Official Protocol Title:	A Phase IIa Multicenter, Open-Label Clinical Trial to Evaluate the Safety and Efficacy of MK-1439A in Treatment-Naïve HIV-1 Infected Subjects with Selected Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) Transmitted Resistance Mutations
NCT number:	NCT02629822
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TITLE:

A Phase IIa Multicenter, Open-Label Clinical Trial to Evaluate the Safety and Efficacy of MK-1439A in Treatment-Naïve HIV-1 Infected Subjects with Selected Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) Transmitted Resistance Mutations

IND NUMBER: 124997

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SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
Multiple (Specified below)	Multiple	Enrollment discontinued after 10 subjects were enrolled.	Enrollment stopped due to an assessment of lack of feasibility of recruiting enough subjects who met the study entry criteria in a reasonable period of time.
8.0 8.1 8.7 8.9.1	Statistical Analysis Interim Analysis Sample Size for Efficacy Analysis	As the enrollment target was changed from 60 to 10, the following changes to the statistical analysis were made: The first futility analysis will be conducted with all evaluable subjects. The criterion for excluding subjects who were non-compliant with study medication from the second futility analysis was added. The sample size and power calculations were updated.	Updated due to change in number of subjects enrolled.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
1.0	Trial Summary	Section updated to reflect the change in target enrollment (number of subjects to be enrolled was changed from 60 to 10).	Enrollment stopped due to an assessment of lack of feasibility of recruiting enough subjects who met the study entry criteria in a reasonable period of time.
2.1	Trial Design	The rationale for amendment -01 was removed. The rationale for -02 amendment (change in number of subjects enrolled) was added. Removed language regarding stratification.	Updated due to change in number of subjects enrolled. Given an updated number of subjects enrolled, the initial stratification plan is no longer applicable.
2.2	Trial Diagram	Statement added indicating subjects who continue into the study extension will have a single 14 day follow-up visit at the end of the study extension only and not in the base study.	Clarification that subjects who continue in the extension only need the 14-day follow-up at the end of the study extension.
2.2	Trial Diagram	Figure 1 “Trial Diagram for Base Study” was updated to reflect the number of subjects enrolled.	Updated due to change in number of subjects enrolled.

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
4.2.1	Rationale for the Trial and Selected Subject Population	Table 1, second row, the term "MK-1495" was changed to "MK-1439."	Typographical error corrected.
5.4	Stratification	Removed language regarding stratification.	Given the number of subjects enrolled, the initial stratification plan is no longer applicable.
7.1.2.5	Adverse Event	Updated instructions for documenting adverse events.	To clarify evaluation for relationship/causality of IRIS.

1.0 TRIAL SUMMARY

Abbreviated Title	MK-1439A in treatment-naïve HIV-1 infected subjects with NNRTI transmitted resistance
Trial Phase	Phase IIa
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	MK-1439A q.d.
Number of trial subjects	Approximately 10 subjects will be enrolled.
Estimated duration of trial	The Sponsor estimates that the trial will require approximately 5 years 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	For subjects who participate in the base study only, but do not continue into the study extension, each subject will participate in the trial for approximately 104 weeks, from the time the subject signs the Informed Consent Form (ICF) through the final contact. For subjects who do continue into the study extension, each subject will participate for approximately 200 weeks from the time the subject signs the ICF through the final contact. After a screening phase of up to 45 days, each subject will receive assigned treatment for approximately 96 weeks in the base study; for subjects who continue into the study extension, study treatment will continue for an additional 96 weeks, approximately, through a total of approximately 192 weeks of treatment. After the end of treatment, each subject will be followed for 14 days. Subjects who do not continue into the study extension will be followed through 14 days after the Week 96 treatment visit, while subjects who continue into the study extension will be followed through 14 days after the Week 192 visit.

A list of abbreviations used in this document can be found in Section 12.6.

2.0 TRIAL DESIGN

2.1 Trial Design

This is a multicenter, open-label trial to evaluate the safety and efficacy of MK-1439A once daily (q.d.) in antiretroviral treatment-naïve subjects with human immunodeficiency virus type 1 (HIV-1) infection with selected non-nucleoside reverse transcriptase inhibitor (NNRTI) transmitted resistance mutations. The study includes a 96 week base study and a 96 week study extension to collect long-term efficacy and safety data with MK-1439A. The study is to be conducted in conformance with Good Clinical Practice.

MK-1439A is a single tablet fixed-dose combination (FDC) that combines MK-1439, an investigational NNRTI with lamivudine (3TC) and tenofovir disoproxil fumarate (TDF), 2 approved and marketed nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs). A single tablet of MK-1439A contains a full daily HIV treatment regimen of MK-1439 100 mg + lamivudine 300 mg + TDF 300 mg.

Subjects are considered evaluable if they receive study treatment and have one of the three NNRTI resistance mutations confirmed by the central laboratory and present as a single mutation (i.e., subjects with multiple mutations are not eligible to enroll). The duration of treatment for a given subject is 96 weeks in the base study. The primary efficacy endpoint of the study is the proportion of subjects with HIV-1 RNA <50 copies/mL (by the Abbott RealTime HIV-1 Assay) at Week 48.

At Study Week 96 (visit 14 flow chart A) subjects who meet the following criteria will be eligible to enter the study extension: (1) completed the Week 96 (visit 14) study visit, (2) considered by the investigator to have derived benefit from participation in the base study, (3) further treatment with MK-1439A is considered clinically appropriate by the investigator, and (4) have provided informed consent to continue into the study extension, thus continuing study treatment for approximately 96 weeks beyond the base study. The total duration of treatment for a given subject in the base study will be 96 weeks (approximately 2 years); for subjects who continue into the study extension, the total duration of treatment will be 192 weeks (approximately 4 years).

Two interim futility analyses will be performed during the base study. Both analyses will be conducted and evaluated by the study team. No external data monitoring committee will be used in this study. If futility criteria are satisfied, the study team will discuss the analysis results with Sponsor management to make the final determination for stopping the study. Refer to Section 8.7 (Interim Analyses) for further information regarding the two futility analyses.

Subjects who meet virologic failure criteria during the base study or study extension (see Section 4.2.4.1) will return to the site for repeat viral RNA testing between one week and 4 weeks (≥1 and ≤4 weeks) later (at a virologic failure confirmation visit). If virologic failure is confirmed and the viral load meets the criteria for resistance testing (>400 copies/mL), viral resistance testing will be performed.

For subjects in the base study with confirmed virologic failure, plasma samples collected for resistance testing from the virologic failure visit and from the confirmation visit will be sent for resistance testing. For subjects in the study extension with confirmed virologic failure, the plasma sample from the virologic failure confirmation visit will be sent for resistance testing. In addition, plasma samples for resistance testing collected at the early discontinuation visit from subjects who discontinue, from either the base study or the study extension, for reasons other than virologic failure will be sent for testing. (Note that if a sample from the early discontinuation visit is not available, a sample from the most recent previous visit will be sent in the base study.)

Blood samples will be collected to support the evaluation of MK-1439 population pharmacokinetics (PK) from all subjects at Day 1 and Weeks 4, 8, 24 and 48.

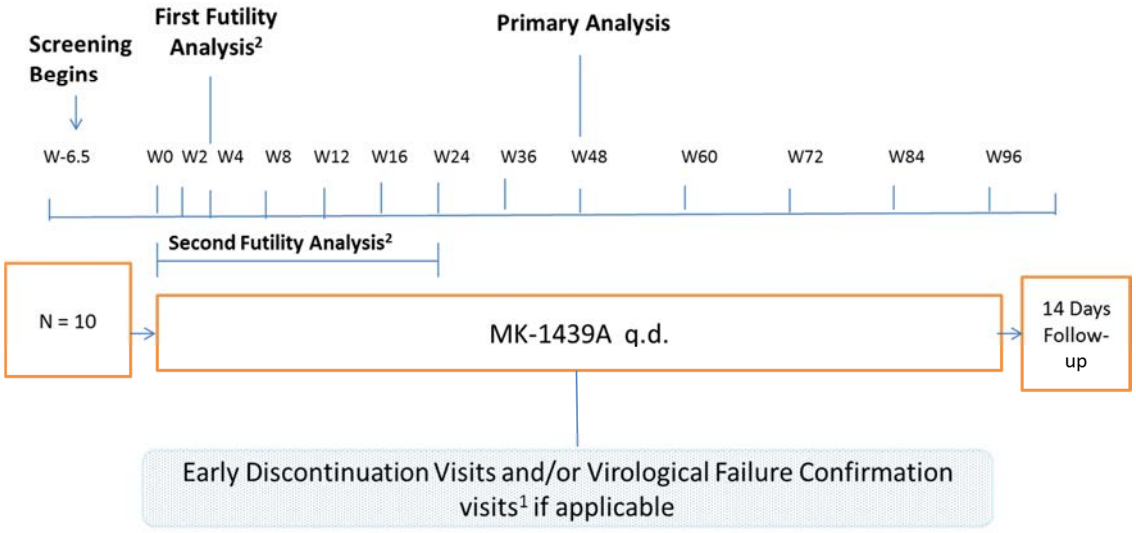
During the study extension, subjects will continue to be monitored for safety, and maintenance of virologic suppression. Long-term safety and efficacy data will be collected during the extension phase of the study and summarized descriptively. No formal hypothesis testing will be conducted for the safety or for efficacy for the study extension.

Initially 60 subjects were to be enrolled in this study. However, enrollment was discontinued after 10 subjects were enrolled due to an assessment of lack of feasibility of recruiting enough subjects who met the study entry criteria in a reasonable period of time.

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.

2.2 Trial Diagram

The trial design is depicted in Figure 1 (base study) and Figure 2 (study extension). Note the subjects who continue into the study extension will have a single 14 day follow-up visit at the end of the study extension only and not in the base study.



[1] Virologic failure is confirmed with 2 consecutive measurements of HIV-1 –RNA at least one week apart. Subjects who discontinue due to virologic failure will be contacted approximately 24 weeks after the Early Discontinuation visit. During this contact, only information on the HIV regimen(s) used after the subject left the study and virologic outcome will be collected. Subjects who discontinue the study for reasons other than virologic failure will only return to the clinic for an Early Discontinuation Visit. In addition, if the study is terminated early following one of the 2 futility analyses, subjects will return to the clinic for an Early Discontinuation Visit.

[2] The first futility analysis will be conducted on the data from the evaluable subjects who reach the week 4 visit. The second futility analysis involves ongoing monitoring of HIV-1 RNA data from Day 1 through Week 24 (section 2.1).

Figure 1 Trial Design for Base Study

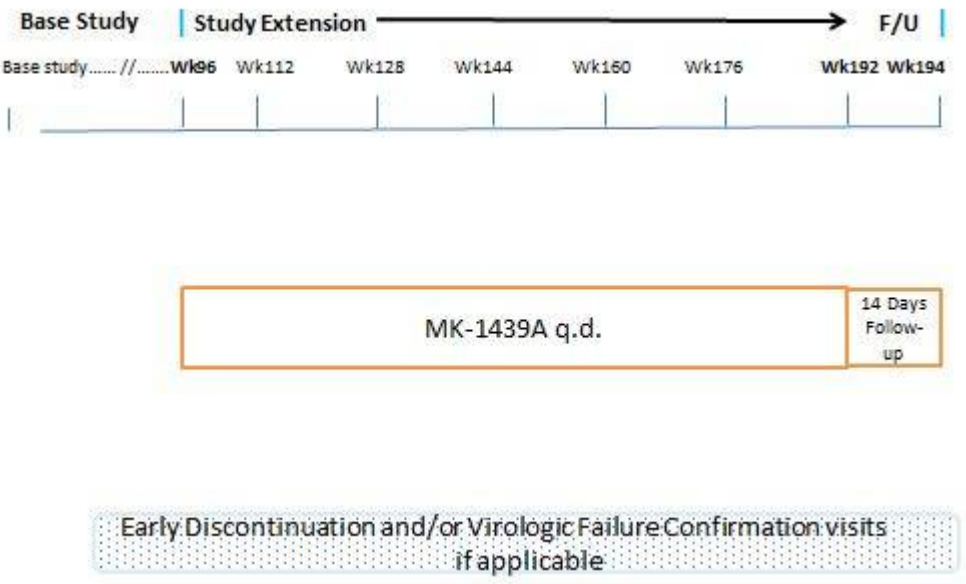


Figure 2 Trial Design for Study Extension

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

As this is an open-label, non-comparative study for estimation purposes only, there will be no formal hypotheses testing.

3.1.1 Base Study

(1) **Objective:** To evaluate the antiretroviral activity of MK-1439A as measured by the proportion of subjects achieving HIV -1 RNA <50 copies/mL (by the Abbott RealTime HIV-1 Assay) at Week 48.

(2) **Objective**: To evaluate the safety and tolerability of MK-1439A, as assessed by review of the accumulated safety data by Week 48 and Week 96.

3.2 Secondary Objective(s) & Hypothesis(es)

3.2.1 Base Study

(1) **Objective**: To evaluate the antiretroviral activity of MK-1439A as measured by the proportion of subjects achieving HIV-1 RNA <50 copies/mL at Week 96.

(2) **Objective**: To evaluate the antiretroviral activity of MK-1439A as measured by the proportion of subjects achieving HIV-1 RNA below the limit of quantification (BLoQ) of the Abbott RealTime HIV-1 Assay (<40 copies/mL) at Week 48 and Week 96.

