Official Protocol Title:	A Single-Dose Clinical Trial to Study the Safety, Tolerability, Pharmacokinetics, and Anti-Retroviral Activity of MK-4250 Monotherapy in Anti-Retroviral Therapy (ART)-Naive, HIV-1 Infected Subjects
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TITLE:

A Single-Dose Clinical Trial to Study the Safety, Tolerability, Pharmacokinetics, and Anti-Retroviral Activity of MK-4250 Monotherapy in Anti-Retroviral Therapy (ART)-Naive, HIV-1 Infected Subjects

EudraCT NUMBER: 2017-001784-21

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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; 2.0; 4.2.2; 5.2; 5.2.1.2; 5.3; 6.0	Trial Summary; Trial Design; Rationale for Dose Selection/Regimen/Modification; Trial Treatment; Dose Modification, Randomization; Trial Flow Chart	Removed Panel C (≤600 mg) and added Panels E and F, resulting in an overall increase in sample size from a maximum of 24 to 30 subjects and an increase in duration of the overall trial. See Table 1 for planned treatment/doses to be evaluated in Panels E and F.	Variability was noted in the emerging PK data from the panels of HIV-infected subjects. Changes are being made to the trial design to allow further evaluation of doses administered in various fed states. Dosing with food will increase exposure and enable exploration of dose- and exposure-response relationship of MK-4250.
5.7.1.1	Diet	Added information regarding timing and contents of the dietary treatments to be evaluated in Panels E and F (low fat and moderate fat breakfast).	Provided operational details in order to execute amended trial design.
7.1.5.5	Trial Design/Dosing/Procedures Modifications Permitted within Protocol Parameters	Added flexibility to modify composition of the meal taken with the trial drug based on newly available data	This flexibility will support objective of amended study design as described in the previous rationale section.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
4.1.1	Pharmaceutical and Therapeutic Background	Updated and streamlined section by moving data from pre-clinical studies to Section 4.1.2.	These changes were made to organize presentation of data.
4.1.2	Pre-clinical Studies	Provided additional pre-clinical data not previously available at the time of the original protocol.	Updates were made to this section to inform the investigator of newly available data.
4.1.3	Completed and Ongoing Clinical Trials	Updated clinical program status with inclusion of new information from completed clinical trials (Protocols 001 and 003) as well as data from ongoing trial (Protocol 002)	These changes were made to provide the background information to support the amended trial design and to further inform the investigator of newly available data.
4.2.2	Rationale for Dose Selection/Regimen/Modification	Per PCLs #2, 4, 5, and 6: Clarified recommendations for timing of ART initiation for Panels A and B (10 days post dose for Panel A [N=6] and Panel B [last 3 subjects enrolled, N=3], and 8 days post dose for Panel B [first 3 subjects enrolled, N=3])	For Panel A: correction of typographical error to align with Section 2.0 Trial Design For Panel B: recommendation based on observed PK results from ongoing trial (as described in Section 4.1.3), and implemented to ensure full antiviral efficacy until initiation of ART

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
5.1.3	Subject Exclusion Criteria	Per PCL #1, clarified criterion #5 to note that subjects with rare hereditary galactose intolerance, lactose deficiency and glucose-galactose malabsorption are considered to have a significant intolerability to the lactose in the study drug and should be excluded from this trial.	The study drug contains a small amount of lactose.
6.0	Trial Flow Chart	Per PCL #2, clarified footnote l, that a portion of the blood collected for viral resistance testing will be sent to Labor Berlin for extraction of proviral DNA (sample to be frozen and analyzed for the presence of VR mutations only if standard Sanger sequencing cannot be performed because plasma VL is too low at this time point).	As there is potential for emergence of InSTI resistance during monotherapy with an InSTI, it is important to confirm at the end of the period of monotherapy that a subject does not have VR mutation which would preclude selection of a given long-term InSTI-containing regimen.

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
6.0	Trial Flow Chart	Per PCL #4, added footnote n: plasma for the MK-4250 PK assay will be collected at 72 hrs post dose (instead of the 240 hours post dose time point) for the first 3 subjects enrolled in Panel B.	For these 3 subjects in Panel B who initiated ART 8 days post dose, the 240 hr time point cannot be used to characterize t1/2 (as MK-4250 PK may be altered by ART). Based on PK from Panel A, inclusion of a 72 hr PK sample is considered important to ensure the t1/2 is well characterized.
7.1.2	Clinical Procedures/Assessments	Per PCL #3, under the subsection on 12-Lead ECG, clarified with additional text in parenthesis: "If the QTc interval is ≥500 msec ***(confirmed upon recheck and manual measurement),*** the Sponsor should be notified and the ECGs should be reviewed by a cardiologist."	Clarified the steps to be taken before notifying Sponsor of a QTc interval ≥500 msec.
7.1.3.4	Future Biomedical Research Samples	Added leftover plasma samples collected for HIV RNA and viral resistance assays to be obtained as part of Future Biomedical Research	Retaining these non-acidified samples for future biomedical research may further inform on PK differences observed between HIV infected and uninfected subjects.

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
12.3	Approximate Blood/Tissue Volumes Drawn/Collected by Trial Visit and by Sample Types	Per PCL #2, ~2.7 mL of the 16 mL total blood volume originally noted for the pre-trial visit for HIV RNA and viral resistance testing is shifted to the timepoint prior to the start of ART. This additional blood collected at the later timepoint during the Treatment Period will be used for potential proviral DNA testing. Total blood volume for the study remains at ~ 208 mL.	The 16 mL of blood specified for the viral load and viral resistance testing at the pre-trial visit is in excess of what is required. This excess blood volume will instead be collected at the end of study treatment (i.e. no later than study Day 11) for additional viral resistance testing which may be necessary if a subject's post-study therapy viral load is too low for standard Sanger sequencing.

1.0 TRIAL SUMMARY

Abbreviated Title	MK-4250 Single Dose Trial in HIV-1 Infected Subjects
Sponsor Product Identifiers	MK-4250
Trial 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 5 panels (Panels A, B, D, E and F) of 6 subjects each will receive a single dose of MK-4250. Panel C has been removed per this amendment. Panel A: 150 mg Panel B: 600 mg Panel D: 900 mg Panel E: ≤ 900 mg, with low fat meal Panel F: ≤ 900 mg, with moderate fat meal
Number of trial subjects	Approximately 30 subjects will be enrolled.
Estimated duration of trial	The Sponsor estimates that the trial will require approximately 10 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 6 weeks from the time the subject signs the Informed Consent Form (ICF) through the final contact. After a screening phase of 4 weeks, each subject will receive a single dose of study medication. After dosing, each subject will be followed for 14 days.

2.0 TRIAL DESIGN

2.1 Trial Design

This is an open-label, single dose, multiple panel trial to evaluate the safety, tolerability, anti-retroviral activity, and pharmacokinetics of MK-4250 monotherapy in antiretroviral therapy (ART)-naïve, HIV-1 infected subjects. The primary study endpoints are the safety and tolerability of MK-4250 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 5 panels of 6 subjects each (Panels A, B, D, E and F) will be enrolled. Panels A through D will be conducted in a sequential manner such that enrollment in Panel B will commence when 6 subjects have been enrolled in Panel A, and so forth. Panel E/F will commence after Panel D, but Panels E and F may be conducted in either order or in parallel. Subjects will receive a single dose of 150 mg of the MK-4250 tablet formulation in Panel A

and 600 mg of the MK-4250 tablet formulation in Panel B. The assumption is made that PK in HIV-infected subjects will be comparable to that observed previously in healthy subjects (Protocol 001). However, PK data from Panel A will be reviewed prior to Panel B to confirm this assumption. The dose in Panel B may be adjusted downward based on review of safety and viral dynamic data out to 7-days post-dose from Panel A in addition to the review of PK data. The exact dose of the tablet formulation of MK-4250 to be administered in subsequent panels will be selected following the review of the safety and viral dynamic data out to 7 days post-dose from the preceding panels, but will not exceed 900 mg.

Based on in vitro potency of MK-4250 and modeling of clinical data from other InSTIs, it is anticipated that the doses tested in Panels A and B will result in similar and maximal efficacy (i.e., approximately -1.4 log10 copies/mL or greater). The intent of additional panels will be to further inform the full range of exposure/viral load reduction and safety in HIV-infected subjects.

For Panels A through D, there will be sufficient time between panels to allow for review of all available safety data and viral load data (up to 7 days post-dose) to inform dose selection in the following panel. In addition, there will be sufficient time between Panels A and B to review Panel A PK data prior to Panel B. All doses of study drug (Panels A through D) will be administered following at least an 8-hour fast. The doses of study drug in Panel E and F will be administered following a breakfast. Panels E and F may be conducted in either order or in parallel and will not begin until all available safety data (up to 7 days post-dose) and viral load data (up to 10 days post-dose) have been reviewed from Panel D. In addition, prior to dosing Panel F at 900 mg (tablet) with a moderate fat meal, safety data (through 168 hrs following the first dose) will be reviewed from the first 8 subjects dosed in Protocol 005 with 1000 mg MK-4250 or placebo (randomized in a 3:1 ratio) following a high fat meal.

