Official Protocol Title:	A Single-Dose Clinical Trial to Study the Safety, Tolerability, Pharmacokinetics, and Anti-Retroviral Activity of MK-8504 Monotherapy in Anti-Retroviral Therapy (ART)-Naïve, HIV-1 Infected Patients
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TITLE:

A Single-Dose Clinical Trial to Study the Safety, Tolerability, Pharmacokinetics, and Anti-Retroviral Activity of MK-8504 Monotherapy in Anti-Retroviral Therapy (ART)-Naïve, HIV-1 Infected Patients

EudraCT NUMBER: 2017-000998-37

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SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
1.0 2.1 4.2.3.3 6.0 7.1.4.1 7.1.5.3 7.2	Trial Summary Trial Design Pharmacodynamic Endpoints Trial Flow Chart Withdrawal/Discontinuation Post-Trial Assessing and Recording Adverse Events	Changed the last safety follow-up visit from 21 days to 25 days.	Extends the safety follow-up period from 21 days to 25 days after last study drug administration to ensure the safety follow-up fully covers the intracellular concentration washout of MK-8504.
5.1.2	Subject Inclusion Criteria	Inclusion Criteria 2a: • Removed "(and/or have their partner use) two (2)"; • Changed "the post-trial visit" to "30 days following cessation of treatment"	Extends the use of acceptable contraceptive method by subjects to one full menstrual cycle following cessation of study drug treatment.
5.2.1.2	Dose Modification (Escalation/Titration/Other)	Changed "may" to "must" in the following sentence: "Pharmacokinetic and pharmacodynamic data must be included in the dose escalation decisions."	Ensures that pharmacokinetic (PK) and pharmacodynamic (PD) data will be included in dose escalation decisions between panels.

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
5.7.3.1	Contraception	• Updated to include only birth control methods that can achieve a failure rate of less than 1% per year when used consistently and correctly. Clarifies that hormonal contraceptives are not allowed. • Changed "2 weeks after administration of the last dose of trial drug in the last treatment period" to "30 days following cessation of treatment" in the 2nd sentence of the first paragraph.	Updated to include only highly effective birth control methods; extends the use of acceptable contraceptive method by subjects to one full menstrual cycle following cessation of study drug treatment.
5.11	Clinical Criteria for Early Trial Termination	• Changed enrollment stopping language Criterion (1) from: "1. Two (2) subjects per panel report severe adverse events with a potential causal relationship to study drug." to: "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." • Changed description of procedures following stopping of enrollment from: "If one or more of the above conditions are met, enrollment will be halted and all available safety data will be reviewed prior to making a decision about terminating the study."	Updated to modify specific criteria for stopping enrollment and dosing and to incorporate detailed procedures for subsequent safety review.

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
		to: "If the circumstances outlined in (1) or (2) or (3) above occur, enrollment and dosing will be halted and an internal safety review will be conducted, and the Sponsor will notify the competent authority where required of a halt to enrollment. Following the internal safety review, if the Sponsor deems it appropriate to restart enrollment and dosing, if required the Sponsor will submit a notification to the competent authority prior to restart. If approved, enrollment and dosing may restart at that time. If the circumstances outlined in (4) occur, enrollment and dosing will be halted and all available safety data will be reviewed to inform a decision about whether the study should continue."	
6 8.2.2	Trial Flow Chart Analysis Endpoints	Changed PK collection timepoints from 336 hr and 504 hr to 384 hr and 600 hr respectively.	Adjusts the final two PK timepoints due to the modification of the last safety follow-up visit from 21 days to 25 days after last study drug administration.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number(s)	Section Title(s)	Description of Change(s)	Rationale
Various sections	Various sections	Correcting minor punctuation, grammar	Typographical changes

1.0 TRIAL SUMMARY

Abbreviated Title	MK-8504 Single Dose Study in HIV-1 Infected Patients
Sponsor Product Identifiers	MK-8504
Trial Phase	Phase Ib
Clinical Indication	Treatment of HIV-1 Infection
Trial Type	Interventional
Type of control	No treatment control
Route of administration	Oral
Trial Blinding	Unblinded Open-label
Treatment Groups	Up to four panels (Panel A, B, C and D) of 6 subjects each will receive a single dose of MK-8504.
Number of trial subjects	Approximately 18- 24 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 seven weeks from the time the subject signs the Informed Consent Form (ICF) through the final contact. After a screening phase of approximately four weeks, each subject will be receiving assigned treatment for one day. After the end of treatment each subject will be followed for 25 days, or longer if ART is not initiated.

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-8504 monotherapy in ART-naïve, HIV-1 infected subjects. The primary study endpoints are the safety and tolerability of MK-8504 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 four panels of 6 subjects each will be enrolled in a sequential manner. In each panel, subjects will receive a single dose of MK-8504. Subjects in Panel A will receive a single oral dose of MK-8504 100 mg. The exact dose administered in Panels B through D will be selected following review of all available safety, PK and viral dynamic data from previous single and multiple dose administrations of MK-8504; the dose will not exceed 240 mg. There will be a break of at least 35 days between dosing of panels to allow for review of PK and viral dynamic data to inform dose selection in the following panel. All doses of study drug will be administered following at least an 8-hour fast.

At a designated time following administration of study drug, subjects will be encouraged to initiate an ART regimen that does not contain a tenofovir (TFV) prodrug (PD). The ART regimen chosen should not contain a TFV PD because of the possibility of unknown emergent mutations following dosing of MK-8504, a TFV PD, that may not be immediately known but that may impact efficacy of other TFV PDs. Subjects enrolled in this study are recommended to begin treatment with ART before MK-8504-related TFV-DP levels fall below the predicted efficacy target. The initiation and timing of follow-on ART initiation is ultimately a decision of the patient in consultation with the Investigator/physician, but should not be prior to 168 hours post-dose. Sponsor recommendation on timing of ART initiation will be contingent on the dose to be tested and will be communicated to the investigator in an official memo. The duration of suppressive ART is recommended to be ~30 days, or 5 half-lives. The Sponsor will not provide this therapy. The initiation of follow-on ART is not a requirement for participation in the study.

Based on the long half-life of the active moiety TFV-DP, changes in viral load (VL) may be assessed through 25 days for subjects who do not initiate follow-on ART. Subjects choosing to forgo follow-on ART may also be asked if they wish to continue to participate in observational monitoring of VL beyond 25 days.