(3) **Objective**: To evaluate the immunologic effect of MK-1439A, as measured by the change from baseline in CD4 cell count at Week 48 and Week 96.

(4) **Objective**: To evaluate the antiretroviral activity of MK-1439A as measured by the time-to-loss-of-virologic-response (TLOVR).

3.3 Exploratory Objectives

3.3.1 Base Study

(1) **Objective:** To evaluate the pharmacokinetics of MK-1439, when administered as a component of MK-1439A, and the pharmacokinetic-pharmacodynamic association, if supported by the data.

(2) **Objective:** To assess the development of resistance to MK-1439A (including assessments through deep sequencing) in subjects who have virologic failure.

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

3.3.2 Study Extension

(1) Objective: To assess long-term efficacy and safety of MK-1439A administered for up to 192 weeks in subjects enrolled in the extension phase of the study.

4.0 BACKGROUND & RATIONALE

4.1 Background

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on MK-1439A.

4.1.1 Pharmaceutical and Therapeutic Background

HIV infection, which causes Acquired Immunodeficiency Syndrome (AIDS) and for many years was associated with substantial morbidity and mortality, has now become a chronic disease that can be controlled through life-long combination antiretroviral therapy (ART) or Highly Active Antiretroviral Therapy (HAART). Currently, there are more than 30 individual drugs and fixed-dose combinations available for the treatment of HIV-1 infection. These agents belong to five distinct mechanistic classes known as reverse transcriptase inhibitors (nucleos[t]ide reverse transcriptase inhibitors [N(t)RTIs] and non-nucleoside reverse transcriptase inhibitors [NNRTIs]), protease inhibitors (PIs), fusion inhibitors, entry inhibitors (CCR5 co–receptor antagonists), and integrase strand transfer inhibitors (InSTIs). Successful combinations of antiretroviral medications generally utilize 3 agents from at least 2 different mechanistic classes. The goal of HAART is to suppress HIV to undetectable levels so that immune function is preserved or restored. Yet, while HAART can delay disease progression and death, as well as reduce the risk of HIV transmission, it does not cure the infection. As a result, lifelong treatment must be maintained, which may lead to therapy fatigue and to noncompliance if the treatment regimen is difficult to adhere to (e.g., pill burden, frequency of treatment) and/or associated with intolerable side-effects. This can potentially lead to treatment failures with possible development of resistant virus.

HIV resistance mutations can be transmitted from infected individuals to uninfected individuals. Thus, "HIV infection with transmitted resistance" occurs when a previously uninfected, HIV-treatment-naïve individual is infected with virus that already has mutations that make it resistant to certain HIV treatments. The presence of Transmitted Drug Resistance (TDR) increases the risk for subsequent regimen failure.

The prevalence of infection with transmitted resistance varies by geographic region, drug class and HIV transmission group. The risk of transmitted resistance is heightened in regions of the world without routine viral load monitoring, as patients are maintained on failing regimens. This is compounded by the reality that routine baseline resistance testing is not feasible in many parts of the world, particularly those most burdened by the problem of TDR, thus increasing the risk that a patient might be started on a regimen to which they are already resistant. NNRTI transmitted resistance has proven to be the most common for a number of reasons. For many years, NNRTI-based therapy has been the most common regimen type used in treatment-naïve patients. NNRTIs have also been key components of prophylactic regimens designed to prevent maternal-to-child transmission of HIV. Finally, there are virologic reasons that transmission of NNRTI resistant virus is more common than that for other drug classes. The fitness of prevalent NNRTI resistant mutants such as K103N and Y181C is comparable to that of wild type (WT) virus; thus, when these mutations are selected for, they often persist for more than a year. These resistant variants are also highly transmissible. The prevalence of transmitted NNRTI resistance has increased over time, though it has slowed with the introduction of new drug classes. Men who have Sex with Men (MSM) have generally been shown to have higher rates of transmitted resistance than People Who Inject Drugs (PWID) or heterosexuals. This largely relates to the size and scope of the social networks from which new infections originate.

A systematic review of the peer-reviewed English literature on TDR (1999–2013) was published in 2014 including a total of 212 studies [1]. The areas with the greatest TDR prevalence were North America [MSM: 13.7%, PWID: 9.1%, heterosexuals: 10.5%]; followed by Western Europe (MSM: 11.0%, PWID: 5.7%, heterosexuals: 6.9%) and South America (MSM: 8.3%, PWID: 13.5%, heterosexuals: 7.5%). Disproportionately high TDR burdens were noted in MSM in Oceania (Australia 15.5%), eastern Europe/central Asia (10.2%) and East Asia (7.8%). The risk of TDR infection was significantly greater in MSM than that in heterosexuals and PWID. Increasing trends of resistance to non-nucleoside reverse transcriptase and PIs were noted in general among MSM.

In Europe, a continuous program (SPREAD) has been in place for ten years to study the transmission of drug resistant HIV [2]. The prevalence TDR was highest in MSM (prevalence of 11.1%), followed by heterosexuals (6.6%) and injection drug users (IDU) (5.1%, $p<0.001$). TDR was predominantly ascribed to NRTIs with a prevalence of 6.6% in MSM, 3.3% in heterosexuals and 2.0% in IDU ($p = 0.001$). A significant increase in resistance to NNRTIs and a decrease in resistance to PIs was observed in MSM ($p = 0.008$ and $p = 0.006$, respectively) but not in heterosexual patients ($p = 0.68$ and $p = 0.14$, respectively). MSM were shown to have significantly higher TDR prevalence compared to heterosexuals and IDU. The increasing NNRTI resistance in MSM is likely to negatively influence the response to first-line therapy, as many include regimens based upon NNRTI drugs.

For initiation of combination antiretroviral therapy for HIV infection, currently available NNRTIs have, for many years, been an important option for use as anchor agents along with two NRTIs. Efavirenz and rilpivirine are the most widely-used NNRTIs and both are included as potential therapies for treatment initiation according to multiple guidelines [3, 4]. However, both have resistance liabilities that have led to the selection for and persistence of specific resistance mutations that are commonly transmitted to uninfected individuals. Virologic failure to EFV is frequently associated with K103N mutations, and virologic failure with rilpivirine is commonly associated with Y181C mutations. The G190A mutation is associated with nevirapine use, either as treatment or as part of prevention of maternal to child transmission regimens.

MK-1439 is a novel NNRTI being studied for the treatment of HIV-1 infection in antiretroviral-naïve HIV-infected subjects. MK-1439 is a potent inhibitor of HIV-1 replication in vitro and has a favorable preclinical toxicity profile. Clinical pharmacology studies indicate that MK-1439 can be dosed once daily, without regard to food and that MK-1439 is not a metabolic inducer or inhibitor, reducing the likelihood of significant drug-drug interactions. Furthermore, the available long term (beyond week 48) data from a Phase 2 study in treatment-naive HIV-infected patients demonstrate that MK-1439 in combination with TDF/emtricitabine has a favorable safety and tolerability profile and potent efficacy, with ~76% of patients receiving MK-1439 achieving undetectable viral load at week 24 (see Section 4.2.3). Based on these data, both MK-1439 and the FDC, MK-1439A, are currently being studied in Phase 3 clinical trials.

In addition to displaying excellent potency against WT HIV with an IC_{50} of 12 nM in the presence of 100% normal human serum (NHS), MK-1439 has been observed in preclinical studies to have a favorable in vitro resistance profile that is distinct from other NNRTIs, with IC_{50}'s of 21, 31, and 55 nM against mutants containing the most frequently transmitted NNRTI mutations, K103N, Y181C and G190A, respectively, under the same conditions. Thus, MK-1439 may be a unique NNRTI that can be used to treat HIV infection in the setting of NNRTI resistance.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

MK-1439 is highly active against the 3 most common NNRTI transmitted resistant viruses in in vitro multiple cycle infectivity assays conducted in the presence of 100% normal human serum (Table 1).

Table 1 Antiviral Activity IC_{50} (nM), in 100% NHS Viking Assay

NNRTI	WT	K103N	Y181C	G190A	Protein Binding (%)
MK-1439	12	21	31	55	26
NPV	246	11520	>21000	NA	62
RPV	56	56	169	88	99.6
EFV	31	1166	92	826	99.6

Results from modeling and simulation based on available clinical data for NNRTIs suggest that the target trough level to achieve maximum viral load reduction with monotherapy is >6*IC_{50}. The clinical trough concentration is 830 nM in plasma for MK-1439 at a daily dose of 100 mg, which is the dose being studied in the Phase 3 clinical trials, and the trough concentrations of EFV and RPV are 5600 nM and 260 nM at 24 hours at doses of 600 mg and 25 mg, respectively. Inhibitory quotient (IQ) has been used as a clinical efficacy predictor for antivirals with higher IQ correlating with better efficacy. It is derived from the ratio of trough concentration over the IC_{50} of the drug candidate. The IC_{50} that was determined in the presence of 100% human serum with the top 11 prevalent NNRTI-mutant viruses was used to calculate the IQ. MK-1439 displayed an IQ of 39, 26 and 16 against K103N, Y181C, and G190A mutants, respectively. In addition, MK-1439 also showed IQ >6 against all other mutants except the Y188L mutant. There are only two mutants (Y181C and G190A) that showed IQ >6 with EFV. The IQ are all <6 with RPV including for WT virus. Furthermore, there are 5 and 7 mutants that have IQ <1 with EFV and RPV, respectively. With higher IQ values against most of the prevalent NNRTI-associated mutants compared to EFV and RPV, MK-1439 may have a higher resistance barrier than EFV and RPV in clinical settings.

Furthermore, in *in vitro* resistance selection experiments with mutant viruses, no additional mutation was observed at clinically relevant concentrations of MK-1439 with K103N and Y181C (and G190A) mutants, whereas breakthrough viruses were detected in the selection with clinically relevant concentrations of RPV (with both the K103N and Y181 mutants) and EFV (with the K103N mutant). Altogether these *in vitro* data provide confidence that the levels of MK-1439 achieved with the selected Phase 3 dose should provide good activity against common transmitted resistant variants.

Patients who have more than one of these selected mutations will not be eligible for this proof-of-concept study. The presence of more than one mutation can be suggestive of infection with a virus from a patient with adherence issues. This heightens the concern that there may be minor variants present as well which could make the overall MK-1439-based regimen less effective. Subjects with resistance mutations other than K103N, Y181C and G190A (as single mutations) will also be excluded from this study as the objective of the study is to assess the efficacy of MK-1439 against the most prevalent NNRTI-associated mutants, i.e. K103N, Y181C, and G190A. The inclusion of other mutations would complicate the interpretation of the clinical results.

The purpose of this study is to demonstrate that the in vitro resistance profile of MK-1439 translates to clinical efficacy (proof-of-concept), to further define the efficacy profile of MK-1439 against TDR mutants, and to investigate the potential for MK-1439 to be used in the presence of selected baseline NNRTI resistance which may be particularly helpful in settings where baseline genotyping is not standard practice.

4.2.2 Rationale for Study Design

Given the novelty of treating patients who have selected NNRTI resistance mutations with an NNRTI that has projected activity against those mutations, this protocol has been designed to include extra precautions. It is open-label in design with frequent early study visits to allow close monitoring of HIV RNA and safety, and it also includes follow-up of subjects (in the base study only) who discontinued due to virologic failures at approximately 24 weeks after the early discontinuation visit to assess whether or not subjects who fail with MK-1439A are successful on subsequent treatment.

4.2.3 Rationale for Dose Selection/Regimen

The investigational FDC, MK-1439A, contains 100 mg of MK-1439, a potent investigational NNRTI, and standard doses of 2 marketed and commonly-used NRTIs, TDF (300 mg) and lamivudine (300 mg).

A 100 mg dose of MK-1439 was selected for Phase 3 development based on Phase 1b and 2 data and several other factors.

In a Phase 1b study (Protocol 005), q.d. oral administration of 25 mg and 200 mg of MK-1439 as monotherapy for 7 days to treatment-naïve HIV-infected patients reduced plasma vRNA (viral ribonucleic acid) burden as compared to placebo-treated controls. The mean change from baseline in $\log_{10}$ HIV RNA copies/mL on Day 7 (24 hours post-dose) was -1.52 for the MK-1439 25 mg group and was -1.41 for the MK-1439 200 mg group, while that for the placebo group was -0.15. The mean differences between MK-1439 25 mg and 200 mg versus placebo in change from baseline in $\log_{10}$ HIV RNA copies/mL were -1.37 and -1.26, respectively.

Protocol 007 (Part 1) is a Phase 2 study designed to assess MK-1439 at doses of 25, 50, 100 and 200 mg q.d. versus efavirenz at 600 mg q.d., both in combination with the fixed-dose combination of TDF/FTC (TRUVADA™) in treatment-naïve HIV-1 infected subjects. The MK-1439 dose range was selected based upon projections from in vitro data as well as the Phase 1b data in HIV-1 infected treatment naïve individuals, which showed comparable virologic suppression at the 25 mg and 200 mg doses given once daily for 7 days.