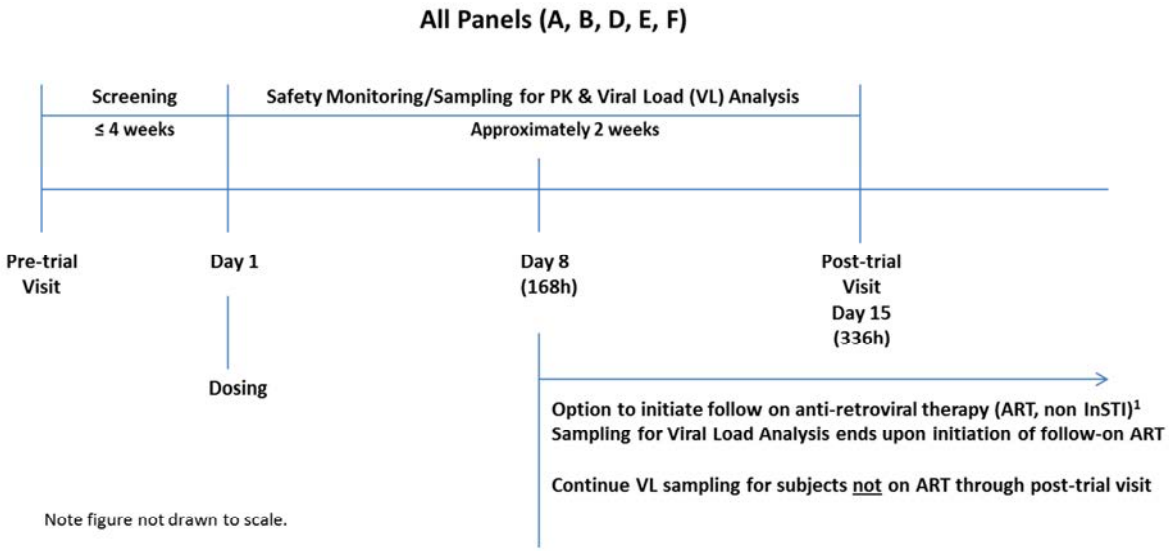
Following the treatment portion of the study, subjects will be encouraged to initiate an ART regimen which does not contain an integrase strand transfer inhibitor (InSTI). Follow-on ART should be administered for at least two weeks (14 days), which corresponds to more than 5 half-lives of MK-4250. The initiation of follow-on ART is not a requirement for participation in the study and is ultimately a decision of the subject in consultation with the primary investigator (PI) and his/her physician. The exact timing of initiation of ART relative to MK-4250 dosing will be dependent on the dose administered in each panel, but will not exceed 10 days post dose. For subjects who do not initiate follow-on ART, changes in viral load (VL) may be assessed through the post-study visit.

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-4250 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.



[1] Exact timing of ART initiation will depend on the MK-4250 dose administered in each panel, but will be no later than 10 days post dose (i.e., Day 11). Follow-on ART should be administered for at least 14 days.
Note: For Panels A and D and the last 3 subjects in Panel B, ART was recommended to start 10 days post dose (i.e. Day 11)
For the first 3 subjects in Panel B, ART was recommended to start at 8 days post dose (i.e., Day 9).

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Figure 1 Trial Design Diagram

Table 1 MK-4250 Dosing Scheme

Panel[a]	Treatment[b]			
Panel A	150 mg, fasted			
Panel B		600 mg, fasted		
Panel D[c]			900 mg, fasted	
Panel E				≤900 mg, with a low fat meal
Panel F				≤900 mg, with a moderate fat meal

[a] In each panel, 6 subjects will receive a single dose of MK-4250. Panel C was removed per this amendment.
[b] The decision to proceed to the next panel and selection of the dose in Panels B and D will be made following review of safety and viral load data out to Day 8 (i.e., 7 days post-dose) from the preceding panel; Panel E and F may be conducted in either order or in parallel but will not begin until the available safety data (up to 7 days postdose) and viral load (up to 10 days postdose) have been reviewed from Panel D. PK data from Panel A will be reviewed prior to proceeding to Panel B to evaluate whether HIV-infected subjects have PK comparable to healthy subjects. In addition, prior to dosing Panel F at 900 mg (tablet) with a moderate fat meal, safety data (through 168 hrs following the first dose) will be reviewed from the first 8 subjects dosed in Protocol 005 with 1000 mg MK-4250 or placebo following a high fat meal.
[c] A decision to enroll Panel D will be made upon completion of Panels A - B and review of the safety 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-4250 in ART-naïve, HIV-1 infected subjects relative to historical subjects receiving placebo.

   Hypothesis: At a dose that is sufficiently safe and generally well tolerated, MK-4250 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-4250 and placebo is ≥1.4 log10 copies/mL.

2) **Objective:** To evaluate the safety and tolerability of MK-4250 in HIV-1 infected subjects.

3.2 Secondary Objective(s) & Hypothesis(es)

1) **Objective**: To characterize the single dose plasma PK profile of MK-4250 and to determine the PK parameter values (including AUC0-last, AUC0-inf, AUC0-168hr, Tmax, Cmax, C168hr, apparent terminal t1/2, CL/F and Vz/F) after single dose administration of MK-4250 to HIV-1 infected subjects.

Hypothesis: The true geometric mean C168hr is > 1250 nM following single dose administration of MK-4250 for at least one dose level of MK-4250.

3.3 Exploratory Objectives

1) **Objective**: To evaluate the pharmacokinetic-pharmacodynamic association of MK-4250 with viral load reduction.
2) **Objective:** To evaluate the relationship between dose and antiretroviral activity of MK-4250.
3) **Objective:** To explore the relationship between genetic variation and response to the treatment 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-4250. A list of nonclinical studies conducted with MK-4250 is presented in the IB. Results from additional pre-clinical studies and the clinical trial currently being conducted with MK-4250 are summarized in the sections below.

4.1.1 Pharmaceutical and Therapeutic Background

Human immunodeficiency virus 1 (HIV-1; referred to hereafter as HIV) is a lentivirus, a subgroup of retroviruses, that causes HIV infection. Without treatment, average survival time after infection with HIV is estimated to be 9 to 11 years. HIV infects CD4+ T cells, macrophages, and dendritic cells, leading to destruction of these critical immune system cells. When CD4+ T cell numbers decline below a critical level, cell-mediated immunity is lost, and the body becomes progressively more susceptible to opportunistic infections. If left untreated, over time HIV infection will nearly always lead to acquired immunodeficiency syndrome (AIDS), a progressive failure of the immune system that is fatal.

While a number of effective and well-tolerated antiretroviral (ARV) agents are available, infection with HIV remains a global health challenge. Medical need for novel ARVs remains high. In particular, there is need for development of compounds possessing better safety and tolerability profiles, better resistance profiles, and properties that simplify drug administration (e.g., fixed dose combinations or extended dosing intervals).

Current HIV treatment guidelines support triple therapy administration of 2 nucleoside reverse transcriptase inhibitors (NRTIs) together with an anchor agent of a different class including InSTIs [1]. InSTIs have become the primary anchor agent of choice in combination HIV ART because of their high antiviral potency, rapid HIV RNA declines, favorable tolerability and safety profiles, and absence of significant drug-drug interactions [1, 2]. Currently approved InSTIs include raltegravir [3], elvitegravir [4] and dolutegravir [5]. Cabotegravir is in Phase 3 development as a longer acting parenteral agent [6,7]. While InSTIs are widely used to treat HIV-1, recent data suggest that there is some evidence of

resistance emergence particularly for raltegravir and elvitegravir, although as a class InSTIs have a high barrier to resistance [2,8]. Additionally, recent reports suggest a high rate (~16%) of discontinuation of dolutegravir due to intolerance [2,9]. There still exists a need for novel InSTIs that possess, simultaneously, an improved barrier to resistance, an improved tolerability profile and, ideally, simplified drug administration.

MK-4250 is a novel, potent, small molecule HIV-1 InSTI. MK-4250 exhibits a high genetic barrier to resistance. The retroviral enzyme integrase is required to catalyze the insertion of viral DNA into the genome of the host cell. Integrase assembles on the ends of the viral DNA and catalyzes two sequential reactions, specifically 3' endonucleolytic processing of the viral DNA ends and strand transfer or joining of the viral and cellular DNAs.

MK-4250 is a low clearance compound with a ~47 hr half-life in humans (see Section 4.1.3), supporting potential extended duration dosing intervals. It is 99.8% bound to proteins in human plasma. Based on *in vitro* metabolism data and studies in rats and dogs, elimination of MK-4250 in humans is anticipated to occur in part by secretion into the GI tract, potentially via P-glycoprotein (P-gp) and/or other transporters, and by metabolism via glucuronidation. Oxidation is expected to be a minor pathway. No circulating metabolites were detected in rat and dog. Only trace amounts of MK-4250 were detected in urine of rats and dogs. Since MK-4250 is a substrate of P-gp and uridine 5'-diphospho-glucuronosyltransferases (UGTs), there is a potential for MK-4250 PK to be affected by strong UGT and/or P-gp inhibitors or inducers. MK-4250 is not a potent reversible inhibitor of UGT1A1 and major CYP enzymes or a time-dependent inhibitor of CYP3A4. It is also not a potent inhibitor of OATP1B1 or P-gp transporters. MK-4250 has shown the potential to induce metabolic enzymes and/or transporters at high concentrations.

4.1.2 Pre-clinical Studies

In vitro experiments were conducted to determine binding of MK-4250 over the concentration range of 2 µM to 800 µM to proteins in rat, dog and human plasma. MK-4250 was highly bound to proteins in plasma from all species. The unbound fractions in rat, dog and human plasma were 0.0004, 0.003, and 0.002, respectively, at 20 µM MK-4250 and were similar at 2 µM MK-4250. The fraction unbound increased at MK-4250 concentrations that are above expected clinical concentration range: approximately two fold at 200 µM, and more significantly at 600 µM and 800 µM.

Additional Pre-clinical Background – Amendment 002-01

MK-4250 does not pose a risk of genotoxicity in clinical use. Target organ toxicity identified in repeat-dose studies was limited to the liver of dogs, with transient minimal to mild biliary ductule hyperplasia correlating with transient increases in ALT, ALP, and/or glutamate dehydrogenase (GLDH). The histomorphologic liver findings were only observed after 4 months (15 weeks) of dosing at the highest dose level tested in dogs, 400 mg/kg/day, and not after 9 months of dosing at the same dose level, indicating the transient nature of the findings. Based on the transient nature of the liver finding, it is considered non-adverse and the no observed adverse effect level (NOAEL) in dogs is set at 400 mg/kg/day (AUC0-168hr of 24710 µM•hr). The 9-month study supports that the findings from the 4-month study were minimal to mild and would not progress to become adverse.

Of note, in rats, there were no liver changes, and the high dose of 1000 mg/kg/day (AUC0-168hr of 40600 µM•hr) was the NOAEL. The changes in rats were limited to slight non-adverse vacuolation of epithelial cells in the nonglandular mucosa and inflammation of the glandular mucosa of the stomach. Stomach findings were limited to rat and were not observed in the repeat dog toxicity studies at equivalent or greater exposures and dose levels. These changes did not progress in severity in the 3-month toxicity study compared to the 2-week study, did not impact the general health status of the animals, and are therefore of low toxicological relevance and non-adverse.

There was no evidence of MK-4250-related maternal or developmental toxicity in a preliminary oral embryo-fetal development study in pregnant rats given doses up to 1000 mg/kg/day once daily from GD 6 through 20. The definitive embryo-fetal developmental studies have not been conducted. Inclusion of women of childbearing potential in clinical trials should be in accordance with the study protocol and applicable regulatory guidances (e.g., ICH M3(R2): Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals).