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-8504 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.

All Panels A - D	~ Day -28 to -1	Day 1	Days 2 - 25
	Screening procedures	Dosing/ Safety monitoring/ Plasma & PBMC Blood Draws/ Viral Load Analysis	Safety monitoring/ Plasma & PBMC Blood Draws/ Viral Load Analysis
	Pre-trial Visit	**Day 1**	**Day 2** **Day 25 Post-trial Visit**

Figure 1 Trial Design Diagram

Table 1 Dose Plan

Panel	Dose[a]			
Panel A[b]	100 mg			
Panel B[b]		≤240 mg		
Panel C[b]			≤ 240 mg	
Panel D (optional)[b,c]				≤240 mg

[a] The exact dose administered in Panels B – D will be selected following review of all available safety, PK, and viral dynamic data and will not exceed the maximum dose previously administered to healthy subjects in single or multiple dose administration. At least 35 days will separate the administration of doses between panels.
[b] In each panel, 6 subjects will receive a single dose of MK-8504.
[c] A decision to enroll Panel D will be made upon completion of Panels A - C and review of the safety, PK and viral PD data in these panels.

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

1) **Objective:** To evaluate the antiretroviral activity of MK-8504 in HIV-1 infected subjects relative to historical subjects receiving placebo.

   Hypothesis: At a dose that is sufficiently safe and generally well tolerated, MK-8504 has superior antiretroviral activity compared to placebo, as measured by change from baseline in plasma HIV-1 RNA (log10 copies/mL) at 168 hours postdose. That is, the true mean difference in the plasma HIV-1 RNA reduction from baseline between MK-8504 and placebo is at least 0.5 log10 copies/mL.

2) **Objective:** To evaluate the safety and tolerability of MK-8504 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 peripheral blood mononuclear cells (PBMC) after administration of single oral doses of MK-8504 to HIV-1 infected subjects.

   Hypothesis: The true geometric mean (GM) in TFV-DP PBMC C168hr is ≥0.1µM 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-8504 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-8504 to HIV-1 infected subjects.

3) **Objective**: To obtain the single dose plasma PK profile of tenofovir and to determine the PK parameter values (including AUC0-last, AUC0-inf, Tmax, Cmax, and apparent terminal t1/2) after administration of MK-8504 to HIV-1 infected subjects.

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

3.3 Exploratory Objectives

1) **Objective:** To evaluate the relationship between dose and antiretroviral activity of MK-8504.

2) **Objective**: To quantify PBMC levels of tenofovir and 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) for detailed background information on MK-8504.

4.1.1 Pharmaceutical and Therapeutic Background

As HIV-1 treatments have improved and permitted patients to live a near-normal lifespan, HIV-1 has shifted from being an acute disease to being a chronic, manageable condition. As the duration of anti-retroviral (ARV) therapy increases in chronically infected individuals, there is 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 decrease treatment fatigue, improving long-term adherence to lifelong ARV therapy. An improved, highly-potent NRTI with superior tolerability and ease of administration would be a valuable addition to the HIV-1 armamentarium.

MK-8504 is a novel potent PD of TFV. TFV and belongs to a class of HIV antiretrovirals (ARVs) known as nucleotide reverse transcriptase inhibitors (NRTIs). After being taken up by cells, TFV is converted to tenofovir-monophosphate (TFV-MP) by adenosine monophosphate kinase, and then to the active antiviral tenofovir-diphosphate (TFV-DP) by 5'-nucleoside diphosphate kinase. TFV-DP inhibits HIV DNA (deoxyribonucleic acid) synthesis by competing with dATP (deoxyadenosine triphosphate), for incorporation into the complementary DNA (cDNA) strand by HIV reverse transcriptase. Following incorporation, the presence of TFV-DP leads to premature termination of the cDNA strand, as the lack of a 3'-hydroxyl group prevents linkage of the next base. While TFV demonstrates favorable intracellular effects due to its metabolism to the active moiety TFV-DP, plasma TFV levels have been associated with chronic adverse clinical events including renal and bone toxicity. Thus, ideally TFV PD therapy would optimize intracellular TFV-DP levels while minimizing plasma TFV levels.

Currently, there are two TFV prodrugs (PDs) approved for HIV treatment. Tenofovir disoproxil fumarate (TDF) is the first generation TFV PD. 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) [2, 3] and mild decreases in bone marrow density (BMD) [4], (approximate 2% loss in BMD in the spine and hip) in treated patients due to associated high levels of TFV in circulation. Tenofovir alafenamide fumarate (TAF), a second generation TFV PD, leads to a lower level of circulating TFV, thus lowering the incidence of renal and bone toxicities.

Other currently marketed NRTIs include lamivudine, emtricitabine, abacavir, didanosine, stavudine, and zidovudine. The current preferred recommendation for the first-line treatment of HIV infection in treatment-naïve patients calls for 3 agents and always includes 2 NRTI agents in combination with either an integrase strand transfer inhibitor, a protease inhibitor, or a non-nucleoside reverse transcriptase inhibitor. While these currently approved NRTIs represent a cornerstone of modern ARV therapy, there are significant class-associated toxicities including loss of bone mineral density, new or worsening renal impairment, severe lactic acidosis, and serious hypersensitivity reactions. Tolerability issues and the burden of complicated treatment regimens are among the most common reasons for lack of adherence and subsequent viral failure. Therefore, a need exists for new NRTIs like MK-8504, that possess an improved safety and tolerability profile as well as properties that could simplify drug administration, such as less frequent dosing and the feasibility to be utilized in single tablet fixed–dose regimens.

4.1.2 Completed Clinical Trial

MK-8504 Protocol 001 was a 2-part, double-blind, randomized, placebo-controlled, single-rising-dose study in healthy male and female (non-childbearing potential) subjects. Overall, single oral doses of MK-8504 up to 120 mg were generally well tolerated in healthy adult males and females. No SAEs, events of clinical interest (ECIs), or deaths were reported. A total of 25 subjects enrolled in the trial. One subject discontinued due to a non-drug related AE of depression after receiving placebo. 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.