In Protocol 007 (Part 1) 208 treatment-naïve HIV-1 infected subjects were treated with study drug (MK-1439 or efavirenz). At Week 24, all MK-1439 doses had rates of virologic suppression comparable to efavirenz for the key efficacy endpoints including the proportion of subjects with HIV-1 RNA levels <40 copies/mL (primary) or <200 copies/mL (secondary). All MK-1439 doses showed numerically higher response rates compared to efavirenz (80.0%, 76.2%, 71.4%, 78.0% versus 64.3% of patients with <40 copies/mL for the MK-1439 25 mg, 50 mg, 100 mg, 200 mg versus efavirenz arms, respectively) [5, 6]. The treatment differences (MK-1439 minus efavirenz) were not significant, and there was no dose-response for efficacy observed. Overall 76.4% of patients receiving MK-1439 (at any

dose) achieved <40 copies/mL compared with 64.3% for efavirenz. In addition, approximately 30% of subjects in the study had baseline HIV RNA above 100,000 copies/mL, and, in this subgroup, MK-1439 at all dosing levels showed virologic responses comparable to efavirenz. It should be acknowledged that this high viral load subgroup was relatively small, with approximately 12 subjects per dosing group. However, the totality of these efficacy data strongly support that the dose range studied (25-200 mg daily) was on the plateau of the dose response curve.

Similarly, the data from Protocol 007 showed an overall favorable safety and tolerability profile for MK-1439 compared with efavirenz, with no differentiation among MK-1439 doses (25 mg - 200 mg daily) with regard to safety. Based upon the 24 week results of Protocol 007, MK-1439 at doses ranging from 25-200 mg was generally well-tolerated, with no apparent dose related toxicity. Fewer drug related AEs were observed for MK-1439 than for efavirenz (34.9% for MK-1439 overall vs. 57.1% for EFV), and fewer neuropsychiatric AEs were reported both at Week 8 and Week 24 (20.5% for MK-1439 overall vs. 33.3% for EFV at Week 8 and 23.4% for MK-1439 overall vs. 33.3% for EFV at Week 24) [7].

Because the safety and efficacy data from Protocol 007 did not distinguish among the doses tested, the selection of the MK-1439 100-mg daily dose for study in Part 2 of Protocol 007 and in the Phase 3 studies has taken into consideration a number of additional factors. Firstly, MK-1439 is a substrate of CYP3A metabolism and is subject to induction and inhibition of CYP3A by other concomitant medications. Consequently, the 100 mg dose is more likely than the lower doses to provide adequate MK-1439 exposures even in the setting of moderate metabolic inducers, and it allows for a safety margin in the setting of moderate metabolic inhibitors (since acceptable safety and tolerability were seen at the 200 mg dose in the Phase 2 study as well as at multiple doses and single doses as high as 750 mg and 1200 mg, respectively, in Phase 1 studies). Secondly, the 100-mg dose may provide forgiveness in the setting of the occasional missed dose. Thirdly, based on modeling and simulation, the 100-mg dose is predicted to provide adequate exposures and C_{trough} concentrations in the setting of certain common NNRTI resistance mutations against which MK-1439 is considered to be active in vitro, including the K103N, Y181C, and G190A mutations, as well as the dual K103N/Y181C mutation.

Patients receiving MK-1439 at 25, 50 or 200 mg in Part 1 of Protocol 007 were switched to 100 mg after dose selection. An additional 132 patients were randomized in Part 2, 66 to receive MK-1439 100 mg and 66 to receive EFV 600 mg. Combining Part 1 and 2, a total of 108 patients received MK-1439 100 mg, and 108 patients received EFV. By Week 8, at least one neuropsychiatric AE was reported in 22.2% of the MK-1439 group and 43.5% of the EFV group ($p<0.001$). The most commonly-reported neuropsychiatric AEs were dizziness (in 9.3% of patients receiving MK-1439 and 27.8% of patients receiving EFV), insomnia (in 6.5% of patients receiving MK-1439 and 2.8% of patients receiving EFV), abnormal dreams (in 5.6% of patients receiving MK-1439 and 16.7% of patients receiving EFV), and nightmares (in 5.6% of patients receiving MK-1439 and 8.3% of patients receiving EFV).

Standard marketed doses of lamivudine and TDF were selected for inclusion in MK-1439A because these dose levels have demonstrated efficacy and safety in treatment-naive subjects, and no antagonism was observed between MK-1439 and either of these drugs in in vitro studies.

4.2.4 Rationale for Endpoints

4.2.4.1 Efficacy Endpoints

The primary efficacy parameter in the study is viral load as measured by HIV-1 RNA, which is consistent with other clinical trials in HIV-infected patients and the current regulatory guidance. Suppressing HIV-1 RNA to low levels preserves the immune system and prevents the development of opportunistic infections and progression of the disease. Clinical trials of antiretroviral agents in multiple classes have demonstrated that suppression of HIV RNA to levels below 50 copies/mL is a clinically meaningful endpoint. Therefore, the primary efficacy endpoint of this study is the proportion of subjects achieving HIV-1 RNA <50 copies/mL by the Abbott RealTime HIV-1 Assay. Week 48 was chosen as the primary efficacy time point, as recommended by regulatory agencies for HIV treatment-naïve studies.

Secondary and exploratory measurements for efficacy include HIV RNA <40 copies/mL (the lower limit of quantification of the Abbott RealTime HIV-1 Assay), change from baseline in CD4 cell counts, time to loss of virologic response (TLOVR), and viral resistance for subjects who meet protocol defined virologic failure criteria and whose virus can be amplified.

Protocol-defined virologic failure (PDVF) for this study is defined as one of the following:

1) Confirmed (two consecutive measures at least one week apart) HIV-1 RNA ≥50 copies/mL after initial response of HIV-1 RNA <50 copies/mL **at any time during the study**

OR

2) Confirmed (two consecutive measures at least one week apart) HIV-1 RNA ≥200 copies/mL at Week 24 or Week 36

OR

3) Confirmed (two consecutive measures at least one week apart) HIV-1 RNA ≥50 copies/mL at Week 48.

Subjects should be discontinued, regardless of compliance with study therapy, if they meet the protocol defined virologic failure criteria.

4.2.4.2 Safety Endpoints

Safety evaluations in the base study will include physical examinations (including vital signs) and laboratory tests (blood) performed at the visits indicated in the Trial Flow Chart A (Section 6.0). For subjects who continue into the study extension, safety evaluations will include physical examinations (including vital signs) and laboratory test (blood) performed at each of the study visits, and if applicable, at the early discontinuation visit and/or a virologic failure confirmation visit and at a 14-day follow-up visit as shown in Trial Flow Chart B. Adverse experiences will be evaluated at each visit and graded according to the guidelines provided in Section 7.2. Subjects may be asked to return for unscheduled visits in order to perform additional safety monitoring.

Primary and exploratory measurements for safety include clinical and laboratory adverse experiences and predefined limits of change in laboratory parameters.

4.2.4.3 Pharmacokinetic Endpoints

Pharmacokinetic (PK) samples to be assayed for MK-1439 plasma concentrations will be collected on the Day 1 visit as a predose sample. Population PK samples will also be taken at Weeks 4, 8, 24 and 48. At Week 4, the sample is to be collected predose. At Weeks 24 and 48, the samples are to be collected predose and within 0.5 to 2 hours postdose; at Week 8, the sample may be collected irrespective of time of dose (time of last dose and time of PK sample collection must be documented).

4.2.4.4 Planned Exploratory Biomarker Research

Planned Genetic Analysis

Understanding genetic determinants of drug response 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. If genetic variation is found to predict efficacy or adverse events, the data might inform optimal use of therapies in the patient population. This research contributes to understanding genetic determinants of efficacy and safety associated with the treatments in this study.

4.2.4.5 Future Biomedical Research

The Sponsor will conduct Future Biomedical Research on specimens collected 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.

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 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. Additional informational material for institutional review boards/ethics committees (IRBs/ERCs) and investigational site staff is provided in Section 12.3.

4.2.5 Rationale for Study Extension

This protocol was previously amended to provide MK-1439A to subjects who have completed the base study (96 weeks of treatment for PN030) for an additional 96 weeks, and to collect long-term efficacy and safety data with MK-1439A. MK-1439A is being evaluated as a potential treatment option for subjects infected with HIV-1, including those with one of

the following NNRTI mutations: K103N, Y181C, or G190A. It is important to assess its long-term safety and efficacy since HIV infection is chronic, with treatment generally lasting for years. Thus, after the 96 week period (base study) to evaluate the key primary and secondary objectives, there will be an extension for an additional 96 week period where all eligible subjects can continue to receive MK-1439A.

4.3 Benefit/Risk

Subjects in clinical trials generally cannot expect to receive direct benefit from treatment during participation, as clinical trials are designed to provide information about the safety and effectiveness of an investigational medicine.

MK-1439 is a promising new NNRTI for the treatment of HIV-1 infection. It is a potent inhibitor of HIV-1 replication in vitro and is active against both wild type virus and most common NNRTI resistant variants at concentrations achieved with once daily dosing. In early studies, MK-1439 has been shown to be efficacious in combination with other ARTs in treatment-naïve patients. MK-1439 is not expected to have many of the safety concerns associated with EFV (especially neuropsychiatric AEs and dyslipidemia). In addition, MK-1439 is not expected to have major drug-drug interactions that would limit its utility in clinical practice. Therefore, MK-1439 could represent a valuable addition to the HIV armamentarium for treatment-naïve patients. Additionally, the FDC, MK-1439A, which is used in this protocol, is a simplified regimen that could result in increased adherence, thereby potentially decreasing the risk of virologic failure.

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 and female subjects 18 years of age or older who are HIV-1 positive, naïve to antiretroviral therapy (ART) and have transmitted resistance to selected NNRTI mutations 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. Be at least 18 years of age on the day of signing the informed consent.
2. Understand the study procedures and voluntarily agree to participate by giving written informed consent (or have a legal representative provide written informed consent, if considered acceptable by local regulatory agencies and/or ERCs/IRBs) for the trial. The subject or his/her legal representative (if considered acceptable by local regulatory agencies and/or ERCs/IRBs) may also provide consent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.

3. Be HIV-1 positive as determined by a positive result on an enzyme-immunoassay, have screening plasma HIV-1 RNA (determined by the central laboratory) ≥1000 copies/mL within 45 days prior to the treatment phase of this study, and have HIV treatment indicated based on physician assessment. Local treatment guidelines should be considered in the decision to initiate therapy.
4. Have a screening CD4 cell count ≥100 cells/mm^3 (completed by the central laboratory) within 45 days prior to the treatment phase of this study.
5. Be naïve to antiretroviral therapy (ART) including investigational antiretroviral agents.

   Note: Naïve is defined as having received no (0 days of) ART therapy for the treatment of HIV infection.
6. Prior to screening, have documentation of genotype performed confirming the presence of one and only one of the following NNRTI mutations: K103N, Y181C, or G190A. An additional sample must be obtained and analyzed by the central laboratory as a part of the screening process to establish a baseline resistance profile. The results of the central laboratory test results must be available prior to subject enrollment. If, upon receipt of the central laboratory results, a discordance between the local sample drawn prior to screening and central laboratory results is identified, such that exclusion criterion #4 is met using the central laboratory results, the subject should not be enrolled in the study. In addition, if the central laboratory test results do not confirm inclusion criteria 6, the subject should not be enrolled.
7. Have the following laboratory values during the screening period of the trial:
   a. Alkaline phosphatase ≤3.0 x upper limit of normal.
   b. AST (SGOT) and ALT (SGPT) ≤5.0 x upper limit of normal.
   c. Hemoglobin ≥9.0 g/dL (if female) or ≥10.0 g/dL (if male).

   Note: A single repeat of a laboratory screening test will be allowed for test results that are unexpected based on documented prior laboratory results.
8. Have a calculated creatinine clearance at the time of screening ≥50 mL/min, based on the Cockcroft-Gault equation which is as follows:

   For males: $Cl_{cr}(mL/min) = \frac{(140\text{-age}) \times \text{weight (in kg)}}{72 \times \text{serum creatinine (mg/dL)}}$

   For females: $Cl_{cr}(mL/min) = \frac{(140\text{-age}) \times \text{weight (in kg)}}{72 \times \text{serum creatinine (mg/dL)}} \times 0.85$
9. In the opinion of the investigator, be considered clinically stable with no signs or symptoms of active infection at the time of entry into the study (i.e. clinical status and all chronic medications should be unchanged for at least 2 weeks prior to the start of treatment in this study).

10. Be highly unlikely to become pregnant or to impregnate a partner since the subject falls into at least one of the following categories:

    a. The subject is a male who is not of reproductive potential, defined as a male who has azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

    b. The subject is a female who is not of reproductive potential, defined as a female who either: (1) is postmenopausal (defined as at least 12 months with no menses in women ≥45 years of age); (2) has had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy, or bilateral tubal ligation/occlusion at least 6 weeks prior to screening; OR (3) has a congenital or acquired condition that prevents childbearing.

    c. The subject is a female or a male who is of reproductive potential and agrees to avoid becoming pregnant or impregnating a partner while receiving study drug and for 14 days after the last dose of study drug by complying with one of the following: (1) practice abstinence[†] from heterosexual activity OR (2) use (or have their partner use) acceptable contraception during heterosexual activity. Acceptable methods of contraception are[‡]:

    Single method (one of the following is acceptable):

    - intrauterine device (IUD)
    - vasectomy of a female subject's male partner

    Combination method (requires use of two of the following):

    - diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
    - cervical cap with spermicide (nulliparous women only)
    - contraceptive sponge (nulliparous women only)
    - male condom or female condom (cannot be used together)
    - hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, contraceptive rod implanted into the skin or subcutaneous contraceptive injection

    Use of barrier methods of contraception is strongly encouraged to reduce the risk of HIV-1 transmission during sexual contact.