4.1.3 Completed and Ongoing Clinical Trials

4.1.3.1 Additional Background – Amendment 002-01

MK-4250 has been evaluated as an oral formulation in two clinical studies in healthy subjects to date: a completed single ascending dose study (Protocol 001) and a clinically complete multiple ascending once weekly dose (up to 4 weeks) and midazolam drug drug interaction study (Protocol 003). The effect of a high fat meal on MK-4250 PK was evaluated in Protocol 001, and the effects of a low fat and moderate fat meal were evaluated in Protocol 003.

Plasma PK data following oral administration indicate that MK-4250 is absorbed with a Tmax of approximately 4 hours; plasma concentrations decline with terminal half-life (t1/2) of about 45 hours. Pharmacokinetic parameter values increase less than dose proportionally as bioavailability decreases with dose. Following multiple once weekly administration, there was minimal accumulation and no change in t1/2. Exposures up to 4800 µM·hr were attained with single dose administration (1600 mg) and 3270 µM·hr with multiple dose administration (900 mg QWk x 4). A high fat meal increased the AUC0-168hr, Cmax and C168hr of MK-4250 by 1.8-fold, 2.1-fold and 1.6-fold, respectively. A moderate fat meal increased the AUC0-168hr, Cmax and C168hr of MK-4250 by 1.8-fold, 1.8-fold and 1.6-fold, respectively. A low fat meal increased the AUC0-168hr, Cmax and C168hr of MK-4250 by 1.6-fold, 1.8-fold and 1.5-fold, respectively. While a high fat and moderate fat meal delayed median Tmax by 2 hours, a low fat meal had no effect on Tmax.

Single doses up to 1200 mg tablet and 1600 mg capsule and multiple doses up to 900 mg tablet QW for 4 weeks of MK-4250 have been generally well tolerated. There were no treatment emergent serious adverse events (SAE) and other than one participant who discontinued due to a flu-like illness (considered not drug related), there have been no discontinuations due to an adverse event (AE). All AEs were mild or moderate in intensity (except for the participant with a flu-like illness which was severe) and generally transient in nature. No consistent dose-related trends in AEs, electrocardiograms (ECGs), vital signs, or

laboratory parameter values have been observed. Some safety data remain blinded and it is unknown if participants received active drug or placebo.

Protocol 001

This was a randomized, alternating panel, placebo-controlled, double-blind trial evaluating the safety and pharmacokinetics of single rising doses of MK-4250 in 40 healthy male subjects. Single oral doses of 20 to 1600 mg capsule formulation and 100 to 1200 mg tablet formulation were administered. Food effect was also evaluated at 400 mg for both formulations. MK-4250 was generally well tolerated, the most common AEs (≥2 incidents) reported by subjects administered MK-4250 were headache, abdominal discomfort, and dizziness. All AEs were mild or moderate in intensity and transient in nature. There were no SAEs and no discontinuations due to an AE. There were no clinically meaningful changes in ECGs, vital signs and laboratory safety evaluations.

Protocol 002 (Panels A and B)

As of 21-Jun-2018, 12 HIV-infected male subjects have been administered (fasted) single oral doses of MK-4250 (6 received 150 mg in Panel A and 6 received 600 mg in Panel B). Panel A and B are clinically complete. Preliminary PK, viral load and safety data are provided. Exposure of MK-4250 in HIV-infected subjects has been, on average, lower than that observed in uninfected subjects (Table 2). In addition, PK variability has been higher with some subjects exhibiting PK comparable to uninfected subjects while others exhibit diminished absorption and/or shorter t1/2 resulting in lower than anticipated C168hr.

Following the 150 mg dose, the mean (range) change from baseline in viral load was -1.56 (-1.21 to -1.89) log10 copies/mL. Following the 600 mg dose, the mean (range) change from baseline in viral load at 7 days post-dose was -1.76 (-1.06, -2.27) log10 copies/mL. This change is comparable to the mean change observed in monotherapy studies following 7 days of dosing for other InSTIs (see Section 4.2.2).

Table 2 Preliminary Geometric Mean (% Coefficient of Variation) MK-4250 Plasma Pharmacokinetics Following Single Dose Administration of MK-4250 to HIV-1 Infected Subjects (N=6 per Dose)

Dose (mg)	Cmax (µM)	Tmax[1] (hr)	t½ (hr)	AUC0-∞ (µM·hr)	AUC0-last (µM·hr)	AUC0-168 (µM·hr)	C168 (µM)	CL_F (L/hr)	V_F (L)
150	16.6 (46.7)	4.00 (1.00 - 4.00)	35.9 (22.9)	785 (54.6)	774 (54)	751 (52.6)	0.558 (117)	0.456 (54.6)	23.6 (45.1)
600	37.6 (26)	4.00 (4.00 - 6.00)	38.5 (31.9)	2120 (18.4)	2040 (17.1)	1980 (16.7)	2.2 (57.4)	0.676 (18.4)	37.6 (23.5)

[1]Median (Min-Max)

Single doses of MK-4250 were generally well tolerated. Eight of the 12 subjects (75%) reported one or more AEs. There were no SAEs. The most common AEs were headache (n=4, 33%), diarrhea (n=4, 33%), and nasopharyngitis (n=3, 25%). All AEs were mild or moderate in intensity and generally transient in nature. No subjects have discontinued due to an AE. Three subjects reported a total of 5 AEs considered by the investigator to be drug

related (headache [n=2], diarrhea [n=1], nausea [n=1], and vomiting [n=1]) There has been no evidence of dose-related abnormalities in ECGs, vital signs and laboratory safety evaluations.

Protocol 003

Protocol 003, is a two part, clinically complete trial. Part 1 is a randomized, placebo-controlled, double-blind multiple ascending dose and midazolam drug interaction, 4-panel trial in 32 healthy adult males and females of non-childbearing potential. Subjects were dosed 100, 300 and 600 mg MK-4250 (or placebo) once weekly for 3 weeks and 900 mg (or placebo) once weekly for 4 weeks. In the 900 mg panel, midazolam was administered prior to the initial dose and concomitantly with the final dose of MK-4250/placebo. Part 2 is a randomized, 3-period food effect assessment. Nine subjects received 400 mg MK-4250 fasted, with a low fat breakfast, and with a moderate fat breakfast.

Preliminary safety data indicate that multiple doses of MK-4250 and single doses with and without food have been generally well-tolerated. Thirty-two of the 41 subjects (78%) reported one or more treatment emergent AEs. There were no treatment associated SAEs (one subject was in a car collision during the screening period and sustained neurological trauma that was an SAE; this subject was not randomized). The most common AEs were headache (n=16, 31%), nasopharyngitis (n=9, 22%), oropharyngeal pain (n=8, 20%), diarrhea (n=4, 10%), and cough (n=4, 10%). One subject in the 600 mg panel was discontinued due to flu-like symptoms which were deemed not drug related. All AEs were generally mild or moderate in intensity and transient in nature. Twenty subjects (49%) reported one or more AEs considered by the investigator to be drug related. The most common were headache, diarrhea, gastrointestinal discomfort, abdominal cramps, and fatigue. It is not known whether these subjects received MK-4250 or placebo. There was no evidence of dose-related abnormalities in ECGs, vital signs and laboratory safety evaluations.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

The primary objective of this study is to assess the single-dose activity of MK-4250 in ART-naïve HIV-1 infected subjects. This study will also assess the relationship between dose, exposure, and short-term in vivo antiretroviral activity of MK-4250. Data from this study will aid dose selection in future HIV-infected subject studies in which MK-4250 will be administered in combination with other antiretroviral agents. The study objectives conform to the EMA guideline describing appropriate clinical development for antiretroviral agents as monotherapy and in combination with established therapy [10]. As described in this Guideline, antiretroviral agents are typically administered in combination to minimize the risk for resistance; therefore, demonstration of antiviral activity in subjects for a new antiviral should be limited to treatment naïve subjects without advanced disease.

Although resistance to InSTIs remains rare [2,8], resistance mutations to all approved InSTIs have been identified. Therefore, prior to enrollment, subjects will be screened for the presence of InSTI resistance mutations to set a baseline standard for MK-4250 sensitivity to

the viral variants present in each subject. Subjects identified with an InSTI mutation (e.g., E92Q, N55H, Q148K, Q148R and Y143R) will be excluded from the study.

4.2.2 Rationale for Dose Selection/Regimen/Modification

Rationale for Doses – 002-00

A single dose of MK-4250, given its long t1/2, is expected to exhibit antiviral activity for at least 7 to 10 days, equivalent to other short-term monotherapy studies with InSTIs administered daily or twice daily for up to 10 days. Evaluation of these other InSTI monotherapy studies suggests that a robust change in VL relative to baseline will be observed a week after initiating InSTI dosing [11]. Limiting monotherapy of InSTIs to ten days is thought to adequately minimize the risk of development of resistance.

In order to inform on the dose selection for future HIV-infected subject studies, it is important that the doses selected in this study provide insight into the exposure-response relationship between MK-4250 and VL. That is, doses will be selected which are anticipated to result in maximal efficacy (at least -1.4 log10 copies/ml a week after initiating InSTI dosing, see Table 3) as well as those which achieve VL reduction which is close to half of the maximal drop (approximately -0.7 log 10 copies/ml a week after initiating InSTI dosing).

Table 3 Summary of Results from InSTI Short Duration Monotherapy Studies (Approved Dosing Regimen for these drugs is listed for reference)

Drug	N	Dose	Approved Dose	Day	Log10 Change from Baseline Viral Load (copies/mL)
Dolutegravir[14]	10	50 mg QD	50 mg QD	7	-2.0
Elvitegravir[15,16]	6	400 mg BID	150 mg QD, boosted*	7	-1.4
Raltegravir[13]	6	400 mg BID	400 mg BID	8	-1.6
Mean					**-1.7**

*Boosted dose has somewhat higher Ctrough compared to the 400 mg BID monotherapy dose [14, 15, 16,13].

Doses in this study will be selected with the intent that Panel A and B doses both demonstrate maximal VL reduction. These two doses are expected to bracket the doses which will be studied in longer duration combination therapy trials. In addition, a lower dose is planned which is intended to also demonstrate VL reduction, but will be selected to target a viral load reduction approximately half of that achieved with the top doses. This dose will provide important information regarding the lower bound of MK-4250 levels associated with antiviral efficacy. Finally, a fourth dose level is included in the event that the first three dose levels do not sufficiently support the objective of evaluating the submaximal through maximal range of the exposure-response relationship and may range from lower than the Panel A, B and C doses to higher.