Following oral administration, MK-8504 is rapidly absorbed (Tmax ~ 0.5h) and displays a biphasic elimination profile with a t1/2 of ~ 8h at high doses. Due to the short t1/2, no plasma accumulation is expected. Following oral administration, MK-8504 is taken up into PBMCs, metabolized into TFV and subsequently phosphorylated to form TFV-DP. TFV-DP only leaves the cells in the form of TFV. Plasma TFV therefore has a delayed Cmax (Tmax in the range of 1to 4h) and larger AUC when compared to the PD MK-8504 because it is formed by multiple metabolic processes following MK-8504 administration. Plasma TFV has a t1/2 in the range of ~29 to 38 h. PBMC TFV-DP has a Tmax in a range of 12 to 24 h and displays a biphasic elimination profile which is only observed at high doses (likely due to the sensitivity of the analytical method). The calculation of the t1/2 considering the last phase provides a t1/2 of ~ 96 to 165 h, which supports a QW regimen. Considering the PBMC target C168h, an accumulation ratio of ~ 1.3 to 1.5 is expected for a QW regimen. Food lowered peak and

extent of exposure of plasma MK-8504 and TFV but did not decrease the exposure of PBMC TFV-DP. Therefore MK-8504 may be dosed without regard to food.

Detailed safety and pharmacokinetic data from Protocol 001 can be found in the Investigator Brochure (IB).

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

This study will assess the short-term antiretroviral activity of MK-8504 monotherapy, and data from this study will aid dose selection in future HIV-1 patient studies. The goals of this study will be achieved by enrolling a minimum number of subjects using the shortest treatment duration possible. 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) [1] to set a baseline standard for MK-8504-sensitivity to the viral variants present in each patient. 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. The study objectives conform to the EMA guideline describing appropriate clinical development for antitretroviral agents as monotherapy and in combination with established therapy (Guideline on the Clinical Development of Medicinal Products for the Treatment of HIV Infection).

4.2.2 Rationale for Dose Selection/Regimen

The doses tested in this study will evaluate the effectiveness of MK-8504 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-8504 will be administered, risk of resistant strain emergence is minimal. In Panels A - D, the single dose safety, tolerability, PK, and antiretroviral PD of MK-8504 will be explored at doses projected to fall within the clinical dose range. In Protocol 001 (PN001, MK-8504 single rising dose study in healthy subjects), a C168h TFV-DP target of 100 nM was achieved at single oral doses of MK-8504 40 mg administered to healthy subjects. This target was based on the PBMC TFV-DP Ctrough at Day 7 of daily dosing of TDF 300 mg QD for one week, which led to a 0.5 log10 reduction in VL and thus serves as a benchmark for this trial. A single 100 mg dose of MK-8504 will be administered to subjects in Panel A. The exact doses administered to subjects in Panels B - D will be selected following review of all available safety, PK, and viral dynamic data. There will be a break of at least 35 days between dosing of panels to allow for review of PK and viral dynamic data to inform dose selection in the following panel. Because plasma MK-8504 and 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 Protocols

001 and 003 also will be used to aid in the selection of doses for the present study to ensure that plasma MK-8504 levels do not exceed the exposure cap. Additionally, safety data through at least 24 hours postdose 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 higher dose level will be based upon acceptable safety of MK-8504 at the previous dose. The doses selected for Panels B – D in this study will not exceed the maximum dose previously administered to healthy subjects in single or multiple dose administration.

Upon completion of Panels A - C and a thorough review of the safety, PK and viral pharmacodynamic data, a decision to enroll Panel D will be made. Depending on the results from Panels A - C, subjects enrolled in Panel D may receive a dose of MK-8504 specifically intended to be on the low end of the HIV-1 RNA reduction response curve. This data will be useful in exploring the PK and PD relationship of MK-8504. 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-8504 in preclinical and clinical testing to date, the need for a placebo control to minimize investigator and patient bias with respect to adverse experiences was deemed not necessary.

As this is a Phase I assessment of MK-8504 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.

4.2.2.1 Starting Dose for This Trial

The proposed starting dose in Panel A is 100 mg. Using single and multiple dose PK data, multiple doses of 100 mg MK-8504 QW at week 5 are predicted to generate similar PBMC TFV-DP Cmin levels as TAF 25 mg QD at day 10. A 100 mg dose of MK-8504 is anticipated to be associated with a VL reduction greater than TDF 300 mg QD and lower or similar to TAF 25 mg QD (approximate 1.2 log 10 VL reduction) at day 7.

Single oral doses up of MK-8504 up to 120 mg have been generally well tolerated when administered to healthy subjects. Protocol 003 is examining the safety and tolerability of single oral doses up to 240 mg in healthy subjects. The safety, MK-8504 plasma exposure, and margins to the NOAEL following the administration of a single dose of 160 mg in PN003 will be evaluated prior to proceeding with dosing of 100 mg of MK-8504 in this study.

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.

Rats were administered MK-8504 at 75, 150, and 400 mg/kg/day in 3-month GLP oral toxicity studies. Changes in clinical pathology parameters were limited to the 400 mg/kg/day dose group in the rodent and there were no test article-related clinical pathology findings at

≤150 mg/kg/day. At 400 mg/kg/day, urine calcium/urine creatinine ratios were very slightly to moderately increased over controls in females and males (1.8x and 8.6x respectively). Test article-related changes determined by exploratory micro-CT analysis were limited to decreased cortical area and cortical bone mineral content in the mid-diaphyseal region of the femur in male rats treated at 400 mg/kg/day. These changes had no histopathological correlate. There were very slight increases in creatinine that were associated with histomorphologic findings in the kidneys. Histopathological changes of MK-8504 were observed at ≥150 mg/kg/day. Degeneration of the renal tubular epithelium was observed in some males and females at 400 mg/kg/day. In addition, karyomegaly was observed in the renal tubular epithelium of some male rats at 150 and 400 mg/kg/day, and in some females at 400 mg/kg/day. Karyomegaly also has been observed in the rat kidney tubular epithelium after treatment with TDF and TAF, and is not considered to be an adverse change for these two TFV PDs. Additionally, karyomegaly associated with MK-8504 did not correlate with degeneration of the tubular epithelium as some animals presented with degeneration without any karyomegaly. For these reasons, observed karyomegaly was considered an adaptive change and not adverse. Based on changes in micro-CT and degeneration of the renal tubular epithelium, the NOAEL in the rodent was 150 mg/kg/day.