    [†]Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

‡If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.

In order to be eligible for participation in the **study extension** at the Week 96 visit, the subject must:

11. Have completed the Week 96 visit.
12. Be considered, in the opinion of the investigator, to have derived benefit from study participation through Week 96.
13. Be considered, in the opinion of the investigator, a clinically appropriate candidate for an additional 2 years (additional 96 weeks) of treatment with MK-1439A.
14. Understand the procedures in the study extension and provide written informed consent to enter the study extension, thus continuing for approximately 2 years beyond the base study.

5.1.3 Subject Exclusion Criteria

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

1. Has a history or current evidence of any condition, therapy, laboratory abnormality or other circumstance that might confound the results of this study or interfere with the subject's participation for the full duration of the study, such that it is not in the best interest of the subject to participate.
2. Is, at the time of signing informed consent, a user of recreational or illicit drugs or has had a recent history of drug or alcohol abuse or dependence. The nature and potential clinical context of the subject's illicit drug use, in relation to their exclusion from this trial, will be at the discretion of the Investigator.
3. Has been treated for a viral infection other than HIV-1, such as hepatitis B, with an agent that is active against HIV-1, including, but not limited to, adefovir, tenofovir, entecavir, emtricitabine, or lamivudine.

   Note: Subjects may be enrolled if treatment occurred prior to the diagnosis of HIV.
4. Has documented or known resistance to study drugs (MK-1439, lamivudine, and/or tenofovir) as defined below:

   - Resistance to MK-1439 for the purpose of this study is considered to include mutant viruses containing any of the following NNRTI-associated mutations.
     - L100I K101E, K101P, K103S, V106A, V106I, V106M, V108I, E138K, E138A, E138G, E138Q E138R, V179L, Y181I, Y181V, Y188C, Y188H, Y188L, G190S, H221Y, P225H, F227C, F227V, F227L, M230I and M230L.
     - Any double or triple NNRTI mutation that includes mutations from the above in combination with K103N, Y181C, or G190A.

- Resistance to lamivudine or tenofovir for the purpose of this study is considered to include following NRTI-associated mutations:
    - M41L, A62V, K65R, D67N, K70E, K70R, L74V, V75I, F77L, Y115F, F116Y, Q151M, M184I, M184V, L210W. T215F, T215Y, K219E, and K219Q as well as the T69S insertion complex.

5. Has participated in a study with an investigational compound/device within 30 days prior to signing informed consent or anticipates participating in such a study involving an investigational compound/device during the course of the study.
6. Has any medical condition requiring, or likely to require, chronic systemic administration of corticosteroids, TNF antagonists, or other immunosuppressant drugs during the course of the trial.
7. Requires or is anticipated to require any of the prohibited medications noted in the protocol (refer to Section 5.5).
8. Has significant hypersensitivity or other contraindication to any of the components of the study drug as determined by the investigator.
9. Has a current (active) diagnosis of acute hepatitis due to any cause.

   Note: Subjects with chronic hepatitis C may enter the study as long as they fulfill all entry criteria, have stable liver function tests, and have no significant impairment of hepatic synthetic function (significant impairment of hepatic synthetic function is defined as a serum albumin <2.8 mg/dL or an INR >1.7 in the absence of another explanation for the abnormal laboratory value).
10. Has evidence of decompensated liver disease manifested by the presence of or a history of ascites, esophageal or gastric variceal bleeding, hepatic encephalopathy or other signs or symptoms of advanced liver diseases

    or

    has liver cirrhosis and a Child-Pugh Class C score or Pugh-Turcotte (CPT) score >9.

    Note: To calculate the CPT score and associated Child-Pugh Class, refer to the following website: http://www.mdcalc.com/child-pugh-score-for-cirrhosis-mortality (see Section 12.8).
11. Is pregnant, breastfeeding, or expecting to conceive.
12. .Is female and expecting to donate eggs (at any time during the study) or is male and is expecting to donate sperm (at any time during the study).
13. 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)

Following completion of the Day 1 procedures and confirmation of eligibility, the site will contact the IVRS/IWRS for assignment of the study drug. Sites should not call IVRS/IWRS to dispense study drug until the subject has met all criteria for the study and is ready to

receive the first dose of study medication on Day 1. The treatment to be used in this trial is outlined below in Table 2.

Table 2 Trial Treatment During Base Study and Study Extension

Drug	Dose/Potency	Dose Frequency	Route of Administration
MK-1439A	Single tablet FDC containing MK-1439 100 mg, lamivudine 300 mg, and tenofovir disoproxil fumarate (TDF) 300 mg	QD	PO

Subjects will receive study medication at the Day 1 visit and should take the first dose of medication the same day.

MK-1439A is to be taken once daily without regard to food at approximately the same time each day.

MK-1439A for the base study and for the study extension (provided that development of MK-1439A is continuing) will be provided centrally by the Sponsor.

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

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/Interruption During the Base Study or the Study Extension

Dose Modification

No dose modification of study therapy is allowed during the study.

Dose Interruption:

Consideration should be given to interrupting study therapy for toxicity management (see Section 7.1.2.6).

Interruptions from the protocol specified treatment plan that are expected to be 7 days or greater require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

5.2.2 Timing of Dose Administration

Subjects will be instructed to take one tablet of MK-1439A once a day (q.d.) orally, with or without food at the approximately the same time each day.

If a subject misses a dose of study drug and it is less than 12 hours before the next dose, the missed dose should be skipped and the normal dosing schedule resumed. The subject should not double the next dose in order to compensate for what has been missed. If a subject misses a dose and it is greater than 12 hours before the next dose, the missed dose should be taken and the normal dosing schedule resumed.

5.2.3 Trial Blinding/Masking

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

5.3 Randomization or Treatment Allocation

Treatment allocation will occur centrally using an interactive voice response system/integrated web response system (IVRS/IWRS). There is one treatment arm. Subjects participating in this trial will be assigned to MK-1439A by non-random assignment.

5.4 Stratification

In the original protocol, enrollment of eligible subjects were to be stratified by mutation type (K103N, Y181C, and G190A), however as enrollment was discontinued at 10 subjects, no stratification will occur.

5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

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 Clinical Director. 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.

No medications are to be taken within 30 days of the start of the study without the knowledge of the investigator.

Listed below are specific restrictions for concomitant therapy or vaccination during the course of the trial:

Permitted Concomitant Medications/Therapies

The concomitant use of other medications/therapies is allowed unless specifically prohibited in the Prohibited Concomitant Medications/Therapies section below. Before placing a subject on a specific medication/therapy, it is the responsibility of the investigator to check on potential drug-drug interactions between that medication/therapy.

1. Use of oral or other hormonal contraception is permitted.

2. Newly approved regimens for the treatment of HCV infection are permitted, as long as there are no known potential drug-drug interactions between those treatments and any of the study medications. The Merck Clinical Director or designee should be contacted if there are any questions about whether there is a potential drug-drug interaction with a specific treatment that the Investigator is planning to give the subject.

Prohibited Concomitant Medications/Therapies

In general, concomitant use of immune therapy agents or other immunosuppressive therapy is not allowed during the course of the study. Important exceptions to this rule include:

- Short courses of corticosteroids (e.g., as for asthma exacerbation) **are allowed**.
- Intralesional or localized electron beam therapy for cutaneous Kaposi's sarcoma **is permitted**.
- If a subject develops a malignancy (for example lymphoma) after treatment allocation, the subject **may receive** chemotherapy (including cancer immunotherapy) and remain in the study if, in the opinion of the investigator, the benefits outweigh the risks. Depending on the type of chemotherapy, study medication may need to be interrupted until completion of the chemotherapy.
- If a subject requires interferon-based treatment for hepatitis after treatment allocation, the subject **may receive** treatment and remain in the study if, in the opinion of the investigator, the benefits outweigh the risks. If it is possible, interferon-based therapy should be deferred until the completion of the study.

Antiretroviral therapies other than those used in the study (MK-1439A) are also not permitted during the course of the study. Subjects who discontinue study therapy due to virologic failure may initiate antiretroviral therapy in the time period between virologic failure confirmation and the contact which occurs approximately 24 weeks after study discontinuation.

Investigational agents must be discontinued30 days prior to signing consent in this study and are not permitted during the course of the study.

Prohibited Concomitant Therapy Due to Potential Interactions with MK-1439A

MK-1439 is expected to be eliminated mainly via CYP (cytochrome)-mediated oxidation.

The medications and/or substances below are prohibited in this study because they are moderate or potent inducers of CYP3A4 and their coadministration with MK-1439A could possibly result in reduced drug levels of MK-1439 or has the potential for additional drug-drug interactions. Since this list is not comprehensive, the investigator should use his/her medical judgment when a subject presents with a medication not on the list or call the Sponsor Clinical Director or Designee for clarification. Prohibited medications/therapy due to MK-1439 interactions are listed in Table 3.

Table 3 Prohibited Medications/Therapy Due to MK-1439 Interactions

Prohibited Medication/Therapy Due to MK-1439 Interactions
Carbamazepine
Phenobarbital
Phenytoin
Rifabutin
Rifampin
Herbal remedies
St. John's Wort
Modafinil
Bosentan
Nafcillin

The investigator should discuss any questions regarding this with the Sponsor Clinical Director.

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

Diet

MK-1439A can be taken without regard to food and should generally be taken at approximately the same time each day.

5.8 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal procedures; including specific details regarding withdrawal from Future Biomedical Research, are provided in Section 7.1.4 – Other Procedures.

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

A subject must be discontinued from the trial for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.

  Note: Please provide additional detail for the reason the subject withdrew consent on the Subject Disposition eCRF.

- The subject has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, places the subject at unnecessary risk through continued participation in the trial or does not allow the subject to adhere to the requirements of the protocol; these may include but are not limited to:
    - clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include symptomatic hyperlactataemia, metabolic/lactic acidosis, progressive hepatomegaly, rapidly elevating aminotransferase levels, and hepatomegaly and steatosis even in the absence of marked transaminase elevations).
- The subject has a confirmed positive serum/urine pregnancy test.

  Note: Subjects who become pregnant during the study will be asked to join a pregnancy registry which collects information about the outcome of the pregnancy.
- The subject fails to comply with the dosing, evaluations, or other requirements of the trial.
- A physician investigator feels it is in the best interest of the subject to discontinue.
- The subject has an adverse experience or tolerability issue related to study medication which requires discontinuation of the medication.
- Subject has a creatinine clearance of <50 mL/min (confirmed by repeat measurement) based on the Cockcroft-Gault equation:

  Male:

  Cl_{cr} (mL/min) = (140-age) x weight (in kg) / 72 x serum creatinine (mg/dL)

  Female:

  Cl_{cr} (mL/min) = (140-age) x weight (in kg) / 72 x serum creatinine (mg/dL) X 0.85
- Subject has serum phosphorous <0.32 mmol/L.
- The subject requires discontinuation of study therapy for a reason other than virologic failure.

Subjects who discontinue the trial prior to the last scheduled treatment visit should have an Early Discontinuation visit and a 14-day follow up visit conducted.

A subject must be discontinued from study therapy, regardless of compliance; if they meet the protocol defined virologic failure criteria in Section 4.2.4.1. Subjects who discontinue study therapy due to virologic failure will complete an Early Discontinuation visit and a 14-day follow-up visit. In addition, subjects who discontinue study therapy due to virologic failure will be contacted by the site approximately 24 weeks after the Early Discontinuation visit. The subject will no longer attend any other scheduled study visits following discontinuation. At this contact, information will be collected on the subjects' subsequent HIV regimens (following discontinuation of the study treatment) and virologic outcome. Details regarding the regimens used and virologic outcome will be recorded on the eCRF.

If approved by the Sponsor, a subject can remain on study if they cannot make it to regularly scheduled study visits due to unforeseen circumstances but are able to remain on study therapy and the Investigator believes it is in the best interest of the subject to do so.

Once discontinued from the base study, a subject is not eligible to enter the study extension. A subject who completes the base study and does not elect to participate in the study extension is considered to have completed the study.

5.9 Subject Replacement Strategy

A subject who discontinues from the trial will not be replaced.

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, discontinues from the trial or is lost to follow-up (i.e. the subject is unable to be contacted by the investigator).

5.11 Clinical Criteria for Early Trial Termination

Early trial termination will be the result of the criteria specified below:

If the futility criterion is met for either of the two interim futility analyses, the study may stop due to lack of efficacy. Refer to Section 8.7 (Interim Analyses) for further information regarding the two futility analyses. Further recruitment in the trial or at a particular trial site(s) may be stopped due to insufficient compliance with the protocol, GCP, and/or other applicable regulatory requirements, procedure-related problems, or the number of discontinuations for administrative reasons is too high.

6.0 TRIAL FLOW CHART

Flow chart A applies to the base study from screening through follow-up after the Week 96 visit; flow chart B applies to those subjects continuing into the extension study from Week 96 through follow-up after the Week 192 visit.

