacogenetics-genomic-data-and-sample-cod.html

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

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

12.3 Approximate Blood/Tissue Volumes Drawn/Collected by Trial Visit and by Sample Types

Panels A, B, and C	Pre-trial	Treatment Periods	Post-trial	Total Collections	mL Per Collection	Total mL/ Test
Laboratory safety tests[‡]	1	3	1	5	10.2	51
Blood for Planned Genetic Analysis		1		1	8.5	8.5
Blood for TFV assays and MK-8583		12		12	4	48
Blood for PBMC assay		10	1	11	16	176
Blood for HIV RNA, viral resistance[§]	1	10	1	12	12	144[%]
Total Blood Volume Per Subject[†]						427.5

† If additional pharmacokinetic/pharmacodynamic and/or safety analysis is necessary, up to 50 mL of additional blood may be obtained.

‡ Blood for Serum β -Human Chorionic Gonadotropin (β-hCG), HIV/Hepatitis screen, FSH, and CD4 cell count are included in the Laboratory Safety blood draw volume.

§ For all panels blood for HIV-1 viral RNA and viral resistance may be collected up to the post-trial visit if subjects do not start ART.

% An additional 4 mLs of blood may be drawn at 168 hours post-dose if ultra-deep sequencing is needed.

* Sample may be urine OR serum

12.4 Algorithm for Assessing Out-of-Range Laboratory Values

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

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

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

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

1. The subject may be excluded from the study;

2. The subject may be included in the study if the abnormal value(s) is not clinically significant (NCS) (the investigator must annotate the laboratory value "NCS" on the laboratory safety test source document).

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

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

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

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

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

12.5 List of Abbreviations Used in this Document

Abbreviation	Definition
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase *or* All Subjects as Treated
ART	Anti-retroviral therapy
AUC	Area Under the Curve
β-hCG	β-human chorionic gonadotropin
BMD	Bone Marrow Density
BMI	Body Mass Index
BP	Blood Pressure (Systolic or Diastolic)
Bpm	Beats per minute
BT	Body Temperature
CBC	Complete Blood Count
CI	Coordinating Investigator
CL/F	Apparent total clearance of drug from plasma after oral administration
C_{max}	Maximum Plasma Concentration
CRU	Clinical Research Unit
$C_{12\ hr}$	Plasma Concentration at 12 hours post-dose
CV	Cardiovascular
DBP	Diastolic Blood Pressure
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
ECI	Event of Clinical Interest
EDC	Electronic data capture
EM	Exposure Margin
EMA	European Medicines Agency
ERB	Ethics Review Board
FBR	Future Biomedical Research
FDAAA	Food and Drug Administration Amendments Act
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice

Abbreviation	Definition
GM	Geometric Mean
HIV	Human Immunodeficiency Virus
hr	Hour
HR	Heart Rate
IB	Investigator's Brochure
ICF	Informed Consent Forms
ICH	International Council on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
IUD	Intrauterine Device
LDA	Longitudinal data analysis
μM	Micromolar (10^{-6})
MRL	Merck Research Labs
NCS	Not Clinically Significant
NDA	New Drug Application
NOAEL	No Observed Adverse Event Level
NRTI	Nucleoside reverse transcriptase inhibitor
NNRTI	Non-nucleoside Reverse Transcriptase Inhibitor
PBMC	Peripheral blood mononuclear cell
PE	Physical exam
PK	Pharmacokinetics
PP	Per-Protocol
QP2	Department of Quantitative Pharmacology and Pharmacometrics
QRS	QRS Complex
QT	QT Interval
QTcF	Corrected QT Interval (Fridericia's)
RNA	Ribonucleic acid
RR	Respiratory Rate
RT	Reverse Transcriptase
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

Abbreviation	Definition
SBP	Systolic Blood Pressure
SOP	Standard Operating Procedure
TAF	Tenofovir alafenamide fumarate
TAM	Thymidine analog mutations
TDF	Tenofovir disoproxil fumarate
TFV-DP	Tenofovir diphosphate
TFV-MP	Tenofovir monophosphate
TFV PD	Tenofovir prodrug
T_{max}	Time to Maximum Concentration
$t_{1/2}$	Half life
VL	Viral load
VS	Vital Signs

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

13.2 Investigator

I agree to conduct this clinical trial in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol). I agree to conduct the trial in accordance with generally accepted standards of Good Clinical Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse events as defined in Section 7.0 – TRIAL PROCEDURES (Assessing and Recording Adverse Events). I also agree to handle all clinical supplies provided by the Sponsor and collect and handle all clinical specimens in accordance with the protocol. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol and the referenced Investigator's Brochure is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the trial is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure or access by third parties.

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	