Dogs were administered MK-8504 at 3, 10, and 30 mg/kg/day in 3-month GLP oral toxicity studies. The 30 mg/kg/day dose group was terminated on Study Day 18 due to test article-related excessive body weight loss and decreased food consumption. Body weight losses of up to -30% compared to pretest were observed. Clinical signs observed in individual dogs at 30 mg/kg/day prior to early sacrifice consisted of decreased activity, decreased skin turgor, thin appearance, loss of appetite, and/or liquid/scant/no feces. Test article-related clinical pathology alterations were observed at 30 mg/kg/day (compared to individual pretest values) in Study Week 3 prior to unscheduled sacrifice. Compared to group mean pretest values, there were slightly increased activated partial thromboplastin time, slightly to moderately increased fibrinogen, moderately increased globulin, slightly decreased albumin, and moderately decreased albumin/globulin ratios. Test article-related serum biochemical changes at 30 mg/kg/day prior to unscheduled sacrifice consisted of moderately increased aspartate aminotransferase activities and very slightly increased alkaline phosphatase activities compared to group mean pretest values. The increase alkaline phosphatase activities may have been associated with the declining clinical condition of the animals.

Test article-related histomorphologic changes in the early terminated dogs at 30 mg/kg/day included cortical tubular degeneration and cortical tubular karyomegaly in the kidney, gastric mucosal degeneration mainly in the pyloric stomach, and mucosal degeneration in the small intestine (mainly in duodenum) and large intestine (mainly in colon). Other test article-related findings in early terminated animals at 30 mg/kg/day included mononuclear cell infiltration in the ciliary body in the eye, infiltration of histiocytes in the lymph node, increased myelopoiesis in the bone marrow, and decreased primary spongiosa in the bone. Additional changes were observed in early terminated dogs at 30 mg/kg/day that were considered secondary to the gastrointestinal mucosal injury (and the associated impairment of the intestinal barrier), stress-related, or a direct consequence of the body weight losses preceding the sacrifice of the animals.

There were no test article-related clinical pathology alterations in the dogs at ≤ 10 mg/kg/day after dosing approximately 3 months, including no test article-related changes in parathyroid

hormone/ionized calcium. At the end of the three-month dosing phase, test article-related cortical tubular karyomegaly was observed in the kidney at 10 mg/kg/day. Karyomegaly was not accompanied by any degenerative changes of affected cells or other structures in the affected kidney. In addition, there were no corresponding abnormalities in clinical pathology parameters. Therefore, karyomegaly was considered an adaptive change and was considered of minimal toxicological significance. In addition, there was increased numbers of vacuoles consistent with increased numbers of intra-mucosal leukocytes in the gastric pyloric mucosa of the stomach of dogs at 10 mg/day/day, as compared to concurrent control dogs and historical control dogs. As this change was not accompanied by any degenerative changes in gastric mucosa, it was considered an adaptive change and of minimal toxicological significance. Because there were no clinical pathology or toxicologically significant histomorphologic changes at ≤ 10 mg/kg/day, the NOAEL in the dog was 10 mg/kg/day.

The maximum dose selected for this study is based on the $AUC_{0\text{-}168hr}$ of MK-8504 at the NOAEL in the more sensitive species. Comparing the predicted $AUC_{0\text{-}168hr}$ at the NOAEL of the dog (12.32 µM·hr at 10 mg/kg/day) to the $AUC_{0\text{-}168hr}$ at the NOAEL of the rat (18.2 µM·hr at 150 mg/kg/day), the dog represents the more sensitive species. Therefore, the maximum allowable exposure is limited to the AUC at the NOAEL of the dog, in this case 12.32 µM·hr.

Predicted plasma MK-8504 AUC0-168hr was evaluated with and without the assumption of linearity. Assuming linearity, the maximum dose of 240 mg projects an AUC0-168 hr of 11.2 µM hr (1.09x EM to the AUC associated with the NOAEL). Using calculations without the assumption of linearity, an AUC0-168hr of 16.1 µM·hr at 240 mg is obtained, which is equivalent to 0.76 x EM to AUC associated with the NOAEL.

Dose relationship and actual maximum dose of the compound to be administered in the study will be confirmed by single doses of MK-8504 ≥160 mg and ≤ 240 mg, administered to healthy subjects in Protocol 003 (PN003) Part I. This portion of PN003 will be completed prior to initiation of this study and will ensure that the exposure cap associated with the NOAEL is not exceeded. While plasma MK-8504 and TFV-DP PK data from healthy subjects are expected to be similar to that of HIV-1 infected subjects, the PK from each panel in this study will also be reviewed prior to dose selection at the next highest dose. There is no intent to study the maximum tolerated dose of MK-8504 in this study.

Dose escalation in this study will also be based on safety data from preceding doses. Prior to dose escalation, clinical safety data will be carefully reviewed to permit a decision on whether to continue dosing. The dose levels and interval between doses may be adjusted based on the safety, PK data, or viral dynamic data from previous periods of the study.

4.2.2.3 Rationale for Dose Interval and Trial Design

MK-8504, a TFV PD, is not considered a compound with higher potential for risk of harm to volunteers according to the publication "Guideline on Strategies to Identify and Mitigate Risks for First-in-Human Clinical Trials with Investigational Medicinal Products" (European Medicine Agency guidance released July 2007) [5]. It is not a biological molecule, does not exhibit highly species-specific action, nor is it directed towards immune system targets. Furthermore, it acts via a well-established mechanism, inhibition of HIV-1 reverse

transcriptase, for which multiple marketed agents act similarly (TDF, lamivudine, emtricitabine, abacavir, didanosine, stavudine, and zidovudine).

The trial design includes up to four sequential panels of six subjects each. If MK-8504 is administered to more than one subject on the same day, it will be dosed in spaced time intervals must have a minimum of five to ten minutes between administering to individual subjects by the Phase I Clinical Research standards for compounds not considered to be of high risk.

There will be a minimum of 35 days between dosing of MK-8504 in consecutive panels to allow for assessment of safety data and potential AEs as well as evaluation of PK and viral dynamic data from previous panels to inform dose selection.

4.2.3 Rationale for Endpoints

4.2.3.1 Safety Endpoints

The safety and tolerability of MK-8504 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 trough concentration (Ctrough) of the active moiety (TFV-DP - same for all the PDs) in PBMCs, rather than to trough concentrations in plasma. Considering that this is a QW compound, C168h is expected to be associated with efficacy. Based on a combined meta-analysis of in vitro and published clinical exposure response data a PBMC TFV-DP Ctrough concentration 0.1 μM has been selected. This target is anticipated to achieve the minimal reduction in HIV viral load in a short duration monotherapy study that is predictive of longer term efficacy.