Flow Chart A: Screening Through Week 96 Plus 14 Days Follow-up (Base Study)

Trial Period:	Screening		Treatment												Post-treatment			
Visit Number/Title:	1 Screen-ing	2	3	4	5	6	7	8	9	10	11	12	13	14	U (Virologic Failure Confirmation)	U (Early Discon-tinuation)[k, l]	U Virologic Failure Follow Up	99
Scheduled Weeks/Days:	Screen	Fasting[a] Day 1[b]	WK 2	WK 4	WK 8	Fasting[a] WK 12	WK 16	WK 24	WK 36	Fast-ing[a] WK 48	WK 60	WK 72	WK 84	Fast-ing[a] WK 96	≥ 1 to ≤ 4 weeks after initial virologic failure	At time of Discon	24 Weeks Post Virologic Failure	Post study 14 day follow up
Visit Windows[m]			+/- 3 days						+/- 7 days									- 2 days
Administrative Procedures																		
Informed Consent	X													X[q]				
Informed Consent for Future Biomedical Research	X																	
Inclusion/Exclusion Criteria	X	X																
Provide Subject Identification Card	X																	
Medical History[d]	X																	
Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X

Trial Period:	Screening		Treatment												Post-treatment			
Visit Number/Title:	1 Screen -ing	2	3	4	5	6	7	8	9	10	11	12	13	14	U (Virologic Failure Confirmation)	U (Early Discon- tinuation)[k, l]	U Virologic Failure Follow Up	99
Scheduled Weeks/Days:	Screen	Fasting[a] Day 1[b]	W K 2	WK 4	W K 8	Fas tin g[a] W K 12	W K 16	WK 24	W K 36	Fast- ing[a] WK 48	WK 60	W K 72	W K 84	Fast- ing[a] WK 96	≥ 1 to ≤ 4 weeks after initial virologic failure	At time of Discon	24 Weeks Post Virologic Failure	Post study 14 day follo w up
Visit Windows[m]			+/- 3 days						+/- 7 days									- 2 days
Register Study Visit via Interactive Voice (Web) Response System (IVRS/IWRS)	X	X		X	X	X	X	X	X	X	X	X	X	X		X		
Dispense Study Therapy via IVRS/IWRS		X		X	X	X	X	X	X	X	X	X	X	X[q]				
Provide/Review Study Medication Diary		X	X	X	X	X	X	X	X	X	X	X	X	X		X		
Clinical Procedures/Assessments																		
Full Physical Examination	X																	
Directed Physical Examination		X	X	X	X	X	X	X	X	X	X	X	X	X		X		X
Height	X																	
Vital Signs (including pulse rate, blood pressure, respiratory rate, and body temperature) and Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X
12-Lead Electrocardiogram (ECG) (Local)[d]		X[f]																
Adverse Events Monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X

Trial Period:	Screening		Treatment												Post-treatment			
Visit Number/Title:	1 Screen -ing	2	3	4	5	6	7	8	9	10	11	12	13	14	U (Virologic Failure Confirmation)	U (Early Discon-tinuation)[k, l]	U Virologic Failure Follow Up	99
Scheduled Weeks/Days:	Screen	Fasting[a] Day 1[b]	W K 2	WK 4	W K 8	Fas tin g[a] W K 12	W K 16	WK 24	W K 36	Fast-ing[a] WK 48	WK 60	W K 72	W K 84	Fast-ing[a] WK 96	≥ 1 to ≤ 4 weeks after initial virologic failure	At time of Discon	24 Weeks Post Virologic Failure	Post study 14 day follo w up
Visit Windows[m]			+/- 3 days						+/- 7 days									- 2 days
Birth Control Confirmation	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X
Assess Subject Eligibility for Extension[q]														X				
Laboratory Procedures/Assessments																		
Serum Pregnancy Test[e]	X																	
Urine Pregnancy Test[e]		X[f]	X	X	X	X	X	X	X	X	X	X	X	X		X		X
Collect Blood for Safety Laboratory Tests (Hematology/Chemistry)[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Subject Contact/Follow Up (For subject who discontinue due to Virologic Failure ONLY)																	X[l]	
Hemostatic Function Test[h]	X																	
HIV/Hepatitis Screen[i]	X																	

Trial Period:	Screening		Treatment												Post-treatment			
Visit Number/Title:	1 Screen -ing	2	3	4	5	6	7	8	9	10	11	12	13	14	U (Virologic Failure Confirmation)	U (Early Discon- tinuation)[k, l]	U Virologic Failure Follow Up	99
Scheduled Weeks/Days:	Screen	Fasting[a] Day 1[b]	W K 2	WK 4	W K 8	Fas tin g[a] W K 12	W K 16	WK 24	W K 36	Fast- ing[a] WK 48	WK 60	W K 72	W K 84	Fast- ing[a] WK 96	≥ 1 to ≤ 4 weeks after initial virologic failure	At time of Discon	24 Weeks Post Virologic Failure	Post study 14 day follo w up
Visit Windows[m]			+/- 3 days						+/- 7 days									- 2 days
Virology Test Plasma HIV RNA quantification test (Abbott Real Time HIV-1)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Collect Blood for CD4 Cell Count[o]	X	X						X		X		X		X				
Collect Blood for MK-1439 PK[J]		X		X	X			X		X								
Collect Plasma for Viral Resistance Test	X[n]			X	X	X	X	X	X	X	X	X	X	X	X	X		
Collect Blood for Genetic Analysis[c]		X																
Collect Blood for Deep Sequencing Analysis		X													X			
Collect Plasma for Future Biomedical Research[p]		X								X				X				

a. Fasting for at least 8 hours.
b. Within 45 days of screening visit and prior to the first dose on Day 1.
c. This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. If there is either a documented law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes, then this sample will not be collected at that site. 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.
d. A local ECG should be performed prior to the subject's first dose of study medication (within 7 days prior to the study Day 1 visit).
e. For women of childbearing potential.
f. Results of test must be available prior to enrolling the subject.
g. Refer to Table 4 for listing of specific blood safety tests.
h. Hemostatic Function Test includes: Prothrombin time (PT), Activated Partial Thromboplastic Time (APTT), and International Normalized Ratio (INR).
i. HIV/Hepatitis Screen tests includes: Enzyme immunoassay HIV antibody screen, Serum Hepatitis B surface antigen, Serum Hepatitis B surface antibody, Serum Hepatitis B e-antigen and Serum Hepatitis C antibody. A plasma hepatitis C virus polymerase chain reaction (PCR) quantitative test will be performed if the Hepatitis C antibody test is positive.
j. One sample for assay of MK-1439 plasma concentrations will be collected at Day 1 (Pre-dose), Week 4 (Pre-Dose), Week 8 (random). At Weeks 24 and 48, two samples will be collected, pre-dose and 30 mins to 2 hours postdose (the subject should be fasting for the Week 48 samples).
k. If virologic failure is confirmed (with a confirmatory HIV-1 RNA at least one week later), and the decision is made to discontinue the subject, plasma for resistance need not be collected again at the early discontinuation visit. All other early discontinuation tests should be performed at the early discontinuation visit.
l. Subjects who discontinue due to virologic failure, will no longer attend scheduled study visits, but will be followed at approximately 24 weeks after study discontinuation to determine virologic outcome and regimen used.
m. The timing of visits 3 through 14 is relative to the Day 1 visit. Every attempt must be made to keep subjects on schedule.
n. Subjects should have a documented genotype performed by local lab prior to screening. An additional sample will be obtained and analyzed by the central lab as a part of the screening process to establish a baseline resistance profile. If, upon receipt of the central laboratory results, a discordance between the local sample drawn prior to screening and central laboratory results is identified, such that exclusion criterion #4 is met using the central laboratory results, the subject should not be enrolled in the study. In addition, if the central laboratory test results do not confirm inclusion criteria 6, the subject should not be enrolled.
o. If the investigator believes more frequent CD4 counts are necessary for clinical care or are required per local treatment guidelines, then he/she has the option to add additional CD4 counts at a scheduled visit. The samples should be sent to the central lab for testing.
p. Plasma samples for FBR should be collected at Day 1, and at Weeks 48 and 96 if the subject signs the FBR consent.
q. If the subject is eligible and elects to enter the study extension, he/she will be considered to have completed the base study and will, after providing informed consent, immediately enter the study extension.

Flow Chart B: Week 112 Through Week 192 Plus 14 Days Follow-up (Study Extension)

Trial Period	Treatment						Post-Treatment		
Visit Number/Title:	**15**[a]	**16**	**17**	**18**	**19**	**20**	**U (Virologic Failure Confirmation)**	**U (Extension Early Discontinuation)**	**99**
Trial Period:		**Extension: Treatment** [b]							**Post-Treatment** [c]
TRIAL PROCEDURES	**Wk 112**	**Wk 128**	**Fasting Wk144**	**Wk 160**	**Wk 176**	**Fasting Wk 192**	**≥ 1 to ≤4 weeks after initial virologic failure**	**At time of Discontinuation**	**14 Day Follow-up**
Visit Windows[j]	**+/- 7 days**								-2 days
Administrative Procedures									
Concomitant Medication Review	x	x	x	x	x	x		x	x
Register Study Visit via Interactive Voice/Web Response System (IVRS/IWRS)	x	x	x	x	x	x		x	
Dispense Study Therapy [d]	x	x	x	x	x				
Provide/ Review Study Medication Diary	x	x	x	x	x	x		x	
Clinical Procedures/Assessments									
Directed Physical Examination	x	x	x	x	x	x		x	x
Vital Signs (including pulse rate, blood pressure, respiratory rate, and body temperature) and weight	x	x	x	x	x	x		x	x
Adverse Events Monitoring	x	x	x	x	x	x		x	x
Birth Control Confirmation	x	x	x	x	x	x		x	x
Laboratory Procedures/Assessments									
Collect Blood for Safety Laboratory Tests (Hematology/Chemistry) [e]	x	x	x [f]	x	x	x [f]	x	x	x
Urine Pregnancy Test (if applicable) [g]	x	x	x	x	x	x		x	x
Virology Test Plasma HIV viral RNA quantification test (Abbott Real Time HIV-1)	x	x	x	x	x	x	x	x	x

Trial Period	Treatment						Post-Treatment		
Visit Number/Title:	**15**[a]	**16**	**17**	**18**	**19**	**20**	**U (Virologic Failure Confirmation)**	**U (Extension Early Discontinuation)**	**99**
Trial Period:		**Extension: Treatment** [b]							**Post-Treatment** [c]
TRIAL PROCEDURES	**Wk 112**	**Wk 128**	**Fasting Wk144**	**Wk 160**	**Wk 176**	**Fasting Wk 192**	**≥ 1 to ≤4 weeks after initial virologic failure**	**At time of Discontinuation**	**14 Day Follow-up**
Visit Windows[j]	**+/- 7 days**								-2 days
Collect Blood for CD4 Cell Count[h]			x			x			
Viral Resistance Test (Plasma)							x	x [i]	

a. Subjects who enter the study extension are considered enrolled in the extension upon providing written informed consent at the Week 96 study visit.
b. The visit windows are approximately +/- 14 days for all visits from Week 112 through Week 192. The timing of each visit is relative to the (Day 1) visit. Every attempt must be made to keep subjects on schedule.
c. The visit window for the post-study 14-day follow-up visit is approximately – 2 to 0 days.
d. IVRS/IWRS will be used to allocate drug and to manage distribution of MK-1439A.
e. Refer to Table 4 for listing of specific blood safety tests.
f. Fasting for at least 8 hours. Fasting is required at these visits for lipids measurement.
g. For women of childbearing potential
h. If the investigator believes more frequent CD4 counts are necessary for clinical care or are required per local treatment guidelines, then he/she has the option to add additional CD4 counts at a scheduled visit. The samples should be sent to the central lab for testing.
i. If virologic failure or relapse is confirmed (with a confirmatory HIV-1 RNA at least one week later), and the decision is made to discontinue the subject, plasma for resistance need not be collected again at the early discontinuation visit. All other early discontinuation tests should be performed at the early discontinuation visit.
j. The timing of visits 15 through 20 is relative to the Day 1 of base study visit. Every attempt must be made to keep subjects on schedule.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

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

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

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The investigator or qualified designee must obtain documented consent from each potential subject or each subject's legally acceptable representative prior to participating in a clinical trial or Future Biomedical Research.

7.1.1.1.1 General Informed Consent

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

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

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

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

The informed consent will adhere to IRB/ERC 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. A review of these criteria should occur at the Screening visit and on the Day 1 visit. For subjects who wish to continue into the study extension, the additional inclusion criteria (11 to 14 Section 5.1.2) are to be reviewed at the Week 96 study visit.

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.

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. The medical history should include information pertaining to the diagnosis of HIV infection and the year diagnosed. If a subject has previously been diagnosed with any AIDS defining condition, or a CD4 count <200, the condition as well as a corresponding medical history of Acquired Immune Deficiency Syndrome must be reported. In addition, the subject's history of smoking, for calculation of Framingham cardiovascular risk, should be obtained and recorded on the appropriate eCRF.

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 and record prior medication taken by the subject within 30 days before starting the trial.

Investigational agents must be discontinued 30 days prior to signing Informed Consent.

7.1.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication and the reason for therapy, if any, for medications taken by the subject during the trial.

7.1.1.6 Assignment of Screening Number

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

subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects.

The site must access the IVRS/IWRS system to register each screening subject.

Specific details on the screening visit requirements are provided in Section 7.1.5.1.