Trough concentration (Ctrough) has been found to be the most reliable PK correlate of HIV VL suppression [11, 12]. Xu et al. conducted a model-based meta-analysis of viral load and PK data from other InSTI monotherapy studies [11]. The results of this analysis predict that a Ctrough of 2.15-fold above the inflection point (IP) in a proprietary in vitro assay of wild type antiviral potency is associated with >95% maximum viral load suppression in monotherapy. Approved doses of raltegravir (400 mg twice daily [BID]), dolutegravir (50 mg once daily [QD]) and elvitegravir (150 mg BID) achieved a Ctrough/IP close to or greater than this value. Raltegravir dosed at 1200 mg QD has recently been shown to be non-inferior to raltegravir 400 mg BID in Phase 3 with a Ctrough/IP of 1.3. For MK-4250, the lower end of the anticipated therapeutic range is a C168hr ≥ 1.25 uM which is 2.5 times the IP for MK-4250. Based on the analysis of Xu et al. and the 1200 mg BID raltegravir Phase 3 results, this Ctrough target is anticipated to result in full efficacy in both monotherapy and in long term combination therapy studies.

Panel A Dose Selection

The proposed dose for Panel A is 150 mg of the tablet formulation which has an anticipated C168hr ≥1.25 µM.

A single 200 mg dose of MK-4250 tablet formulation had an AUC0-168hr of ~1250 µM*hr in healthy subjects. This is ~9-fold below the 11620 uM*hr AUC0-168hr exposure achieved in the 4 month dog safety study at the NOAEL.

Panel B Dose Selection

The planned dose to be studied in Panel B will be 600 mg of the MK-4250 tablet formulation and will explore safety, tolerability, pharmacokinetics, and the potential for viral pharmacodynamic differentiation at higher exposures to confirm that the efficacy at 7 days post dose (i.e. Day 8) in Panel A was indeed maximal. Based on mean VL change from baseline a week following initiating dosing in InSTI monotherapy studies, the maximal decrease in VL should be ≥1.4 log10 copies/mL (see Table 3).

Although it is anticipated that MK-4250 PK in HIV-infected subjects will be similar to that in healthy subjects in Protocol 001, to confirm this assumption, the decision to proceed to Panel B at the 600 mg tablet dose will be made following review of PK data from Panel A. In addition, safety and VL data out to 7 days post dose (i.e. Day 8) from Panel A will also be reviewed prior to proceeding to Panel B.

The highest dose tested in Protocol 001 was 1600 mg of the capsule formulation with AUC0-168hr and Cmax of 4270 µM*hr and 64.9 µM, respectively. This is 2.7-fold and 1.7-fold below the AUC0-168hr and Cmax at the NOAEL observed in the 4-month oral toxicity study in dogs. Table 4 shows projected exposures for the planned doses in this study. The projected exposure is scaled from the 200 mg tablet dose in Protocol 001, which assumes that bioavailability remains constant at ~40%. Based on preclinical data, bioavailability at doses above 200 mg may be anticipated to either stay constant or decrease, but would not be expected to increase; therefore, actual PK at higher tablet doses may be lower than that predicted in Table 4. The 600 mg dose of tablet is projected to result in exposures slightly below those observed at the 1600 mg dose of capsule in Protocol 001. This dose was shown to be well tolerated. Furthermore, the 600 mg dose is anticipated to be 3.1-fold below the NOAEL. See Section 4.1.1 for further information on the NOAEL.

Table 4 Exposure Predictions for the Tablet Doses

Single Dose (mg)	MK-4250						
	AUC0-168			Cmax		C168	
	Observed (uM·hr)[a]	Predicted (uM·hr)[b]	Exposure Margin[c]	Observed (uM)[a]	Predicted (uM)[b]	Observed (uM)[a]	Predicted (uM)[b,d]
100	967	--	--	16.3	--	1.2	--
200	1250	--	--	19.6	--	1.6	--
600	--	3800	3.1	--	60	--	4.8
900	--	5700	2.0	--	90	--	7.2

[a] Observed AUC0-168, Cmax, and C168 from Protocol 001
[b] Predicted AUC0-168, Cmax, and C168 is based on the assumption of linear dose proportionality relative to the 200 mg tablet geometric mean data.
[c] MK-4250 exposure margin was calculated based on MK-4250 NOAEL of 11620 µM*hr (AUC0-168hr) in dogs at 20 mg/kg/day from a 4-month safety study.
[d] The MK-4250 efficacy target is a C168 of 1.25 uM or greater based on an *in vitro* potency assay.

Panel C Dose Selection

The dose in Panel C will be selected following review of safety and VL data from at least 7 days post dose from the preceding panels (A and B) with the intent to achieve an average log reduction that is approximately half of the anticipated maximal reduction, or approximately -0.7 log10 copies/mL seven days after dosing (i.e. Day 8). The primary reason for targeting the lower end of the efficacy curve is to develop a dose- or exposure-response relationship for MK-4250 and viral load. Based on the analysis by Xu et al. [11], the Ctrough anticipated to result in a half-maximal viral load drop in monotherapy is ~0.15xIP. In a monotherapy study of raltegravir, a 100 mg BID dose (Cmin of ~0.5xIP) resulted in maximal efficacy through ~10 days of dosing [13]. While the exact dose in Panel C will be based on analysis of the PK data from Panel A, and safety and VL data from both Panels A and B, the raltegravir monotherapy data [13] and the Xu et al. analysis [11] suggest that the dose in Panel C may be as low as 10 mg (projected Cmin of ~0.3xIP).

Although doses lower than 100 mg of tablet were not tested in Protocol 001, bioavailability of both the capsule and tablet formulations are anticipated to be similar at doses ≤50 mg based on preclinical data. In addition, the oral bioavailability of a 50 mg dose of the capsule formulation was ~50%, comparable to the 100 mg dose of tablet formulation.

While the dose for Panel C is anticipated to be close to 10 mg, if data from Panel A and B suggest that a higher dose be studied (e.g., VL reduction with Panel A is less than in Panel B), the dose will not exceed 600 mg.

Panel D Dose Selection

The dose for Panel D will be selected once safety and VL data (from at least 7 days post dose) obtained from Panels A, B and C are reviewed. This dose will be selected to gain further clarity on the exposure-VL relationship and/or to explore the safety, PK and VL effects at higher doses of MK-4250. The dose for Panel D will not exceed 900 mg of tablet formulation. The dose will not be selected until safety and PK data are available from Protocol 001 at a tablet dose higher than that to be administered in Panel D.

For All Panels

After completion of the treatment phase of this study, subjects will be encouraged to initiate a non-InSTI containing ART regimen according to local guidelines. The timing of ART initiation is contingent on the doses administered and will be communicated in an official memo. Based on the results of the raltegravir monotherapy study, InSTI concentrations greater than ~0.5xIP would be anticipated to be associated with full antiviral efficacy out to 10 days of dosing [13]. At the Panel A dose of 150 mg, ART should be initiated 10 days following dosing. Concentrations are not anticipated to drop below 0.5xIP until more than 10 days post-dose; therefore, initiation of ART at Day 10 should minimize the risk of selection for resistant virus. The timing of initiation of ART for subsequent panels will be informed by the ultimate selected dose, but will not exceed 10 days post-dose, consistent with the EMA Guideline for HIV drugs [10]. Viral load data will continue to be collected in all Panels until initiation of ART or 14 days post-dose, whichever is earlier. The duration of suppressive ART should be at least 14 days, which is more than 5 half-lives of MK-4250. The Sponsor will not provide this therapy, nor will it be mandated for participation in the study.

Rationale for Doses – Amendment 002-01

As described in Section 4.1.3, exposure of MK-4250 in HIV-infected subjects was on average lower and more variable compared to healthy subjects. Although viral load reduction was achieved in both Panels A and B, the increased variability led to some subjects having C168hr well below the PK target. As viral load reduction and C168hr were generally correlated, a portion of subjects with lower C168hr also appeared to have sub-maximal virologic response. The results of Panel A and B support the omission of Panel C as submaximal viral load response was observed in some subjects and the conduct of Panel D at a dose of 900 mg, fasted. In addition, the protocol is being amended to include Panel E at a dose up to 900 mg with a low fat meal and Panel F at a dose up to 900 mg with a moderate fat meal. As MK-4250 exposures increase less than dose proportionally, dosing with food allows for further increases in exposure to further explore the dose- and exposure-response relationship of MK-4250. Additional PK and safety data are available and demonstrate doses up to 1200 mg to be generally well-tolerated, supporting conduct of Panel D at 900 mg.

Panel E Dose Selection

The dose for Panel E will be selected once safety and VL data (from at least 7 days post dose) obtained from Panel D have been reviewed. This dose will be selected to gain further clarity on the exposure-VL relationship and/or to explore the safety, PK and VL effects at higher exposures of MK-4250. The selected dose for Panel E will not exceed 900 mg of tablet formulation. This dose will be administered with a low fat meal in order to further boost exposures above those achieved with 900 mg, fasted. Table 5 shows the predicted PK parameter values for a 900 mg dose of MK-4250 with food in an HIV-infected population. These projections were made using a Population PK model including healthy subject data from Protocols 001 and 003 and HIV-infected subject data from Protocol 002 Panels A and B. The effect of a low fat meal is anticipated to be similar to that observed in uninfected subjects in Protocol 003. The projected AUC0-168hr in Panel E does not exceed that obtained following a single 1200 mg, fasted dose of MK-4250 shown to be generally well tolerated in Protocol 001.