The pharmacokinetics of MK-8504 and its metabolites in HIV patients 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-8504 and TFV.

4.2.3.3 Pharmacodynamic Endpoints

A PD endpoint of a ≥ 0.5 $\log_{10}$ suppression of HIV-1 RNA from baseline on Day 7, relative to historical placebo data, will be used. This target is consistent with prior NRTI monotherapy studies and with past feedback from regulatory agencies that limit NRTI monotherapy studies to 7-10 days in duration.

Based on the long half-life of the active moiety TFV-DP, changes in viral load may be assessed through 25 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.

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 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
    b. 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

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

        NOTE: These procedures must be confirmed with medical records. In the absence of documentation, hysterectomy may be confirmed by pelvic exam or if necessary by ultrasound; oophorectomy may be confirmed by hormone levels, particularly FSH in the post-menopausal range, but tubal ligation subjects without records should be excluded. Information must be captured appropriately within the site's source documents

    d. Male subjects with female partner(s) of childbearing potential must agree to use a medically acceptable method of contraception (refer to Section 5.7.3.1) during the study and for 120 days after the last dose of trial drug. If their partner is pregnant, males must agree to use a condom and no additional method of contraception is required for the pregnant partner. If their partner is of child-bearing potential, males should use a condom with spermicide.

        NOTE: Spermicides alone are not an acceptable method of contraception. Their partner must additionally be using one of the following methods: hormonal contraception, intra-uterine device, diaphragm with spermicide, cervical cap with spermicide.
3. Have a Body Mass Index (BMI) $\leq$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 test(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 antiretroviral agent OR the following:

   ≤30 consecutive days of an investigational antiretroviral agent, excluding an NRTI,

   OR

   ≤60 consecutive days of combination ART not including an NRTI
10. Have not received an investigational agent or marketed ART within 30 days of study drug administration.
11. Be willing to receive no other ART for the duration of the treatment phase of this study.
12. 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.
13. Have the following laboratory values at screening, in accordance with the normal ranges of the clinical laboratory.
    a. INR ≤ 1.6
    b. Hemoglobin ≥ 10.0 g/ld.
    c. Absolute neutrophil count ≥ 1000/mm^3
    d. Platelet count ≥ 100,000/mm^3
    e. Direct bilirubin ≤ 1.0 mg/ld.
    f. Alkaline phosphatase ≤ 1.5 x upper limit of normal
    g. AST (SGOT) and ALT (SGPT) ≤ 2 x upper limit of normal
14. Agree to follow the smoking restrictions defined by the CRU.
15. Be willing to comply with the trial restrictions (see Section 5.7 for a complete summary of trial restrictions).

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).

   Exceptions: (1) Subjects with adequately treated non-melanomatous skin carcinoma or carcinoma in situ of the cervix may participate in the trial; (2) Subjects with other malignancies which have been successfully treated ≥10 years prior to the pretrial (screening) visit where, in the judgment of both the investigator and treating physician, appropriate follow-up has revealed no evidence of recurrence from the time of treatment through the time of the pretrial (screening) visit; or, (3) Subjects, who, in the opinion of the trial investigator, are highly unlikely to sustain a recurrence for the duration of the trial.
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. Patient 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.
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 Day 1 Dosing visit. The 4 week window will be derived from the date of the last trial medication and / or blood collection in a previous trial and/or AE related to trial drug to the Day 1 Dosing visit of the current 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.
14. Have 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 QTc interval ≥ 470 msec (for males) or ≥ 480 msec (for females).
16. Has a positive urine drug screen (except for cannabis) at screening and/or predose, rechecks are allowed.
17. 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).
18. 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 2.

Table 2 Trial Treatment

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Panel	Use
MK-8504	100 mg	1	Oral	Single Dose/Panel A	Experimental
MK-8504	≤240 mg	1	Oral	Single Dose/Panel B	Experimental
MK-8504	≤240 mg	1	Oral	Single Dose/Panel C	Experimental
MK-8504	≤240 mg	1	Oral	Single Dose/Panel D	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.

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

Dose escalation decisions will be based on key safety variables including: vital signs, 12-lead ECGs, laboratory safety tests, adverse events and review of viral dynamic data from the previous dose levels up to at least 24 hours (or longer depending on the compound). Pharmacokinetic and pharmacodynamic data must be included in the dose escalation decisions. See Background & Rationale - Section 4.0.

If, as judged by the Sponsor and investigator, the safety and tolerability data do not justify dose escalation, the dose will not be increased 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 parameters 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 higher dose level. No dose escalation will occur without the joint agreement of the investigator and the Sponsor.

5.2.2 Timing of Dose Administration

The trial treatment will 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.

MK-8504 capsules will be dosed per the instructions outlined in the Study Operations Manual.

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 3.

Table 3 Sample Allocation Schedule

Subjects	Panel A [a]	Panel B [a]	Panel C [a]	Panel D [a]
N=6	**MK-8504 100 mg**	**MK-8504 ≤240 mg**	**MK-8504 ≤240 mg**	**MK-8504 ≤240 mg**

[a] Subjects will participate in only one panel; each panel will consist of 6 subjects. Doses may be adjusted based upon data from the single ascending dose trial (PN003) and/or from previous panels within this trial.

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.

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

Subjects will fast from all food and drink, 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 timepoints indicated in the trial flowchart. Subjects will fast from all food and drink except water between meals and snacks. The caloric content and composition of meals will be the same for all subjects in a panel, within a

clinical site. After the 24-hour postdose 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-8504 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 trial drug, throughout the trial and until the post-trial visit.

On the dosing day (Day 1), subjects will also refrain from the consumption of all fruit juices 24 hours prior to and after study 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 and after trial drug administration. At all other times, caffeinated beverages or xanthine-containing products will be limited to no more than 6 units per day amounts (>6 units: 1 unit=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 may be enrolled. However, acceptable methods of contraception as described below must be used beginning at least 2 weeks prior to administration of the initial dose of trial drug, throughout the trial (including the washout intervals between treatment periods) and until at least 30 days following cessation of treatment.