7.1.1.7 Assignment of Treatment/Randomization Number

All eligible subjects will be allocated, by non-random assignment, and will receive a treatment/randomization number. The treatment/randomization number identifies the subject for all procedures occurring after treatment allocation/randomization. Once a treatment/randomization number is assigned to a subject, it can never be re-assigned to another subject.

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

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

Subject Diary Cards will be used to ensure and document drug compliance.

On Day 1, the investigator/study coordinator will give the subject a diary card to be completed during the study period. The study coordinator will be responsible for entering the subject's identification number on the subject diary card prior to giving the diary card to the subject. The subject should follow the instructions on the diary card for recording study drug. Aside from the initial information entered by the study coordinator, only the subject should enter information on the diary card. The subject is to return the completed diary card at each scheduled visit. The study coordinator will be responsible for reviewing the diary card for completeness and accuracy with the subject. Only the subject shall make any changes to the entries on the card. The subject will initial the card to confirm that the information is accurate. The study coordinator will be responsible for transferring the appropriate information from the diary card onto the appropriate case report form.

Rigorous monitoring is especially important during the early part of the study, specifically between the Day 1 and Week 4 visits to ascertain if there are problems with non-compliance as early as possible, to access whether the subject is taking study medication as directed and to ensure that subjects experiencing difficulties are re-educated, as appropriate.

Interruptions from the protocol specified treatment plan that are expected to be 7 days or greater due to non-compliance require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Physical Examination

All physical examinations should be performed as indicated in the Trial Flow Chart (Section 6.0). All physical examinations must be performed by the principal investigator or sub-investigator (physician, physician assistant or nurse practitioner).

A complete (full) physical examination (including vital signs [weight, pulse, respiratory rate, blood pressure, and body temperature]) must be obtained at the Screening visit. A complete

physical examination generally includes the following assessments: general appearance, head, eyes, ears/nose/throat, neck, lymph nodes, skin, lungs, heart, abdomen, musculoskeletal, and neurologic evaluations. Breast, rectal, and genitourinary/pelvic exams should be performed when clinically indicated.

Physical examinations after the Screening visit will be directed exams and will include vital signs. Any significant changes between the Screening and Day 1 visits should be noted on the Medical History eCRF at Day 1. Any significant changes in the physical examination after receiving study therapy at Day 1 must be reported as AEs and entered on the AE eCRF. If the subject is discontinued for any reason during the treatment phase, every attempt should be made to perform a final physical examination.

7.1.2.2 Height Assessment

The subject's height should be assessed as indicated in the Trial Flow Chart A (Section 6.0). If height is measured after the Screening visit, the site should indicate whether or not the result is clinically significant and the result should be documented in the subject's chart. If the result is clinically significant, it should be captured as an AE on the eCRF.

7.1.2.3 Vital Signs and Weight

Vital signs, including pulse rate, respiratory rate, blood pressure and body temperature, and weight should be assessed as indicated in the Trial Flow Charts (Section 6.0). Subjects should be resting in a semi-recumbent position for at least 10 minutes prior to having vital sign measurements obtained.

Note: Oral temperatures should be taken. If an oral temperature measurement is not possible, a tympanic, rectal, or axillary temperature measurement may be taken and should be recorded appropriately.

After the Screening visit, the site should indicate whether or not the result is clinically significant and document the result in the subject's chart. If any result is clinically significant, it should be captured as an AE on the eCRF.

7.1.2.4 12-Lead ECG (performed locally)

A local 12-Lead ECG should also be performed prior to the subject's first dose of study medication (within 7 days prior to the Study Day 1 visit), as indicated in the Trial Flow Chart A (Section 6.0), and any abnormalities should be documented. Results must be available prior to the subject receiving study medication. Subjects should be resting in a semi-recumbent position for at least 10 minutes prior to having ECG readings obtained. Clinically significant findings from the pre- Day 1/Day 1 ECG must be documented in the subject's chart and captured on the medical history eCRF.

If an ECG is performed for any medical reason while the patient is on the study treatment or during the follow-up period, any clinically significant changes compared with the Day 1 ECG must be captured as AEs on the eCRF and documented in the subject's chart.

7.1.2.5 Adverse Events

When evaluating an adverse event, the investigator should document in the eCRF if there is a likely causality relationship to immune reconstitution syndrome (IRIS).

If a subject has been diagnosed with an AIDS defining condition following initiation of study medication, the condition must be reported as an AE.

Due to the use of lamivudine and tenofovir in this trial, subjects should be monitored for symptoms of hyperlactataemia.

Details on assessing and recording AEs can be found in Section 7.2.

7.1.2.6 Toxicity Management

Guidelines for grading the severity of laboratory AEs are based on Division of Acquired Immunodeficiency Syndrome (DAIDS) criteria for grading severity of AEs (Section 12.7). Decisions to temporarily withhold study therapy because of an adverse experience will be reviewed on a case-by-case basis by the investigator.

The investigator should consider temporarily withholding study therapy if the severity of the adverse experience is Grade 3 or above and/or if clinically indicated. The decision to interrupt study therapy should take into account the subject's baseline laboratory values and any concomitant medication that could be contributory. At the discretion of the investigator, therapy may generally be reinitiated when laboratory abnormalities or clinical AEs return to near normal or baseline values.

If the adverse experience is considered serious and may have been caused by study medication (as defined in Section 7.2.4) or if re-exposure to the test drug poses additional potential significant risk to the subject, then the re-challenge must be approved in advance by the Merck Clinical Director or Designee and the Independent Ethics Committee/Institutional Review Board and a re-challenge consent is needed prior to re-initiation of study therapy. If advance approval of re-challenge is not required by local regulations, the IEC/IRB will receive notification for information only.

If, after re-initiation of study therapy, there is a recurrence of the laboratory abnormality or clinical AE, consideration should be given to permanently discontinuing all study therapy. Whenever study drugs are interrupted, the Merck Clinical Director or Designee should be notified.

7.1.2.7 Birth Control Confirmation

Care must be taken to avoid pregnancy in female subjects of childbearing potential and in the female partners of childbearing potential of male subjects.

Site personnel must confirm that subjects and their partner(s) are using acceptable methods of contraception. This confirmation must be documented in the subject's chart.

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 12.4.

7.1.3.1 Serum/Urine Pregnancy Test

For women of childbearing potential, serum pregnancy is to be done at the Screening visit, and urine pregnancy is to be done at the Day 1 visit prior to dispensing study drug. Urine pregnancy tests must also be subsequently done at each study visit, including the Early Discontinuation Visit (if applicable) and 14 day Follow-up Visits in both the base study and the study extension. Results must be documented in the subject's chart. A subject found to be pregnant must be discontinued from the study.

7.1.3.2 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry and urinalysis are specified in Table 4.

Table 4 Laboratory Tests

Hematology	Chemistry	Other
Hematocrit	Alkaline phosphatase	Prothrombin time (PT)[3]
Hemoglobin	Alanine aminotransferase (ALT, SGPT)	Activated partial thromboplastin time (APTT)[3]
Platelet count	Aspartate aminotransferase (AST, SGOT)	International Normalized Ratio (INR)[3]
Red Blood Cell Count	Creatine Kinase	Hepatitis B Virus surface antigen[3]
Erythrocyte Mean corpuscular volume	Total Bilirubin	Hepatitis B Virus surface antibody[3]
White Blood Cell Count (Total and Differential)	Direct Bilirubin	Hepatitis B e-Antigen[3]
CD4% and Absolute CD4/Lymphocytes	Indirect Bilirubin	Hepatitis C Antibody[3]
CD8% and Absolute CD8/Lymphocytes	Amylase	Plasma hepatitis C virus PCR quantitative[4]
CD4/CD8 ratio	Lipase	Enzyme immunoassay HIV antibody (with confirmation WB)[3]
	Glucose, fasting[1]	HIV viral RNA Quantification
	Glucose, non-fasting[2]	Serum β-human chorionic gonadotropin (hCG) test[5]
	Blood Urea Nitrogen	Urine β-human chorionic gonadotropin (hCG) test[6]
	Creatinine[8]	HIV Viral resistance[7]
	Phosphorus	
	Magnesium	
	Calcium	
	Protein	
	Albumin	

Hematology	Chemistry	Other
	Sodium Potassium Chloride Bicarbonate High-density lipoprotein cholesterol (HDL-C) (fasting[1]) Low-density lipoprotein cholesterol (LDL-C) (fasting[1]) Triglycerides (fasting[1]) Total Cholesterol (fasting[1])	

1. Perform at the Day 1, Week 12, 48, and 96 visits and, for subjects who continue into the extension, at the Week 144 and 192 visits. Subjects should be fasting for 8 hours.
2. Perform at the Screening visit, Day 1 and the Weeks 2, 4, 8, 16, 24, 36, 60, 72 and 84 visits, and, in the extension, at the Study Week 112, 128,160 and 176 visits and the 14 day follow-up visit.
3. Perform at the screening visit only.
4. If the result of the Hepatitis C Antibody testing is positive, then a plasma hepatitis C virus PCR quantitative test will also be performed.
5. Serum β hCG test at the Screening visit to be performed by central laboratory.
6. Urine β hCG test to be performed at the investigator site at Day 1 and every study visit thereafter.
7. Perform at the Screening visit, Weeks 4, 8, 12, 16, 24, 36, 48, 60, 72, 84 and 96 visits, the Virologic Failure confirmation visit, and the Early Discontinuation visit (if not collected at Virologic Failure confirmation visit). In the extension, resistance sample will be collected only at Virologic Failure and Discontinuation Visit.
8. Creatinine clearance will be computed at every visit by the central laboratory and provided to the site in the report that the site receives from the central laboratory.

7.1.3.3 HIV/Hepatitis Screening

At the Screening visit, serum HIV/Hepatitis screening tests will be performed including: Enzyme immunoassay HIV antibody (with confirmation WB), serum Hepatitis B surface antigen, serum Hepatitis B surface antibody, serum Hepatitis B e-antigen and serum Hepatitis C antibody. A plasma hepatitis C virus PCR quantitative test will be performed if the Hepatitis C antibody test is positive.

7.1.3.4 Virology Test

Plasma HIV-1 RNA quantification will be performed at all visits. The testing will be performed at the central laboratory using the Abbott RealTime HIV-1 assay.

7.1.3.5 Viral Resistance Testing

Blood samples will be collected for genotypic HIV viral resistance testing at the Screening visit for study inclusion purposes and to determine MK-1439, tenofovir, and lamivudine resistance. Additional resistance testing on screening samples may be performed. Blood samples will also be collected for HIV viral resistance testing at Weeks 4, 8, 12, 16, 24, 36, 48, 60, 72, 84 and 96, in the base study and at the Virologic Failure Confirmation visit or the Early Discontinuation Visit (if not already obtained at Virologic Failure Confirmation visit) in both the base study and the study extension.

Prior to screening, subjects must have documentation of genotype performed confirming the presence of one and only one of the following NNRTI mutations: K103N, Y181C, or G190A. An additional sample must be obtained and analyzed by the central laboratory as a

part of the screening process to establish a baseline resistance profile. The results of the central laboratory test results must be available prior to subject enrollment. If, upon receipt of the central laboratory results, a discordance between the local sample drawn prior to screening and central laboratory results is identified, such that exclusion criterion #4 is met using the central laboratory results, the subject should not be enrolled in the study. In addition, if the central laboratory test results do not confirm inclusion criteria #6, the subject should not be enrolled. All other resistance testing will be performed by the central laboratory only.

7.1.3.6 CD4 Cell Counts

CD4 cell count (absolute and percentage) will be determined at Screening, Day 1, and at Weeks 24, 48, 72 and 96, for subjects who continue into the study extension, CD4 cell count will also be determined at the Study Week 144 and 192 visits. The testing will be performed at the central laboratory using a commercially available assay. If the investigator believes that more frequent CD4 cell counts are necessary for clinical care or are required per local treatment guidelines, then he/she has the option to add additional CD4 counts at a scheduled visit. The samples should be sent to the central lab for processing.

7.1.3.7 Pharmacokinetic/Pharmacodynamic Evaluations

MK-1439 population PK samples will be collected from all subjects as outlined in Table 5. The exact time the dose of study medication was taken prior to the sample collection will be recorded on the appropriate eCRF. The type of meal (full, medium, light or no meal) consumed with the last dose of study medication prior to the collection of the PK sample will also be recorded on the appropriate eCRF. The type of meal is defined as the following:

- No Meal - the subject did not have a meal
- Light Meal - the subject consumed a snack (less than 250 calories)
- Medium Meal - the subject consumed a small meal (from 250 to 750 calories)
- Full Meal - the subject consumed a large meal (greater than 750 calories)

Note: At Weeks 24 (Visit 8) and 48 (Visit 10), two PK samples will be collected, one pre-dose and one 0.5-2.0 hours post dose. Subjects should be fasting for the collection of the Week 48 samples. Subjects will be given their dose of MK-1439A in the office following the collection of the pre-dose sample and may stay in the office or return to the office for the collection of the post dose sample.

Table 5 Pharmacokinetic Sampling Timepoints

Visit Number	Study Day/Week	Time Relative to MK-1439A Dose
2	Day 1	Sample to be collected predose
4	Week 4	Sample to be collected predose
5	Week 8	Sample to be collected pre or postdose
8	Week 24	Sample to be collected predose and within 0.5 to 2 hours postdose.
10	Week 48	Sample to be collected predose and within 0.5 to 2 hours postdose (Subject should remain fasting until the postdose PK sample is collected).