Table 5 Observed Geometric Mean (%Coefficient of Variation) MK-4250 Plasma PK and for Population Pharmacokinetic Model Predicted 50th Percentile MK-4250 PK for Panels E and F

MK-4250 Dose and Population	AUC0-168hr (µM*hr)	Cmax (µM)	C168hr (µM)
1200 mg, Fasted Healthy Subjects (observed)	4110 (11.2)	77.9 (11.7)	4.7 (30.3)
900 mg, Fasted HIV-infected Subjects (simulated)	2480	59	2.2
900 mg, Low Fat Meal HIV-infected Subjects (simulated)	3970	94	3.4
900 mg, Moderate Fat Meal HIV-infected Subjects (simulated)	4470	106	3.9

Panel F Dose Selection

The dose for Panel F will be selected once safety and VL data (from at least 7 days post dose) obtained from Panel D have been reviewed. As with Panel E, this dose will be selected to gain further clarity on the exposure-VL relationship and/or to explore the safety, PK and VL effects at higher exposures of MK-4250. The selected dose for Panel F will not exceed 900 mg of tablet formulation. This dose will be administered with a moderate fat meal in order to further boost exposures above those achieved with 900 mg, fasted and with a low fat meal. As the projected AUC0-168hr in Panel F slightly exceeds that obtained following a single 1200 mg, fasted dose of MK-4250 in Protocol 001 (Table 5), Panel F will not be conducted until safety data through 168hrs post-dose are available from the first dose in the first 8 subjects of Protocol 005 (healthy subjects to receive 1000 mg MK-4250 or placebo with a high fat meal, randomized in a 3:1 ratio). If the results of Panel D or E support conduct of Panel F at a lower dose with or without food, Panel F may be conducted prior to availability of the described Protocol 005 data provided that the predicted exposures do not exceed those observed at the 1200 mg dose of tablet in Protocol 001.

For All Panels

After completion of the treatment phase of this study, subjects will be encouraged to initiate a non-InSTI containing ART regimen according to local guidelines. The timing of ART initiation is contingent on the doses administered and will be communicated in an official memo. Based on the results of the raltegravir monotherapy study, InSTI concentrations greater than ~0.5xIP would be anticipated to be associated with full antiviral efficacy out to 10 days of dosing [13]. As described in Section 4.1.3, ART was recommended to initiate at 10 days post-dose in Panel A (N=6) and for the latter 3 subjects enrolled in Panel B (N=3); ART was recommended to initiate at 8 days post dose for the first 3 subjects enrolled in Panel B (N=3). Based on PK and virologic results in Panels A and B, ART will be initiated at 10 days post-dose (ie, 240 hrs or Day 11) in Panels D, E and F. If a lower dose is selected for

Panels E and F, the timing of initiation of ART for will be informed by the ultimate selected dose, but will not exceed 10 days post-dose (i.e., 240 hrs or Day 11), consistent with the EMA Guideline for HIV drugs [10]. Viral load data will continue to be collected in all Panels until initiation of ART or 14 days post-dose, whichever is earlier. The duration of suppressive ART should be at least 14 days, which is more than 5 half-lives of MK-4250. The Sponsor will not provide this therapy, nor will it be mandated for participation in the study.

As this is a Phase I assessment of MK-4250 in humans, and the pharmacokinetic, pharmacodynamic 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 Rationale for the Use of Historical Placebo

The reduction in VL for each dose level will be compared to historical placebo data from clinical trials previously conducted by the Sponsor. Evaluation of VL data from other HIV monotherapy studies has indicated that results are consistent between trials and that on average, subjects receiving placebo do not exhibit a change from baseline that differs from the anticipated within-subject variability in VL.

Furthermore, given the overall favorable safety profile of MK-4250 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.

4.2.2.2 Starting Dose for This Trial

See Section 4.2.2 for the starting dose and related rationale.

4.2.2.3 Maximum Dose/Exposure for This Trial

See Section 4.2.2 for the maximum dose and associated rationale.

4.2.2.4 Rationale for Dose Interval and Trial Design

The trial design will consist of 5 panels. Each panel will consist of 6 subjects. Up to all 6 subjects in a given panel may be dosed on the same day, in spaced time intervals by Phase I Clinical Research standards for compounds not considered to be of high risk. The decision to escalate to the next dose panel will be made based on the viral load data, laboratory safety tests, vital signs and ECGs obtained up to 7 days after dosing. In addition, PK from Panel A will be reviewed prior to dosing of Panel B to assess whether PK in HIV-infected subjects are comparable to those observed in healthy subjects in Protocol 001. Dosing of consecutive panels will be spaced 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 on dose selection. Panel E and F may occur in parallel with each other or one may be conducted prior to the other. Neither Panel E nor F will be initiated until safety data and virologic data from Panel

D have been reviewed. In addition prior to dosing Panel F at 900 mg with a moderate fat meal, safety data (through 168 hrs following the first dose) will be reviewed from the first 8 subjects dosed in Protocol 005 (in which healthy subjects will receive once weekly doses of 1000 mg MK-4250 or placebo with a high fat meal.) If the results of Panel D or E support conduct of Panel F at a lower dose with or without food, Panel F may be conducted prior to availability of the described Protocol 005 data provided that the predicted exposures do not exceed those observed at the 1200 mg dose of tablet in Protocol 001.

4.2.3 Rationale for Endpoints

Rationale for the safety, pharmacokinetic, and pharmacodynamics endpoints, as well as the planned exploratory biomarker research and future biomedical research are presented in the following sections.

4.2.3.1 Safety Endpoints

As described in detail in the IB, the target organ/system toxicities observed in the 4-month dog (more sensitive species) study at the top dose (400 mg/kg/day) was minimal to mild hyperplasia of biliary ductules characterized by increased biliary epithelial cells in dogs accompanied by elevations to serum biochemistry tests (e.g., alanine aminotransferase [ALT], alkaline phosphatase [ALP]). Individual animals with notable serum biochemistry changes correlated well with animals having the observed histological changes to liver. Although there were no histological findings at this same dose level at the end of the 9-month dog study, suggesting any liver toxicity is reversible, due to the findings in the 4-month study, liver tests (e.g., AST, ALT, ALP, bilirubin) will be monitored throughout the study and up to 14 days after the last dose of study drug. Liver function tests will be conducted throughout the study up until the post-study visit. To date, no elevations in liver function tests have been observed in Protocols 001 or 003 in which single doses up to 1200 mg of tablet formulation and multiple doses up to 900 mg of tablet formulation have been administered to healthy subjects.

4.2.3.2 Pharmacokinetic Endpoints

This study will establish if the PK target concentration can be achieved at a dose which is well-tolerated following a single dose of MK-4250. To provide confidence that the PK target has been achieved at this dose, the criteria of achieving the PK target with a 70% a posterior probability has been set. The antiviral efficacy of InSTIs has been associated with potency and Ctrough in plasma. The PK target of C168hr (i.e., Ctrough for once weekly dosing) was set at ≥1250 nM. This is 2.5-fold above the in vitro potency in the ViKInG assay, a margin above in vitro potency which has been associated with robust viral load reduction in monotherapy proof of concept clinical trials and with sustained viral suppression below 50 copies/mL in long term combination therapy trials in HIV-1 infected study participants [11].

The study will also characterize plasma PK parameters of MK-4250 (AUC0-last, AUC0-inf, AUC0-168hr, Tmax, Cmax, C168hr, CL/F, Vz/F and apparent terminal t½) to evaluate relationship between PK and pharmacodynamics.

4.2.3.3 Pharmacodynamic Endpoints

A PD endpoint of a ≥ 1.4 $\log_{10}$ copies/mL reduction of HIV-1 RNA from baseline 7 days post dose (i.e. Day 8), relative to historical placebo data will be used. This target is consistent with prior InSTI monotherapy studies (Table 3) and with regulatory guidance limiting InSTI monotherapy studies to 7-10 days in duration [10]. To provide confidence that the PD target has been achieved at this dose, the criteria of achieving the PD target with an 80% posterior probability has been set.

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 male or non-pregnant and non-breast feeding female, 18 to 60 years of age, inclusive, 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 a highly effective method of birth control with a failure rate of <1% beginning at the pretrial (screening) visit until 30 days after the dose of trial drug. Acceptable methods of birth control are defined in Section 5.7.2.5.
    b. if postmenopausal female: subject is without menses for at least 1 year and has a documented follicle stimulating hormone (FSH) level in the postmenopausal range at pretrial (screening),

        AND/OR

    c. subject is status post hysterectomy or oophorectomy.

        NOTE: These procedures must be confirmed with medical records. In the absence of documentation, hysterectomy may be confirmed by pelvic exam or if necessary by ultrasound; oophorectomy may be confirmed by hormone levels, particularly FSH in the post-menopausal range. Information must be captured appropriately within the site's source documents
3. Be documented HIV-1 positive as determined by a positive ELISA or QT-PCR with confirmation (e.g., Western Blot).
4. Have no evidence at screening for mutations (e.g., E92Q, N55H, Q148K, Q148R and Y143R) affecting susceptibility to InSTIs.
5. Be diagnosed with HIV-1 infection ≥ 3 months prior to screening or perform the French 2008 HAS Algorithm to confirm chronic HIV infection.

6. Have a screening plasma CD4+ T cell count of >200/mm^3.
7. Have a screening plasma HIV-1 RNA ≥ 5,000 copies/mL within 30 days prior to the treatment phase of this study.
8. Be ART-naïve, which is defined as having never received any antiretroviral agent OR the following:

   ≤30 consecutive days of an investigational antiretroviral agent which is not an InSTI, and no exposure to such an investigational antiretroviral agent within 60 days (or 5 t1/2s, whichever is longer) prior to screening

   OR

   ≤60 consecutive days of combination ART which does not include an InSTI, and no exposure to such ART within 60 days (or 5 t1/2s, whichever is longer) prior to screening.
9. Must have never received any InSTI.
10. Be willing to receive no other ART for the duration of the treatment phase of this study.
11. Have a Body Mass Index (BMI) ≤35 kg/m^2. BMI = weight(kg)/height $(m)^2$.
12. Other than HIV infection, have baseline health judged to be stable based on medical history, physical examination, vital sign measurements, and laboratory safety tests (see Section 7.1.3.1) performed at the prestudy (screening) visit and/or prior to administration of the initial dose of study drug.
13. Have the following laboratory values at screening: direct bilirubin ≤ 1.0 mg/dL, AST (SGOT) and ALT (SGPT) ≤ 2 x upper limit of normal.