Subjects should use birth control methods that can achieve a failure rate of less than 1% per year when used consistently and correctly and are considered as highly effective birth control methods. Such methods include:

- Intrauterine device (IUD)
- Bilateral tubal occlusion
- Vasectomised partner
- Sexual abstinence*

*Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse from the day of study medication initiation, throughout the study period, as well as up to 30 days after the last dose of trial therapy. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Hormonal contraceptives are not allowed as a method of birth control 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 120 days after the last dose of trial drug. If their partner is pregnant, males must agree to use a condom and no additional method of contraception is required for the pregnant partner. If their partner is of child-bearing potential, males should use a condom with spermicide. Spermicides alone are not an acceptable method of contraception. Their partner must additionally be using one of the following methods: hormonal contraception, intra-uterine device, diaphragm with spermicide, cervical cap with spermicide. Sperm donation is not permitted during the trial and for 120 days following the last dose of trial medication.

Additionally, use of condoms by male subjects and male partners of study subjects is advisable in view of the risk of transmission of HIV-1 infection, in particular, the risk of transmitting resistant strains.

5.7.3.2 Pregnancy Testing

Female subjects of childbearing potential will be tested for serum β-human chorionic gonadotropin (hCG) at pretrial, for urine and/or serum β-human chorionic gonadotropin (hCG) predose 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 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 of Treatment

Discontinuation of treatment does not represent withdrawal from the trial.

As certain data on clinical events beyond treatment discontinuation may be important to the study, they must be collected through the subject's last scheduled follow-up, even if the subject has discontinued treatment. Therefore, all subjects who discontinue trial treatment prior to completion of the treatment period will still continue to participate in the trial as specified in Section 6.0 - Trial Flow Chart and Section 7.1.4.1 – Withdrawal/Discontinuation, or if available, Protocol Clarification Letter.

Subjects may discontinue treatment at any time for any reason or be dropped from treatment at the discretion of the investigator should any untoward effect occur. In addition, a subject may be discontinued from treatment by the investigator or the Sponsor if treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at treatment discontinuation are provided in Section 7.1.4 – Other Procedures.

A subject must be discontinued from treatment but continue to be monitored in the trial for any of the following reasons:

- The subject or subject's legally acceptable representative requests to discontinue treatment.
- The subject has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the subject at unnecessary risk from continued administration of study drug.
- The subject has a confirmed positive serum pregnancy test.
- The subject has a positive urine drug screen (except cannabis) at predose and during the course of the trial.

For subjects who are discontinued from treatment but continue to be monitored in the trial, all visits and procedures, as outlined in the trial flowchart, should be completed.

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.

5.8.2 Withdrawal from the Trial

A subject must be withdrawn from the trial if the subject or subject's legally acceptable representative 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.

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

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 appraised 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 the maximum 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) severe but not life threatening adverse experiences or severe clinically significant laboratory abnormalities that are similar in nature OR one (1) severe and life threatening adverse experience laboratory abnormality OR participant death thought to be potentially related to the investigational product.

4. Two (2) or more of the enrolled subjects experience confirmed QTcF > 500 ms or QTcF change from baseline >60ms in a given panel.

If the circumstances outlined in (1) or (2) or (3) above occur, enrollment and dosing will be halted and an internal safety review will be conducted, and the Sponsor will notify the competent authority where required of a halt to enrollment. Following the internal safety review, if the Sponsor deems it appropriate to restart enrollment and dosing, if required the Sponsor will submit a notification to the competent authority prior to restart. If approved, enrollment and dosing may restart at that time. If the circumstances outlined in (4) occur, enrollment and dosing will be halted and all available safety data will be reviewed to inform a decision about whether the study should continue. 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.

6.0 TRIAL FLOW CHART

Panels A, B, C and D																			
	Scheduled Time																		
				Hours Postdose															
	Prestudy	Pre-dose	0	0.25	0.5	1	2	4	6	12	24	36	48	72	96	168	240	384	600/Post-trial[a]
Administrative Procedures																			
Informed Consent	X																		
Informed Consent for Future Biomedical Research[b]	X																		
Inclusion/Exclusion Criteria	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
Clinic Procedures/Assessments																			
Full Physical Examination	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) [f]	X	X				X					X					X			X
Orthostatic Vital Signs (heart rate, blood pressure) [f]	X	X				X					X					X			X
Vital Signs (respiratory rate, oral/tympanic temperature)	X	X				X					X					X			X
Standard Meals [g]								X----------			X								
MK-8504 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																	
HIV/Hepatitis Screen	X																		
Blood for Genetic Analysis[b]		X																	
Pharmacokinetic/Pharmacodynamic Evaluations																			
Blood for Plasma MK-8504 and TFV Assay [k]		X		X	X	X	X	X	X	X	X	X	X	X					

Panels A, B, C and D																			
	Scheduled Time																		
				Hours Postdose															
	Prestudy	Pre-dose	0	0.25	0.5	1	2	4	6	12	24	36	48	72	96	168	240	384	600/Post-trial[a]
Blood for MK-8504 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
CD-4 cell Count	X																		

a. The post-trial visit will occur approximately 25 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 25 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.
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, predose, on Day 1 (or with the next scheduled blood draw) or at a later date.
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 and laboratory assessments may be performed within 24 hour prior to dosing.
e. Pre-dose ECG will be performed within 3 hours prior to study drug administration and will consist of 3 repeat measurements with at least 1 minute intervals between ECG measurements. Recording may commence after the subject has remained in a semi-recumbent position for at least 10 minutes. (See Section 7.1.2 for additional details).
f. Pre-dose semi-recumbent HR and BP will be duplicate 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 2 minutes and then orthostatic HR and BP will be obtained. 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 postdose 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 at predose.
i. For postmenopausal woman only.
j. Additional urine drug screen tests may be performed at the discretion of the PI.
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 and viral resistance may be collected up to the post-trial visit if subjects do not start ART. Blood for HIV-1 viral RNA and viral resistance will only be collected if subjects do not initiate follow-on ART for timepoints >168 hours.
n. For blood collection at 240, 384 and 600 hour timepoints, a window of +/- 24 hrs is acceptable. The 600 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.

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 or each subject's legally acceptable representative 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 or by the subject's legally acceptable representative'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 or his/her legally acceptable representative 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 or by the subject's legally acceptable representative'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 ($BMI=kg/m^2$).

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 as necessary.

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 Fredericia.

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

Prior to dose, ECGs will be obtained in triplicate at least 1-2 minutes apart within 3 hours prior to dosing MK-8504. The average of these measurements will be used as the baseline. Post-dose ECG measurements will be single measurements.