Sample collection, storage and shipment instructions for the PK samples will be provided in the operations/laboratory manual.

7.1.3.8 Planned Genetic Analysis Sample Collection

Sample collection, storage and shipment instructions for Planned Genetic Analysis samples will be provided in the operations/laboratory manual.

7.1.3.9 Future Biomedical Research Sample Collection

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

- Leftover DNA for future research
- Plasma for future research

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws from participation in the trial, all applicable activities scheduled for the Early Discontinuation Visit should be performed at the time of discontinuation. 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. In addition all investigative products must be retrieved from the subject.

7.1.4.1.1 Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. 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), and a form will be provided by the Sponsor to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. A letter will

be sent from the Sponsor to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for 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 specimen destruction cannot be processed.

7.1.4.2 Blinding/Unblinding

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

7.1.4.3 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:

A centrifuge and -20 degrees Celsius freezer will be required for the processing and storage of lab samples.

Please refer to the central laboratory manuals for equipment requirements and necessary maintenance or calibration.

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

Written informed consent/assent must be obtained from the subject prior to performing any study-specific procedures. Potential subjects will be evaluated to determine if they fulfill the Inclusion/Exclusion entry requirements as set forth in Section 5.1. The investigator will discuss with each potential subject the study, its requirements, and its restrictions. The study screening period is up to 45 days.

- All procedures listed for the Screening visit (Visit 1) in the Trial Flow Chart A (Section 6.0) must be completed and the subjects eligibility confirmed by the investigator prior MK-1439A administration on Day 1.

- Blood will be collected for safety laboratory evaluations, Hemostatic function tests, HIV/Hepatitis Screen, HIV-1 RNA quantification, CD4 cell counts, and viral resistance testing. These samples will be sent to the appropriate central laboratory(ies) following the procedure(s) set forth in the manual(s).
- Female subjects of childbearing potential will have a serum pregnancy test (hCG) collected at the screening visit. Women who are found to be pregnant will be excluded from the study.
- Subjects will be instructed about the restrictions for concomitant medications, as noted in Section 5.5.
- Subjects will be given a study participation identification card. The card will contain contact information (including direct telephone numbers) to be utilized in the event of an emergency.

7.1.5.2 Treatment Period Visits (Visits 2 – 14)

Study Day 1 (Visit 2)

- Procedures listed for Day 1 (Visit 2) on the Trial Flow Chart A (Section 6.0) should be performed prior to the dispensing study drug on Day 1, unless otherwise specified.
- For a female subject who is of childbearing potential, a urine pregnancy test will be performed at the site prior to study drug initiation. If the urine pregnancy test result is negative and the subject meets the other criteria, the remainder of the pretreatment (Day 1) testing/procedures will be performed. If the urine pregnancy test result is positive, the subject must be discontinued from further participation.
- Blood will be collected for safety laboratory evaluations, HIV-1 RNA quantification, CD4 cell counts, and PK measurements. These samples will be sent to the appropriate central laboratory(ies) following the procedure(s) set forth in the manual(s).
- Following completion of the Day 1 pretreatment procedures and confirmation of eligibility, the site pharmacist or study coordinator will contact the IVRS/IWRS for assignment of the drug to be administered. Sites should not call IVRS/IWRS for drug administration until the subject has met all criteria for the study and are ready to receive the first dose of study medication on Day 1. Eligible subjects will receive a 4-week supply of MK-1439A on Day 1 (Visit 2). Subjects will be instructed to take their first dose of study medication on the same day as the Day 1 study visit.
- The investigator/study coordinator will give the subject a study medication diary to be completed starting on Day 1 and continuing through the treatment period. The site must ensure that the subject is properly trained and comfortable with completing the medication diary prior to leaving the clinic.

Drug Administration

- Subjects will be dispensed a bottle of study drug and will be instructed to take one tablet of MK-1439A q.d. orally, with or without food at approximately the same time each day. The MK-1439A tablets must be kept in the bottle prior to taking study medication since the formulation being used in this study is moisture sensitive.

Week 2 (Visit 3) to Week 96 (Visit 14)

- All procedures for treatment Week 2 (Visit 3) to Week 96 (Visit 14) listed on the Trial Flow Chart A (Section 6.0) should be performed.
- Blood will be collected for safety laboratory evaluations, HIV-1 RNA quantification, CD4 cell counts, HIV viral resistance and PK measurements at the time points specified on the Trial Flow Chart. These samples will be sent to the appropriate central laboratory(ies) following the procedure(s) set forth in the manual(s).
- For a female subject who is of childbearing potential, a urine pregnancy test will be performed at all study visits. If the urine pregnancy test result is positive, the subject must be discontinued.
- Subjects will be required to fast for at least 8 hours prior to study visits at Weeks 12, 48 and 96.
- All bottles of study drug will be returned to the study coordinator at each visit, at which time the drug supplies for the following time period will be dispensed. The number of tablets remaining in the bottle will be counted and recorded in the source documentation. The primary source of adherence data, however, will be the subjects study medication diary.
- Subjects will receive a 4-week supply of study drug at Week 4 (Visit 4), Week 8 (Visit 5) and Week 12 (Visit 6); an 8-week supply at Week 16 (Visit 7) and a 12-week supply at Week 24 (Visit 8), Week 36 (Visit 9), Week 48 (Visit 10), Week 60 (Visit 11), Week 72 (Visit 12) and Week 84 (Visit 13) and, for subjects who are considered eligible and elect to enter the study extension, a 16-week supply at Study Week 96 (Visit 14).
- At each treatment visit, the study coordinator and subject will review the study medication diary information.

7.1.5.3 Treatment Period Visits for Study Extension (Visit 15-20)

- All procedures for Study Week 112 (Visit 15), Week 128 (Visit 16), Week 144 (Visit 17), Week 160 (Visit 18), Week 176 (Visit 19), and Week 192 (Visit 20) listed on the Trial Flow Chart B (Section 6.0) should be performed.
- Blood will be collected for safety laboratory evaluations and HIV-1 RNA quantification at the time points specified in the Trial Flow Chart B. Samples for CD4 counts will also be collected at the Study Week 144 and 192 visits. Subjects will be required to fast for at least 8 hours prior to the Study Week 144 and 192 visits. Samples for HIV viral resistance will be collected only at the virologic failure confirmation visit or, for subjects who discontinue due to any other

reason, at the early discontinuation visit. These samples will be sent to the appropriate central laboratory(ies) following the procedure(s) set forth in the manual(s).

- For a female subject who is of childbearing potential, a urine pregnancy test will be performed at all study visits. If the urine pregnancy test result is positive, the subject must be discontinued.
- All bottles of study drug will be returned to the study coordinator at each visit, at which time the drug supplies for the following time period will be dispensed. The number of tablets remaining in the bottle will be counted and recorded in the source documentation. The primary source of adherence data, however, will be the subject's study medication diary.
- Site staff will access the IVRS/IWRS for registration of visits. Subjects will receive a 16-week supply of study drug at each study visit through Week 192.
- At each study visit the study coordinator and subject will review the study medication diary information.

7.1.5.4 Virologic Failure Confirmation Visit

- When a subject has a virologic failure confirmation visit performed, all procedures for the virologic failure confirmation visit listed on the Trial Flow Charts should be performed.

Protocol defined virologic failure (PDVF) for this study is defined as one of the following:

1) Confirmed (two consecutive measures at least one week apart) HIV-1 RNA ≥50 copies/mL after initial response of HIV-1 RNA <50 copies/mL at any time during the study

OR

2) Confirmed (two consecutive measures at least one week apart) HIV-1 RNA ≥200 copies/mL at Week 24 or Week 36

OR

3) Confirmed (two consecutive measures at least one week apart) HIV-1 RNA ≥50 copies/mL at Week 48.

The virologic failure confirmation visit should be done between 1 and 4 weeks after the first measurement of HIV-1 RNA ≥50 copies/ml.

Subjects should be discontinued, regardless of compliance with study therapy, if they meet the protocol defined virologic failure criteria. Subjects who discontinue study therapy due to virologic failure will complete an Early Discontinuation visit and a 14-day follow-up visit. In addition, subjects who discontinue study therapy due to virologic failure in the base study will be contacted approximately 24 weeks after the Early Discontinuation visit. During this contact, information will be collected on the subjects' subsequent HIV regimens (following discontinuation of the study treatment) and virologic outcome. Details regarding the regimens used and virologic outcome will be recorded on the eCRF.

7.1.5.5 Early Discontinuation Visit

- When a subject discontinues/withdraws from participation in the trial, all procedures for the Early Discontinuation visit listed on the Trial Flow Charts should be performed.
- At a minimum, the following information should be collected when a subject discontinues:
  - The reason the subject discontinued
  - The date of the last dose of study medications from the trial
  - The date of the last assessment and/or contact
  - All Adverse events (AEs) (including any Serious Adverse Events)
- Any AEs 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.
- Subjects who discontinue early from the study are expected to return for a 14-day post therapy follow-up visit.

7.1.5.6 Post-Trial

- Following the completion of study therapy (in the base study or study extension) or in the event of early discontinuation, subjects will be required to return to the clinic approximately 14 days after the last dose of study drug for the post-study visit as outlined in the Trial Flow Charts (Section 6.0).
- If the post-study visit occurs less than 14 days after the last dose of study drug, a subsequent follow-up phone call should be made at 14 days post the last dose of study drug to determine if any AEs have occurred since the post-study clinic visit.
- Follow-up of virologic failures in the base study at approximately 24 weeks after the early discontinuation visit to assess whether or not subjects who fail with MK-1439A are successful on subsequent treatment.

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.

All adverse events 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. 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 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

In this trial, an overdose is any dose higher than twice the recommended daily dose in a calendar day.

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 6 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 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 may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events with respect to the elements outlined in Table 6. The investigator's assessment of causality is required for each adverse event. Refer to Table 6 and Appendix 12.7 for instructions in evaluating adverse events.

Table 6 Evaluating Adverse Events

Maximum Intensity	**Mild**	awareness of sign or symptom, but easily tolerated (for pediatric trials, awareness of symptom, but easily tolerated)
	Moderate	discomfort enough to cause interference with usual activity (for pediatric trials, definitely acting like something is wrong)
	Severe	incapacitating with inability to work or do usual activity (for pediatric trials, extremely distressed or unable to do usual activities)
Seriousness	A serious adverse event (AE) is any adverse event occurring at any dose or during any use of Sponsor's product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred [Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.]; or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect (**in offspring of subject taking the product regardless of time to diagnosis); or	
	Is a cancer (although not serious per ICH definition, is reportable to the Sponsor within 24 hours to meet certain local requirements); **or**	
	Is associated with an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Sponsor's product to be discontinued?	
Relationship to Sponsor's Product	Did the Sponsor's product cause the adverse event? The determination of the likelihood that the Sponsor's product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information **The following components are to be used to assess the relationship between the Sponsor's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the adverse event:	
	Exposure	Is there evidence that the subject was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Sponsor's Product (continued)	**The following components are to be used to assess the relationship between the Sponsor's product and the AE: (continued)**	
	Dechallenge	Was the Sponsor's product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the Sponsor's product in this trial? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time.) NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AND IF REQUIRED, BY THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE. IF ADVANCED APPROVAL OF RECHALLENGE IS NOT REQUIRED BY LOCAL REGULATIONS, THE IRB/IEC WILL RECEIVE NOTIFICATION FOR INFORMATION ONLY.
	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

This section outlines the statistical analysis strategy and procedures for the study. Changes to analyses made after the protocol has been finalized, but prior to data base lock, will be documented in a supplemental Statistical Analysis Plan (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Separate analysis plans (i.e., separate documents from the sSAP) will be developed to detail other planned analyses (e.g., analysis of PK data and future biomedical research). Post hoc exploratory analyses will be clearly identified in the CSR.

8.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 8.2-8.12. Analysis of data from the study extension does not require changes to the SAP: all data from the extension will be summarized descriptively only, as will be described in the sSAP. These data will be summarized separately from data generated from the base study.

Study Design Overview	A Phase IIa Multicenter, Open-Label, Clinical Trial to Evaluate the Safety and Efficacy of MK-1439A in Treatment-Naïve HIV-1 Infected Subjects with Selected Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) Transmitted Resistance Mutations
Treatment Assignment	Subjects meeting screening criteria were to be allocated to receive MK-1439A until the 20 evaluable subject minimums are met for both the K103N and Y181C single mutations or until a total of 60 evaluable subjects are enrolled (whichever comes first). However, the study discontinued enrollment early with only 10 subjects.
Analysis Populations	Efficacy: mFAS Evaluability criteria for a modified Full Analysis Set (mFAS) population require that subjects take at least one dose of MK-1439A and meet eligibility criteria regarding the presence of selected NNRTI resistance mutations based on central lab confirmation of the local lab results used for screening purposes. Safety: All Patients as Treated (APaT) Note, although subjects will be contacted for status after discontinuation due to virologic failure this data will not be used in the planned analysis populations but summarized separately.
Primary Endpoint(s)	1. Proportion of subjects with HIV-1 RNA <50 copies/mL (by the Abbott RealTime HIV-1 Assay) at Week 48. 2. Safety and tolerability by Week 48 and Week 96.