5.1.3 Subject Exclusion Criteria

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

1. Is under the age of legal consent.
2. Is mentally or legally institutionalized / incapacitated, has significant emotional problems at the time of pretrial (screening) visit or expected during the conduct of the trial or has a history of clinically significant psychiatric disorder within 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., kidney stones with no recurrence in the last 5 years, 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 (except those cancers identified at the beginning of exclusion criterion 4); 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; or has hereditary galactose intolerance, lactose deficiency and glucose-galactose malabsorption.
6. Is positive for hepatitis B surface antigen.
7. Has a history of chronic hepatitis C infection Subjects with a documented cure and/or a positive serologic test for HCV with a negative HCV viral load may be included.
8. Had major surgery or donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks prior to the pretrial (screening) visit.
9. Participated in another investigational trial within 4 weeks (or 5 half-lives, whichever is longer) 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, whichever is longer) 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. Does not agree to follow the smoking restrictions defined by the CRU.
15. Has a clinically significant abnormality on the electrocardiogram (ECG) performed at the prestudy (screening) visit and/or prior to administration of the initial dose of study drug.

16. Has QTc interval ≥ 470 msec (for males) or ≥ 480 msec (for females).
17. Has a positive urine drug screen (except for cannabis) at screening and/or predose; rechecks are allowed.
18. Is any concern to the investigator regarding the safe participation of the subject in the trial or for any other reason the investigator considers the subject inappropriate for participation in the trial.
19. Is unwilling to comply with the trial restrictions (see Section 5.7 for a complete summary of trial restrictions).
20. 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 6

Table 6 Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Panel	Use
MK-4250 tablet	150 mg, fasted	Single dose	Oral	Day 1/ Panel A	Experimental
MK-4250 tablet	600 mg, fasted	Single dose	Oral	Day 1/ Panel B	Experimental
MK-4250 tablet	900 mg, fasted	Single dose	Oral	Day 1/ Panel D	Experimental
MK-4250 tablet	≤ 900 mg, low fat meal	Single dose	Oral	Day 1/ Panel E	Experimental
MK-4250 tablet	≤ 900 mg, moderate fat meal	Single dose	Oral	Day 1/ Panel F	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

For Panels A – D, prior to proceeding to the next Panel, viral load data for 7 days post-dose (out to C168hr, Day 8) will be reviewed. In addition, key safety variables including vital signs, 12-lead ECGs, laboratory safety tests, and adverse events up to 7 days post-dose will be reviewed. Before proceeding to Panel B, PK data will be reviewed from Panel A to determine whether or not PK from HIV-infected subjects is similar to that observed in healthy subjects from Protocol 001. The dose in Panel B may be reduced based on these data. In addition, prior to proceeding to doses above 600 mg, PK and safety data from higher doses of the tablet formulation being tested in Protocol 001 will be reviewed. Panels E and F may be conducted in either order or in parallel and will not begin until all available safety data (up to 7 days post-dose) and viral load data (up to 10 days post-dose) have been reviewed from Panel D. Prior to proceeding to a dose of 900 mg with a moderate fat meal, safety data from a higher dose with food tested in Protocol 005 will be reviewed (see Section 4.2.2). Pharmacokinetic and pharmacodynamic data may 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.

5.2.2 Timing of Dose Administration

All doses of MK-4250 will be given in the morning at approximately the same time. Subjects will receive a single oral dose of MK-4250 with approximately 240 mL of water. Additional water (in increments of 50 mL) maybe provided for subjects receiving a dose of MK-4250 requiring more than 2 tablets.

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 7.

Table 7 Sample Allocation Schedule

Subjects	Panel A	Panel B	Panel D	Panel E	Panel F
N=6 (per panel)	150 mg, fasted	600 mg, fasted	900 mg, fasted	≤ 900 mg, low fat meal	≤ 900 mg, moderate fat meal
With the exception of Panel A, the suggested doses may be adjusted downward. The decision to select the precise dose will be based on viral load data for the 7 days post-dose (out to C168hr, Day 8), and review of key safety variables (including vital signs, 12-lead ECGs, laboratory safety tests, and adverse events) up to 7 days post-dose. Before proceeding to Panel B, PK data will be reviewed from Panel A to determine whether or not PK from HIV-infected subjects is similar to that observed in healthy subjects in Protocol 001. In addition, prior to proceeding to doses above 600 mg, PK and safety data from higher doses of the tablet formulation being tested in Protocol 001 will be reviewed. Prior to proceeding to a dose of 900 mg with a moderate fat meal, safety data from a higher dose with food tested in Protocol 005 will be reviewed (see Section 4.2.2).					

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.

Ibuprofen may be used for minor ailments without prior consultation with the Sponsor.

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

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Sponsor.

The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on trial therapy or vaccination schedule requires the mutual agreement of the investigator, the Sponsor and the subject.

5.6 Rescue Medications & Supportive Care

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

5.7 Diet/Activity/Other Considerations

5.7.1 Diet and Fruit Juice Restrictions

5.7.1.1 Diet

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

Panels A through D

In each panel, subjects will fast from all food and drinks, except water, for at least 8 hours prior to trial drug administration.

Panels E and F

Subjects will fast from all food and drinks except water for at least 10 hours prior to the start of breakfast (when dosed with a moderate fat meal or a low fat meal). Water will be restricted 1 hour prior to and 1 hour after trial drug administration.

Approximately 30 minutes prior to trial drug administration, subjects will begin to consume specified breakfast (Panel E—low fat meal, Panel F—moderate fat meal). The contents of the low fat breakfast are listed in Table 8 and moderate fat breakfast in Table 9. Breakfast should be consumed in its entirety within approximately 20 minutes. The start and stop time of the breakfast will be recorded. Within approximately 10 minutes after consuming the breakfast, subjects will be administered trial drug as indicated in Section 5.2. The specific nutritional contents of the meals may be modified during the trial based on newly available data.

Table 8 Contents of Low Fat Breakfast

2 slices brown bread (70 g)
Light cream cheese (60 g)
Semi-skim milk (150 mL)

Total fat: 8.5 g (~25% of calories)

Total carbohydrates: 38.5 g (~50% of calories)

Total protein: 18.8 g (~25% of calories)

Total calories: 312 Kcalories

The exact low fat meal contents may be substituted with agreement between sponsor and investigator and must be documented in an administrative letter. The substituted meal should have a fat content of 20% to 30% and a caloric content of 300 ± 25 Kcalories.

Table 9 Contents of Moderate Fat Breakfast

2 Slices brown bread (70 g)
Butter (15 g)
Cheese (45 g)
Jam (15 g)
250 mL Whole milk

Total fat: 34.4 g (~50% of calories)

Total carbohydrates: 50.5 g (~30% of calories)

Total protein: 26.7 g (~20% of calories)

Total calories: 626 Kcalories

The exact moderate fat meal contents may be substituted with agreement between sponsor and investigator and must be documented in an administrative letter. The substituted meal should have a fat content of 40% to 50% and a caloric content of 600 ± 30 Kcalories.

<u>All Panels</u>

Subjects will fast from all food and drinks except water between trial drug administration and the first scheduled meal. Meals and snack(s) will be provided by the investigator at time points indicated in the trial flowchart. Subjects will fast from all food and drinks except water between meals and snacks. The caloric content and composition of meals will be the same for each panel (except for the breakfast). After the 24-hour post-dose procedures have

been completed, subsequent meals and snacks will be unrestricted in caloric content, composition and timing.

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

Instructions on whether to take MK-4250 with or without food and/or drink or the nutritional content of the meal 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 trial drug administration, throughout the trial and until the post-trial visit.

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

5.7.2 Alcohol, Caffeine, Tobacco, Activity

5.7.2.1 Alcohol Restrictions

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

5.7.2.2 Caffeine Restrictions

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

5.7.2.3 Smoking Restrictions

Smoking is restricted to ≤10 cigarettes per day, and subjects will follow the smoking restrictions defined by the Clinical Research Unit.

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.

5.7.2.5 Contraception and Pregnancy Testing

5.7.2.5.1 Contraception

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

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

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

Male subjects with female partner(s) of child-bearing potential must agree to use a medically acceptable method of contraception during the trial and for 90 days after the last dose of trial drug. Males should use a condom. Female partners must additionally use one of the following methods if they are not pregnant: hormonal contraception, intra-uterine device, diaphragm, or cervical cap. If their partner is pregnant, males must agree to use a condom and no additional method of contraception is required for the pregnant partner. Male subjects must also agree to not donate sperm during the study and for a period of 90 days after the last dose of study drug.

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

5.7.2.5.2 Pregnancy Testing

Female subjects of childbearing potential will be tested for serum β-human chorionic gonadotropin (hCG) at pretrial. Serum or urine β-hCG will be tested at 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 or urine β-hCG pregnancy test during the trial, the pregnancy test should be repeated and confirmed positive. If the pregnancy has been confirmed the subject must be discontinued from the trial immediately and the pregnancy must be reported to 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 discontinued 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.

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

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

5.8.2 Withdrawal from the Trial

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

If a subject withdraws from the study, he/she 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 as the subject being replaced. The replacement subject will be assigned a unique treatment/randomization number. The trial site should contact the Sponsor for the replacement subject's treatment/randomization number.

5.10 Beginning and End of the Trial

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

A trial may be paused during review of newly available preclinical/clinical safety, pharmacokinetic, pharmacodynamic, efficacy or biologic data or other items of interest, prior to a final decision on continuation or termination of the trial. It may be necessary to keep the trial open for gathering/reviewing of additional supportive data to optimally complete the objective(s) of the trial. If necessary, the appropriate amendment(s) to the protocol and/or

appropriate communication(s) will be generated. The overall trial end will then not be identified until the Sponsor has made the decision to end the trial following this review period. The Competent Authority(ies) and Institutional Review Board(s)/Independent Ethics Committee(s) [IRB(s)/IEC(s)] will be 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 and further dosing 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 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 with a potential causal relationship to study drug.
4. One (1) serious adverse experience/laboratory abnormality which is life threatening, results in persistent or significant disability/incapacity, results in or prolongs an existing inpatient hospitalization or is another important medical event OR participant death thought to be potentially related to the investigational product.
5. Two (2) or more of the enrolled subjects experience confirmed QTcF > 500 ms or QTcF change from baseline > 60 ms in a given panel with a potential causal relationship to study drug.