If a subject demonstrates an increase in QTcF interval ≥60 msec compared with mean predose 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 postdose 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, the ECG will repeated twice within 5 min. If these 3 ECGS confirmed high values, 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 QTc 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

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 signs will include heart rate (HR) and blood pressure (BP). The correct size of the blood pressure cuff and the correct positioning on the patients'' 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 same for all subjects at each site.

Prior to dosing, HR and BP will be duplicate measurements obtained at least 1-2 minutes apart within 3 hrs of dosing MK-8504. The average of these measurements will be used as the baseline. 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 postdose except to stand for the measurement of orthostatic vital signs or other trial related procedure. Predose 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 to be drawn/collected over the course of the trial (from pre-trial to post-trial visits), including approximate blood 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 4.

Table 4 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Follicle Stimulating Hormone (FSH) in WONCBP*
Hemoglobin	Alkaline phosphatase	Glucose	Urine/Serum β-human chorionic gonadotropin (β-hCG)
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 INR* CD4+ T cell count*
	Bicarbonate	Microscopic exam, if abnormal results are noted	Urine/Blood Drug Screen
	Calcium		
	Chloride		
	Creatinine		
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Total Bilirubin		
	Direct Bilirubin		
	Total protein		
	Blood Urea Nitrogen		
*Only collected at prestudy. Urine pregnancy test may be performed at predose.			

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 pharmacokinetics/pharmacodynamics will be collaboratively determined by the Department of Quantitative Pharmacology and Pharmacometrics (QP2) and the appropriate department within Early-Stage Development, (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 pharmacodynamic markers.

7.1.3.2.1 Blood Collection for Plasma TFV and MK-8504

Sample collection, storage and shipment instructions for plasma MK-8504 and TFV samples will be provided in a Study Specific Procedure Manual.

7.1.3.2.2 Blood Collection for PBMC

Sample collection, processing, storage and shipment instructions for PBMC samples will be provided in a Study Specific Procedure Manual.

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 Section 12.4.

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
- Leftover main study PBMC stored for future research
- Leftover main study plasma from MK-8504 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 25 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 25 days after the last dose of trial drug is given, the investigator should perform a follow-up phone call 25 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 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 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 sign, ECG and centrifuge equipment
- Equipment and specified supplies necessary for PBMC sample collection and processing:
  - o Equipment such as, but not limited to, centrifuges with refrigeration function, microscope, and pipettes
  - o 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 randomization, potential subjects will be evaluated to determine whether 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 randomization if there are Day -1 procedures planned per protocol.

7.1.5.2 Treatment Period

7.1.5.2.1 Predose Procedures (All Panels)

Prior to each treatment, the clinical and laboratory safety parameters 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 escalation 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 predose 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 postdose procedures are listed in the Study Flow Chart, Section 6.0 of this protocol.

Subjects will be administered a single dose of MK-8504 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 25 days after the last dose of trial drug for the post-trial visit. If the post-trial visit occurs less than 25 days after the last dose of trial drug, a subsequent follow-up phone call should be made at 25 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-8504 PBMC are the critical procedures.

At any post-dose timepoint, the blood samples for viral load and MK-8504 PBMC needs to be collected as close to the exact timepoint 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 5 below

Table 5 PK (Blood)/PBMC Collection Windows

PK collection	PK Collection Window
0-1 hr	5 min
> 1 hr	15 min
> 24 hr-168 hr	2 hrs
> 168 hr	24 hr

- Predose standard safety evaluations: vital signs & ECG 3 hrs; laboratory safety tests & physical exam 24 hrs prior to dosing

- Postdose standard safety evaluations (vital signs, ECG, laboratory safety tests, physical exam):
    - until 24h postdose may be obtained within 30 min of the targeted sampling time
    - >24h - 168 h postdose may be obtained within 2 hours of the targeted sampling time
    - >168h postdose may be obtained within 24 hours of the targeted sampling time

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

This is a Phase I assessment of MK-8504 in humans, and the pharmacokinetic, pharmacodynamic 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
- Interchange of doses between panels
- 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 postdose pharmacokinetic/pharmacodynamic sample collection

The pharmacokinetic/pharmacodynamic sampling scheme currently outlined in the protocol may be modified during the trial based on newly available pharmacokinetic or pharmacodynamic 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.

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.

- Additional blood or urine samples may be taken for laboratory safety tests or other tests, such as measurement for pharmacokinetic analysis. Any additional urine collections may include continuous, total collections, if necessary. Up to an additional 50 mL of blood may be drawn for safety, pharmacokinetic, and/or pharmacodynamic 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).
- Additional non-invasive, painless procedures that are already specified in this protocol may be done based on newly available safety, tolerability, pharmacokinetic or pharmacodynamic data.
- Addition of pharmacokinetic pauses in each Panel of the 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.

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 25 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

The subject has taken (accidentally or intentionally) any drug administered as part of the protocol and exceeding the dose as prescribed by the protocol. It is up to the investigator or the reporting physician to decide whether a dose is to be considered an overdose, in consultation with the Sponsor.

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

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

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

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 25 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 another important medical event.

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

- Is a cancer;
- Is associated with an overdose.

Refer to Table 6 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 25 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 25 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 6. The investigator's assessment of causality is required for each adverse event. Refer to Table 6 for instructions in evaluating adverse events.

Table 6 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 24 hours to meet certain local requirements); **or**	
	Is associated with an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical 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-8504 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 pharmacodynamics hypothesis.

Power

If the true SD of the log10 reduction from baseline in plasma HIV-RNA at 168 hours postdose is 0.4 (0.5), 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-8504 and placebo is at least 0.5 log10 copies/mL, if the true mean log10 reduction is at least 1.0 log10 (1.1 log10) with N=6 subjects in a Panel.

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 Pharmacodynamics Hypothesis: At a dose that is sufficiently safe and generally well tolerated, MK-8504 has superior antiretroviral activity compared to placebo, as measured by change from baseline in plasma HIV-1 RNA (log10 copies/mL) at 168 hours postdose. That is, the true mean difference in the plasma HIV-1 RNA reduction from baseline between MK-8504 and placebo is at least 0.5 log10 copies/mL.

Secondary Pharmacokinetics Hypothesis: The true geometric mean (GM) in TFV-DP PBMC C168hr is $\geq$ 0.1µM 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 all types of adverse experiences, in addition to laboratory safety tests, ECGs, and vital signs.