If one or more of the above conditions are met, enrollment and further dosing will be halted and all available safety data will be reviewed prior to making a decision about terminating

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

6.0 TRIAL FLOW CHART

All Panels/Periods																			
	Scheduled Time																		
		Study Day																	
		1								2	3	4	6	8	9	11	13	15	
			Hours Postdose																
	Prestudy	Pre-dose	0	0.5	1	2	4	6	8	12	24	48	72	120	168	192	240	288	336/ Post-trial [k]
Administrative Procedures																			
Informed Consent	X																		
Informed Consent for Future Biomedical Research	X																		
Inclusion/Exclusion Criteria	X	X																	
Subject Identification Card	X																		
Medical History	X																		
Concomitant Medication Review	X	----	-----	-----	----	----	----	---	---	----	----	---	----	---	----	----	----	---	X
Subject Domiciling in Clinical Research Unit (CRU)		X[a]	-----	-----	----	----	----	---	---	----	X								
Clinic Procedures/Assessments																			
Full Physical Examination	X	X[m]																	X
Height	X																		
Weight	X																		
12-Lead Electrocardiogram[c]	X	X					X				X				X				X
Vital Signs (heart rate, blood pressure) [d]	X	X					X				X				X				X
Orthostatic Vital Signs (heart rate, blood pressure) [d]	X	X					X				X								X
Vital Signs (respiratory rate, temperature)	X	X					X				X				X				X
Dosing Breakfast (Panels E and F only)[o]		X																	

All Panels/Periods																			
	Scheduled Time																		
		Study Day																	
		1									2	3	4	6	8	9	11	13	15
			Hours Postdose																
	Prestudy	Pre-dose	0	0.5	1	2	4	6	8	12	24	48	72	120	168	192	240	288	336/ Post-trial [k]
Standard Meals [e]							X	---	---	----	X								
MK-4250 Administration			X																
Adverse Events Monitoring	X	-------	-----	-----	----	----	----	---	---	----	----	---	----	----	----	----	----	---	X
Laboratory Procedures/Assessments																			
Hematology [j]	X	X[m]									X				X				X
Urinalysis [j]	X	X[m]									X				X				X
Chemistry [j]	X	X[m]									X				X				X
Serum/Urine β-Human Chorionic Gonadotropin (β-hCG) [f]	X	X																	X
Serum Follicle Stimulating Hormone (FSH) - if applicable [g]	X																		
Urine Drug Screen [h]	X	X[m]																	
HIV/Hepatitis Screen	X																		
Blood for Genetic Analysis [b]		X																	
Pharmacokinetics Evaluations																			
Blood for Plasma MK-4250 assay [i]		X		X	X	X	X	X	X	X	X	X	X[n]	X	X	X	X[n]		
Pharmacodynamic Evaluations																			
Blood for HIV RNA, viral resistance [t,l]	X	X					X			X	X	X	X	X	X	X	X	X	X
CD-4 cell count	X																		

a. Subjects will be admitted to the CRU the evening before scheduled dosing.
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.
c. ECGs are performed after the subject has remained in a semi-recumbent position for at least 10 minutes. Only the baseline ECG (pre-dose on Day1, obtained within 3 hours prior to dosing) will be repeated 3 times with at least 1-minute intervals between ECG measurements.
d. Only the predose semi-recumbent HR and BP (obtained within 3 hours prior to dosing) will be triplicate measurements obtained at least 1-2 minutes apart. Subjects should be resting in the semi-recumbent position for at least 10 minutes prior to obtaining HR and BP. Following selected measurement of the semi-recumbent HR and BP, subjects assume a standing position for at least 2 minutes and then orthostatic HR and BP will be obtained.
e. 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 meals and snacks will be unrestricted in terms of caloric content, composition and timing.
f. For female subjects of childbearing potential only. Serum pregnancy test must be performed at screening. Urine pregnancy test is an option only for the predose and posttrial visits.
g. For postmenopausal female subjects only.
h. Screening drug screen is mandatory; any additional drug screens are conducted per site SOP and/or at the investigator's discretion.
i. Leftover plasma will be stored for future biomedical research if the subject consents to future biomedical research.
j. Safety laboratory samples will be collected after at least an 8-hour fast. Screening hematology labs will include PT/INR measurements.
k. For all subjects, the post-trial visit should occur approximately 14 days (+2 days) following administration of the study drug.
l. For all subjects, blood for HIV-1 viral RNA and viral resistance will be collected at timepoints up to the initiation of ART. For subjects who do not initiate follow on ART, blood for HIV-1 viral RNA and viral resistance will continue to be collected until the post trial visit. Ultra-deep sequencing (UDS) may be performed if viral resistance cannot be measured due to low viral load. At the timepoint immediately preceding initiation of ART, a portion of the blood collected for viral resistance testing will be sent to Labor Berlin for extraction of proviral DNA. This proviral DNA will be frozen and analyzed for the presence of viral resistance mutations only if standard Sanger sequencing cannot be performed because plasma viral load is too low at this timepoint.
m. The predose PE and laboratory assessments (including drug screen) may be performed within 24 hour prior to dosing.
n. The 72 hour post-dose PK sample will be drawn only for the first 3 subjects enrolled in Panel B; in addition, the 240 hr timepoint will not be drawn for these three subjects.
o. For Panels E and F only, a dosing breakfast will be provided at approximately 30 mins pre-dose on Day 1.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

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

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

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

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

7.1.1.1.1 General Informed Consent

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

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

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

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

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

7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or qualified designee will explain the Future Biomedical Research consent to the subject, answer all of his/her questions, and obtain written informed consent before

performing any procedure related to the Future Biomedical Research sub-trial. A copy of the informed consent will be given to the subject.

7.1.1.2 Inclusion/Exclusion Criteria

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

7.1.1.3 Subject Identification Card

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

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

7.1.1.4 Medical History

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

7.1.1.5 Prior and Concomitant Medications Review

7.1.1.5.1 Prior Medications

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

7.1.1.5.2 Concomitant Medications

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

7.1.1.6 Assignment of Screening Number

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur prior to 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.

Randomization number will be assigned just prior to dosing on Day 1.

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

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

7.1.2 Clinical Procedures/Assessments

Physical Exam:

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

Body Weight and Height

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

Body Mass Index (BMI)

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

12-Lead ECG

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

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

The correction formula to be used for QTc is Fridericia.

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.

Predose ECGs will be obtained in triplicate at least 1-2 minutes apart within 3 hours prior to dosing MK-4250. The mean of these measurements will be used as the baseline to calculate change from baseline for safety evaluations (and for rechecks, if needed). Post-dose ECG measurements will be single measurements.

If a subject demonstrates an increase in QTc interval ≥60 msec compared with mean predose baseline measurement, the ECG will be repeated twice within 5 minutes. The mean value of the QTc interval from the 3 ECGs will represent the value at that time point. If the mean QTc 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 QTc is within 60 msec of baseline. If prolongation of the QTc interval ≥60 msec persists, a consultation with a study cardiologist may be appropriate and the Sponsor should be notified.

If the QTc interval is ≥500 msec (confirmed upon recheck and manual measurement), the Sponsor should be notified and the ECGs should be reviewed by a cardiologist. The subject should be telemetry-monitored (until the QTc 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 QTc is noted, concomitant medications that prolong QTc should be held until the QTc is within 60 msec of baseline and the QTc is <500 msec.

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

Body Temperature

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

Vital Sign Measurements (Heart Rate and Blood Pressure)

Subjects should be resting in a semi-recumbent position for at least 10 minutes prior to having vital sign measurements obtained. Semi-recumbent vital signs will include heart rate (HR) and blood pressure (BP). The correct size of the blood pressure cuff and the correct positioning on the subjects' arm is essential to increase the accuracy of blood pressure measurements.

Predose HR and BP will be triplicate measurements obtained at least 1-2 minutes apart within 3 hours of dosing MK-4250. The mean of these measurements will be used as the baseline to calculate change from baseline for safety evaluations (and for rechecks, if needed). 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 at least 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 (if needed) or other trial related procedure.

7.1.3 Laboratory Procedures/Assessments

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

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry and urinalysis are specified in Table 10.

Table 10 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Glucose	Follicle Stimulating Hormone (FSH) – for postmenopausal females only
Hemoglobin	Alkaline phosphatase	Protein	Serum/Urine β-human chorionic gonadotropin (β-hCG) – for females of childbearing potential only
Platelet count	Alanine aminotransferase (ALT)	Red blood cell	Hepatitis B surface antigen
WBC (total and differential) Including:	Aspartate aminotransferase (AST)	White blood cell	Hepatitis C antibodies
Absolute neutrophils	Bicarbonate	Microscopic exam, if abnormal results are noted	HIV (including HIV-1 RNA, resistance mutations to InSTIs)
Absolute lymphocytes	Calcium	pH	Urine Drug Screen
Absolute monocytes	Chloride		
Absolute eosinophils	Creatinine		
Absolute basophils	Glucose		
PT/INR (screening)	Phosphorus		
CD4+ T-cell count (screening)	Potassium		
	Sodium		
	Total Bilirubin		
	Direct Bilirubin		
	Total protein		
	Urea		

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 samples collected will be assayed for evaluation of pharmacokinetics/pharmacodynamics will be collaboratively determined by the Department of Quantitative Pharmacology and Pharmacometrics (QP2) and Translational Pharmacology. If indicated, these samples may also be assayed and/or pooled for assay in an exploratory manner for metabolites and/or additional pharmacodynamic markers.

7.1.3.2.1 Blood Collection for Plasma MK-4250

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

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

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

7.1.3.3 Planned Genetic Analysis Sample Collection

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

7.1.3.4 Future Biomedical Research Samples

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

- DNA for future research
- Leftover main study plasma from MK-4250 assay stored for future research
- Leftover main study plasma from HIV RNA and viral resistance assays stored for future use

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 14 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 14 days after the last dose of trial drug is given, the investigator should perform a follow-up phone call 14 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:

- Equipment for taking VS
- ECG equipment and electrodes
- Equipment (including freezers) for the PK and PD samples

7.1.5 Visit Requirements

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

7.1.5.1 Screening

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

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

7.1.5.2 Treatment Period (All Panels)

Subjects will report to the CRU the day prior to the scheduled day of dosing or at a 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.

After the Day 1 predose procedures have been completed, subjects will be assigned a unique allocation number associated with a specific study treatment as defined by a computer-generated allocation schedule. All subjects in each panel will be administered a single dose of MK-4250 in the morning. The exact clock time of dosing should be recorded.

7.1.5.3 Post-Trial

Subjects will be required to return to the clinic at least 14 days (+2 days) after the last dose of trial drug for the post-trial visit.

7.1.5.4 Critical Procedures Based on Trial Objectives: Timing of Procedure

For this trial, the blood samples for plasma MK-4250 and HIV-1 viral RNA data are the critical procedures.

At any post-dose timepoint, the blood sample for MK-4250 and the blood sample for viral RNA need 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.

- Blood collection for PK and PD as outlined in Table 11 below

Table 11 Plasma PK and HIV RNA - Blood Collection Windows

PK/PD collection	PK/PD Collection Window
0 to < 1 hr	5 min
1 to < 24 hr	15 min
24 to < 48 hr	2 hr
48 to 168 hr	3 hr
> 168 hr	24 hr

- Predose standard safety evaluations: vital signs & ECG 3 hrs; laboratory safety tests including drug screen & physical exam 24 hrs
- Postdose standard safety evaluations (vital signs, ECG, laboratory safety tests, physical exam) as outlined in Table 12 below.

Table 12 Postdose Scheduled Time – Data Collection Windows

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

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

This is a Phase I assessment of MK-4250 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 in any given panel
- Entire panel(s) may be omitted
- Addition of a study pause
- Instructions to take trial drug with or without food or drink may also be modified based on newly available data
- Composition of the meal taken with the trial drug may also be modified based on newly available data
- Modification of the PK/PD sample processing and shipping details based on newly available data

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) but the number of samples will not increase. If indicated, these collected samples may also be assayed in an exploratory manner for metabolites and/or additional pharmacodynamic markers.

Up to additional 50 mL of blood may be drawn for safety, 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).

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

It is understood that the current trial may employ some or none of the alterations described above. Any alteration made to this protocol to meet the trial objectives must be detailed by

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

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

7.2 Assessing and Recording Adverse Events

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

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

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

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

For randomized subjects only, all adverse events that occur after the consent form is signed but before treatment allocation/randomization must be reported by investigator if they are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. From the time of treatment allocation/randomization through 14 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 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 14 days following cessation of Sponsor's product must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

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

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

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

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

Note: In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor 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 13 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 14 days following cessation of treatment, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

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

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

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 14 days following cessation of treatment, any ECI, or follow up to an ECI, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor, either by electronic

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

Events of clinical interest for this trial include:

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.

7.2.3.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

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 13. The investigator's assessment of causality is required for each adverse event. Refer to Table 13 for instructions in evaluating adverse events.

Table 13 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-4250 and placebo is at least 1.4 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 0.2 (0.3), 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-4250 and placebo is at least 1.4 log10 copies/mL, if the true mean log10 reduction is at least 1.56 log10 (1.63 log10) with N=6 for MK-4250 in a panel and N=20 historical placebo subjects. The SD values of 0.2 and 0.3 are chosen based on a SD of 0.26 observed for Day 8 change from baseline in log10 HIV RNA for 400 mg BID raltegravir.

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-4250 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-4250 and placebo is at least 1.4 log10 copies/mL.

Secondary Pharmacokinetic Hypothesis: The true geometric mean C168hr is > 1250 nM following single dose administration of MK-4250 for at least one dose level of MK-4250.

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 at the time points listed in the Study Flow Chart up until the time at which ART is initiated.

Secondary Endpoints

The secondary endpoints in this study include: MK-4250 plasma AUC0-last, AUC0-inf, AUC0-168hr, Tmax, Cmax, C168hr, t1/2, CL/F and Vz/F.

8.2.3 Approaches to Analyses

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

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

Per-Protocol (PP): The Per-Protocol Population consists of the subset of subjects who comply with the protocol sufficiently to ensure that generated data will be likely to exhibit the effects of treatment, according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements and absence of major protocol deviations. Major protocol deviations will be identified to the extent possible by individuals responsible for data collection/compliance, and its analysis and interpretation. Any subjects or data values excluded from analysis will be identified, along with their reason for exclusion, in the CSR. At the end of the study, all subjects who are compliant with the study procedure as aforementioned and have available data from at least one treatment will be included in the Per-Protocol dataset. This population will be used for the PK and PD analyses.

8.2.4 Statistical Methods

Primary (Safety)

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

Primary (Pharmacodynamics)

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

HIV-1 RNA reduction from baseline between MK-4250 and placebo is at least 1.4 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 1.4 log10 copies/mL will also be calculated. Similar exploratory analyses may be performed using viral load measurements at baseline and specified post-baseline timepoints.

Descriptive statistics for VL reduction will be provided by dose level and time point. Mean and individual plots of VL reduction over time will also be provided by dose.

Secondary (Pharmacokinetics):

Separately for each PK parameter, individual values of MK-4250 plasma pharmacokinetic parameters AUC0-last, AUC0-inf, AUC0-168hr, Cmax, C168hr, CL/F and Vz/F from subjects in all panels will be pooled, natural log transformed and analyzed based on a linear model containing a fixed effect for dose level. The 95% confidence intervals for the least squares means by dose level will be constructed on the natural log scale and will reference the t-distribution. Exponentiating the least-squares means and lower and upper limits of these confidence intervals will yield estimates for the population geometric means and confidence intervals about the geometric means on the original scale.

The secondary hypothesis that the true geometric mean C168hr is > 1250 nM following single dose administration of MK-4250 for at least one dose level of MK-4250 will be tested using the previously-defined model. The posterior probability that the true GM C168hr is >1250 nM will be calculated for each dose using flat priors under an assumption of normality. A 70% posterior probability that the true C168hr is > 1250 nM for at least one dose level will satisfy the secondary pharmacokinetic hypothesis.

Descriptive Statistics

Individual values will be listed for each PK parameter by treatment, and the following (non-model-based) descriptive statistics will be provided: N (number of subjects with non-missing data), arithmetic mean, standard deviation, arithmetic percent 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).

Exploratory (Pharmacokinetic/Pharmacodynamic)

The pharmacokinetic-pharmacodynamic and dose-pharmacodynamic association of MK-4250 will be explored. Graphs to visualize the association of the Day 7 reduction in log10 plasma HIV-1 RNA levels with MK-4250 C168hr plasma concentration and dose will be generated. Exposure levels and doses that result in various proportions of the population (e.g., 80%, 90%) that have at least 1.4 log10 reduction from baseline in plasma HIV-1 RNA levels with high confidence may be estimated.

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 and it is being evaluated with Bayesian methods, no multiplicity adjustment will be made.

8.2.6 Sample Size and Power

If the true SD of the log10 reduction from baseline in plasma HIV-RNA at 168 hours postdose is 0.2 (0.3), 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-4250 and placebo is at least 1.4 log10 copies/mL, if the true mean log10 reduction is at least 1.56 log10 (1.63 log10) with N=6 for MK-4250 in a panel and N=20 historical placebo subjects. The SD values of 0.2 and 0.3 are chosen based on a SD of 0.26 observed for Day 8 change from baseline in log10 HIV RNA for 400 mg bid raltegravir.

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 14

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 14 Product Descriptions

Product Name & Potency	Dosage Form
MK-4250 1 mg	tablet
MK-4250 10 mg	tablet
MK-4250 100 mg	tablet

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 from supplies packaged in bulk open label bottles. No kitting is required.

9.3 Clinical Supplies Disclosure

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

9.4 Storage and Handling Requirements

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

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

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

9.5 Discard/Destruction/Returns and Reconciliation

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

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

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

10.1.2 Confidentiality of Subject Records

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

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

10.1.3 Confidentiality of Investigator Information

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

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

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

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

10.1.4 Confidentiality of IRB/IEC Information

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

10.2 Compliance with Financial Disclosure Requirements

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

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

10.3 Compliance with Law, Audit and Debarment

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

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by Merck, is provided in Section 12.1 - Merck Code of Conduct for Clinical Trials.

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

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

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

Trial documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the trial site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are

requested by the Sponsor as a result of an audit to cure deficiencies in the trial documentation and worksheets/case report forms.

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

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

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

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

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

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center trial (including multinational). When more than one trial site is open in an EU country, Merck, as the Sponsor, will designate, per country, a national principal coordinator (Protocol CI), responsible for coordinating the work of the principal investigators at the different trial sites in that Member State, according to national regulations. For a single-center trial, the Protocol CI is the principal investigator. In addition, the Sponsor must designate a principal or coordinating investigator to review the trial report that summarizes the trial results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the trial [Clinical Study Report (CSR) CI]. The Sponsor may consider one or more factors in the selection of the

individual to serve as the Protocol CI and or CSR CI (e.g., availability of the Protocol/CSR CI during the anticipated review process, thorough understanding of clinical trial methods, appropriate enrollment of subject cohort, timely achievement of trial milestones). The Protocol CI must be a participating trial investigator.

10.4 Compliance with Trial Registration and Results Posting Requirements

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

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

10.5 Quality Management System

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (SOPs) to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical trial.

10.6 Data Management

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

Detailed information regarding Data Management procedures for this protocol will be provided separately.

10.7 Publications

This trial is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. The Sponsor will work with the

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

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

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

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

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

11.0 LIST OF REFERENCES

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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/products/guidelines/efficacy/efficacy-single/article/definitions-for-genomic-biomarkers-pharmacogenomics-pharmacogenetics-genomic-data-and-sample-cod.html

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

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

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

Panels A, B, D, E, and F	Pre-trial	Treatment Periods	Post-trial	Total Collections	mL Per Collection	Total mL/ Test
Laboratory safety tests [a]	1	3	1	5	10	50
PT/INR	1	0	0	1	3	3
Blood for Planned Genetic Analysis	0	1	0	1	8.5	8.5
Blood for MK-4250	0	14	0	14	4	56
Blood for HIV RNA, viral resistance [b, c]	1[e]	11[e]	1	13	16[e]	208
Total Blood Volume Per Subject for Panels A, B, D, E, and F [d]						325.5 mL

[a] Blood volume includes CD4 cell count, HIV/Hepatitis Screen, β-hCG, and FSH.
[b] Blood volume includes proviral DNA and ultra-deep sequencing (UDS) which may be performed if viral resistance cannot be measured due to low viral load.
[c] The number of collections denoted in this row reflects the maximum quantity required if a subject does not initiate ART during the trial and the 14 days post trial period.
[d] If additional pharmacokinetic/pharmacodynamic and/or safety analysis is necessary, additional blood (up to 50 mL) may be obtained during the trial.
[e] At the Pre-trial visit only 13.3mL will be drawn. During the Treatment Period (at the final timepoint prior to initiation of ART), an additional 2.7 mL will be drawn for proviral DNA testing. The decrease in blood volume at the pre-trial visit offsets the increase at the single timepoint during the Treatment Period.

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	