Pharmacodynamics: The primary pharmacodynamics variables in this study include plasma HIV-1 RNA pre-dose and 4, 12, 24, 48, 72, 96, 168, 240, 384 and 600 hours post-dose.

Secondary Endpoints

The secondary endpoint in this study include: TFV-DP PBMC AUC0-168hr, Cmax, Tmax, C168hr and t1/2; MK-8504 plasma AUC0-last, AUC0-inf, AUC0-168hr, Tmax, Cmax, t1/2, CL/F and Vz/F; tenofovir plasma AUC0-last, AUC0-inf, Tmax, Cmax and t1/2.

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 (AST): 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 set of data generated by the subset of subjects who comply with the protocol sufficiently to ensure that these data will be likely to exhibit the effects of treatment, according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements and absence of major protocol deviations. Major protocol deviations will be identified to the extent possible prior to unblinding by individuals responsible for data collection/compliance, and its analysis and interpretation. Any 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 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-8504 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 pharmacodynamics 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 timepoints.

Secondary (Pharmacokinetics):

Separately for each PK parameter, individual values of TFV-DP in PBMC pharmacokinetic 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 square 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 ≥ 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 pharmacokinetics hypothesis.

MK-8504 plasma AUC0-last, AUC0-inf, Cmax, CL/F and Vz/F, 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 treatment and time, 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).

Secondary and Exploratory (Pharmacokinetic/Pharmacodynamic)

The pharmacokinetic-pharmacodynamic and dose-pharmacodynamic association of MK-8504 will be explored. Graphs to visualize the association of the reduction in log10 plasma HIV-1 RNA levels with TFV-DP in PBMC 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 antiretroviral suppression after single dose MK-8504 will be evaluated with individual plots across time.

For PBMC levels of tenofovir and tenofovir monophosphate, 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 pharmacodynamic hypothesis, 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 postdose is 0.4 (0.5), 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-8504 and placebo is at least 0.5 log10 copies/mL, if the true mean log10 reduction is at least 1.0 log10 (1.1 log10) with N=6 subjects in a Panel.

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 7.

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 7 Product Descriptions

Product Name & Potency	Dosage Form
MK-8504 10 mg	Capsules
MK-8504 100 mg	Capsules

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 doses dispensed by an unblinded pharmacist 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

1. Yeni P, Hammer S, et al. Treatment for Adult HIV Infection 2004 Recommendations of the International AIDS Society-USA Panel. JAMA, July 14 2004; Vol 292, No. 2: 251-265
2. Cooper RD, Wiebe N, Smith N, Keiser P, Naicker S, Tonelli M. Systematic review and meta-analysis: renal safety of tenofovir disoproxil fumarate in HIV-infected patients. Clin Infect Dis. 2010;51:496-505
3. Horberg M, Tang B, TownerW, et al. Impact of tenofovir on renal function in HIV-infected, antiretroviral-naive patients. J Acquir Immune Defic Syndr. 2010;53:62-69.
4. Bolland, M., Grey, A. and Reid, I. (2015) Skeletal health in adults with HIV infection. Lancet Diabetes Endocrinol 3: 63–74.
5. European Medicines Agency. Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products. Committee for Medicinal Products for human use (CHMP) Ref.EMEA/CHMP/SWP/28367/07

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

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

12. Questions

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

13. References

1. National Cancer Institute: http://www.cancer.gov/dictionary/?searchTxt=biomarker
2. International Conference on Harmonization: DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES - E15; http://www.ich.org/LOB/media/MEDIA3383.pdf
3. Industry Pharmacogenomics Working Group. Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/
4. Industry Pharmacogenomics Working Group. Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

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

Panels A, B, C and D	Pre-trial	Treatment Periods	Post-trial	Total Collections	mL Per Collection	Total mL/ Test
Laboratory safety tests[‡]	1	3	1	5	12.5	62.5
Serum β -Human Chorionic Gonadotropin (β-hCG)	1		1	2	5	10
HIV/Hepatitis Screen	1			1	3.5	3.5
Blood for Planned Genetic Analysis		1		1	8.5	8.5
Blood for TFV assays and MK-8504		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 Male Subject[†]						442..5
Total Blood Volume Per Female Subject[†]						452.5

[†] If additional pharmacokinetic/pharmacodynamic and/or safety analysis is necessary, up to 50 mL of additional blood may be obtained.
[‡] Blood for 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 postdose if ultra-deep sequencing is needed.

12.4 PAXgene ™ Blood for DNA Analysis Specimen Collection Procedure

PAXgene™ BLOOD FOR DNA ANALYSIS

SPECIMEN COLLECTION PROCEDURE

SPECIMEN COLLECTION NOTES* SCP124-00

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

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

Supplies and Materials (per patient, per time point)

Provided to the Institution

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

Precautions

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

Required Equipment

- Freezer for -20 ^{O}C for PAXgene™ tube storage (For storage exceptions/monthly batch shipments).

Labeling

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

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

Preparation

1. Ensure the patient has signed the appropriate IRB/ERC-approved consent for genetic specimen collection prior to collecting the specimen.
2. Ensure the PAXgene™ Blood DNA collection tubes are at room temperature prior to collecting blood.

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

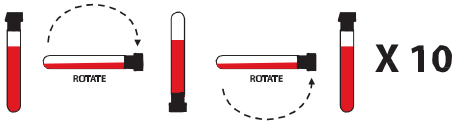
3. The PAXgene™ Blood DNA collection tubes should not be the first tubes drawn during venipuncture. **It should be the last tube collected**.

Specimen Collection

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

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

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



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

Specimen Processing & Handling

1. Within 5-10 minutes of the blood draw, place tubes upright in a wire or hard plastic rack at ambient temperature (18-25 °C).
2. Tubes **must be shipped within 24 hrs of collection** to the laboratory at ambient temperature.

Storage Exceptions (special circumstances only)

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

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

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

Packaging and Shipping

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

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

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

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

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

***NOTE:** For storage exceptions where ambient shipment was not possible, and specimens were frozen (-20 °C), always ship frozen specimens on DRY ICE.

Shipping Address:

BioProcessing Solutions Alliance
Attn: CommStaff
Nelson Biological Laboratories
604 Allison Road, C120
Piscataway, NJ 08854

Phone: PPD

Fax: PPD

Email: PPD

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	