Key Secondary Endpoints	1. Change from baseline in CD4 cell count at Week 48 and Week 96. 2. The proportion of subjects achieving HIV-1 RNA< 40 copies/mL (BLoQ) (by the Abbott RealTime HIV-1 Assay) at Week 48 and Week 96. 3. The proportion of subjects achieving HIV-1 RNA< 50 copies/mL (by the Abbott RealTime HIV-1 Assay) at week 96. 4. Time-to-Loss-Of-Virologic-Failure (TLOVR)
Statistical Methods for Key Efficacy Analyses	The observed failure (OF) missing data approach will be the primary approach to handling missing data. Descriptive statistics will be provided with regard to the key efficacy endpoints including 95% confidence intervals. The mFAS population using the OF missing data approach (primary) will be used wherein only subjects with observed viral loads post treatment at Week 48 or subjects who have previously discontinued due to lack of efficacy (imputed as failures) will be included. Key efficacy analyses will also be summarized by mutation type.
Statistical Methods for Key Safety Analyses	Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse experiences (AEs), laboratory tests and vital signs. Descriptive statistics will be provided for these safety parameters.
Interim Analyses	Two interim futility analyses will be performed in this study. The interim futility analyses are summarized below. Details are provided in Section 8.7. Both futility analyses will be performed using the mFAS population. **1st Futility Analysis** This analysis was originally to be performed when the first 10 evaluable subjects belonging to the mFAS population have Week 4 HIV-1 RNA data. Given the study discontinued enrollment early this analysis will be conducted with the evaluable subjects remaining on study. **2nd Futility Analysis** An ongoing assessment of the number of subjects belonging to the mFAS population who fail to achieve HIV-1 RNA <200 copies/mL by Week 24 or who discontinue due to lack of efficacy (not otherwise attributed to non-compliance to study medication) at any time point up to and including Week 24.
Multiplicity	No multiplicity adjustment is necessary as there are no statistical hypothesis tests for this protocol.
Sample Size and Power	There are no hypotheses in this study and all objectives will be addressed through summary statistics. The primary objective will be assessed based on the proportion of subjects with HIV-1 RNA <50 copies/mL at Week 48. Assuming an observed response rate of 80%, a sample size of 10 would provide a 2-sided exact 95% CI of [44.4%, 97.5].

8.2 Responsibility for Analyses/In-House Blinding

Although the trial is open label, analyses or summaries generated by either the overall single-arm cohort or by the cohort's mutation type will be limited and documented. The interim futility analyses will be conducted by the Clinical Biostatistics department of the SPONSOR.

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the SPONSOR.

This trial is being conducted as a single-arm, open-label study, i.e., subjects, investigators, and SPONSOR personnel will be aware of subject treatment assignment after each subject is allocated and treatment is assigned.

The Clinical Biostatistics department will generate the allocation schedule for study treatment assignment. Allocation numbers will be assigned via an interactive voice response system (IVRS).

8.3 Hypotheses/Estimation

Objectives of the study are stated in Section 3.0.

8.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated are listed below, followed by the descriptions of the derivations of selected endpoints.

8.4.1 Efficacy/Immunogenicity/Pharmacokinetics Endpoints

An initial description of efficacy measures is provided in Section 4.2.4.

Proportions of Subjects with HIV-1 RNA <50 and <40 copies/mL

The Abbott RealTime HIV-1 Assay, which has a lower limit of reliable quantification (LoQ) of 40 copies/mL will be used to measure the HIV-1 RNA level in blood samples obtained at each visit. The proportions of subjects with HIV-1 RNA <50 and <40 copies/mL will be estimated at each time point.

The primary objective assesses the proportion of subjects achieving HIV-1 RNA <50 copies/mL at Week 48. The secondary objectives assess the proportion of subjects achieving HIV-1 RNA<50 copies/mL at Week 96 and <40 copies/mL (BLoQ of the Abbott RealTime HIV-1 Assay) at Week 48 and Week 96.

Change from Baseline in CD4 Cell Count

Change from baseline in CD4 cell count will be estimated at each time point at which CD4 cell count is collected with a key interest at Week 48.

For the calculations of change from baseline, baseline measurements are defined as the Day 1 value for each subject. In the rare event when data for this visit are missing, the value obtained at the most recent screening visit will be used as baseline. This rule will also be applied to define the baseline measurements for other laboratory tests.

Time to Loss Of Virologic Response (TLOVR)

For subjects who achieve HIV-1 RNA <50 copies/mL and subsequently have two consecutive HIV-1 RNA values (measured at least 1 week apart) ≥50 copies/mL, time to loss of virologic response is the time between Day 1 and the date of the first of the two consecutive values ≥50 copies/mL. For subjects who achieve and sustain HIV-1 RNA <50 copies/mL, time to loss of virologic response is censored at the time of the last available measurement. For subjects who do not achieve HIV-1 RNA values <50 copies/mL, time to loss of virologic response is 0 weeks.

Protocol Defined Virologic Failure (PDVF)

Subjects with PDVF as defined in Section 4.2.4.1 will be summarized.

Change from Baseline in $\log_{10}$ HIV-1 RNA

Change from baseline in $\log_{10}$ HIV-1 RNA at Week 4 (Week 4 – baseline) will be calculated for the first interim futility analysis. The use of this endpoint will provide a more sensitive measure of study drug activity at an early timepoint than the proportion of patients falling below a threshold (e.g., <50 copies/mL).

8.4.2 Safety Endpoints

An initial description of safety measures is provided in Section 4.2.4.

Adverse Experiences

The following clinical and laboratory adverse experiences will be summarized: 1) subjects with at least one adverse experience; 2) subjects with at least one drug related adverse experience; 3) subjects with at least one serious adverse experience; 4) subjects with at least one serious and drug related adverse experience; and 5) subjects who discontinue study therapy due to an adverse experience. Specific adverse experiences by system organ class tests will also be summarized.

Predefined Limits of Change in Laboratory Parameters

For the summaries of laboratory tests, subjects must have both a baseline and on-treatment measurement to be included. Subjects' laboratory values (based on their most abnormal laboratory test values, in the direction of interest, while on study therapy) will be classified as to whether or not they fall outside of the Pre-Defined Limit of Change (PDLC) and are worse in grade (i.e., more abnormal in the direction of interest) than at baseline. The criteria are adapted from DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS, PUBLISH DATE: AUGUST 2009 Version 1 (Section 12.7). A listing of the subjects who meet the criteria will be provided.

8.5 Analysis Populations

Eligible subjects enter the trial when the treatment allocation number is centrally assigned using IVRS/IWRS (see Section 5.3).

8.5.1 Efficacy Analysis Populations

The modified Full Analysis Set (mFAS) population will serve as the primary population for the analysis of efficacy data in this study. The modified FAS population consists of all allocated subjects who:

- receive at least one dose of study treatment,
- have baseline data for those analyses that require baseline data, meet eligibility criteria regarding the presence of NNRTI resistance mutations based on central lab results
- Details on the approach to handling missing data are provided in Section 8.6 Statistical Methods.

8.5.2 Safety Analysis Populations

The All Patients as Treated (APaT) population will be used for the analysis of safety data in this study. The APaT population consists of all allocated subjects who received at least one dose of study treatment.

At least one laboratory or vital sign measurement obtained subsequent to at least one dose of study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

Details on the approach to handling missing data for safety analyses are provided in Section 8.6 Statistical Methods.

8.6 Statistical Methods

As this is an open-label, single arm study, only descriptive summary statistics and confidence intervals will be provided for both efficacy and safety endpoints with no tests of hypotheses.

Demography, efficacy and safety data from the study extension, for those subjects who continue into the extension, will be summarized separately using descriptive statistics only.

8.6.1 Statistical Methods for Efficacy Analyses

TimeWindow

Table 7 lists the definition of time windows and the target day relative to Day 1 for the scheduled visits in the study that will be used for all analyses by timepoint. The measurement closest to the target date within a window will be used for analyses at a specific timepoint.

Table 7 Definition of Study Timepoint

Treatment Phase	Treatment Period	Protocol Time	Day-Range Rules	Target Day[1]	CSR Time[2]
Pre-treatment	Baseline	Day 1 (Baseline)	≤1	1	Day 1
Treatment	Open-Label	Week 2	≥2 and ≤21	15	Week 2
		Week 4	≥22and ≤42	29	Week 4
		Week 8	≥43 and ≤70	57	Week 8
		Week 12	≥71 and ≤98	85	Week 12
		Week 16	≥99 and ≤140	113	Week 16
		Week 24	≥141 and ≤210	169	Week 24
		Week 36	≥211 and ≤294	253	Week 36
		Week 48	≥295 and ≤ 378	337	Week 48
		Week 60	≥379 and ≤462	421	Week 60
		Week 72	≥463 and ≤546	505	Week 72
		Week 84	≥547 and ≤630	589	Week 84
		Week 96	≥631 and ≤728	673	Week 96
Treatment Extension	Open Label	Week 112	≥729 and ≤840	785	Week 112
		Week 128	≥841 and ≤952	897	Week 128
		Week 144	≥953 and ≤1064	1009	Week 144
		Week 160	≥1065 and ≤1176	1121	Week 160
		Week 176	≥1177 and ≤1288	1233	Week 176
		Week 192	≥1289	1345	Week 192

[1] Relative days and target day are counted from the first day of study medication.
[2] The clinical study report (CSR) time is the time label to be used in the analysis tables.

Missing Values

There are 3 types of missing values:

- intermittent missing values due to a missed or skipped visit or due to an inadequate sample;
- non-intermittent missing values due to premature discontinuations because of treatment-related reasons such as, "clinical adverse experience" (regardless of relationship to study drug), "laboratory adverse experience" (regardless of relationship to study drug), and "withdrew based on HIV-1 RNA results";
- non-intermittent missing values due to premature discontinuations because of other reasons which are not related to treatment such as loss to follow-up, protocol violation, subject withdrew consent, etc.

Two approaches will be used to handle missing values (Table 8). The primary approach for the analysis of the proportion of subjects achieving HIV-1 RNA <50 copies/mL is the Observed Failure (OF) approach. Under this approach, non-intermittent missing data for subjects who prematurely discontinued assigned treatment due to lack of efficacy are considered as failures at timepoints thereafter. Subjects with other reasons for missing data will be excluded from the analyses.

A second supportive approach will use a Non-Completer=Failure (NC=F) approach as defined by the FDA "snapshot" approach. Under this approach, only subjects meeting the following can be classified as virologic success at a given time point: 1) subject is on study-assigned treatment, 2) subject has HIV-1 RNA measurement(s) within the time window specified in Table 7, and Table 3) subject has the measurement closest to the target date of the time point <50 copies/mL. The other subjects, either with an HIV-1 RNA measurement of ≥50 copies/mL or no virologic data within the time window due to intermittent missing or premature discontinuation regardless of reasons, will be considered as failures in the analyses of the proportion of subjects achieving HIV-1 RNA <50 copies/mL at that timepoint.

The same approaches as described above will be used for the analysis of the proportion of subjects achieving HIV-1 RNA <40 copies/mL.

Table 8 Summary of the Two Approaches to Handle Missing Values

Approaches[§]	Intermittent Missing	Non-intermittent Missing Not Related to Treatment		Non-intermittent Missing Related to Treatment	
		Success at Study Therapy Discontinuation	Failure at Study Therapy Discontinuation	Study Therapy Discontinuation Due to Clinical/Lab Adverse Experience	Study Therapy Discontinuation Due to Lack of Efficacy
OF	Excluded	Excluded	Failures[†]	Excluded	Failures[†]
NC=F	Failure	Failures	Failures	Failures	Failures

[§] OF (Observed Failure) is the primary approach; NC=F (Non-Completer=Failure).

[†] Subjects will be excluded in the OF approach if central lab test results based on baseline samples indicate NNRTI mutant types for a subject that are resistant to MK-1439.

Proportion of Subjects Achieving HIV-1 RNA <50 copies/mL

The proportion of subjects achieving HIV-1 RNA <50 copies/mL will be summarized by mutation type at each time point, with primary interest at Week 48. A 95% confidence interval will be calculated using the exact binomial method proposed by Clopper and Pearson (1934) [8] for the proportion of subjects achieving HIV-1 RNA <50 copies/mL at each time point.

The primary analysis approach will be based on the OF approach under which subjects with non-intermittent missing data because they prematurely discontinued assigned treatment due to lack of efficacy are considered as failures at timepoints thereafter. The NC=F approach as defined by FDA "snapshot" approach will be used as the secondary approach to analysis wherein all missing data will be treated as failures regardless of the reason.

To provide a full picture of virologic outcome at a timepoint, subjects who are not classified as virologic success will be further categorized as virologic failure (HIV-1 RNA ≥50 copies/mL) or as having no virologic data within the time window with reasons of 1) discontinued study due to an AE, 2) discontinued study for other reasons (includes withdraw consent, loss to follow-up, moved, etc.), or 3) on study but missing data in window. The full categorization of virologic outcome at Week 48 will be summarized.

Proportion of Subjects Achieving HIV-1 RNA <40 copies/mL

The proportion of subjects achieving HIV-1 RNA <40 will be analyzed using the same approach as described above for the proportion of subjects achieving HIV-1 RNA <50 copies/mL.

Change from Baseline in CD4 cell counts

Change from baseline in CD4 cell counts will be summarized at each time point at which CD4 cell count is collected, with a key interest at Week 48.

The OF approach will be used for the calculations of change from baseline in CD4 cell count. Under this approach, baseline values will be carried forward for subjects who discontinue due to lack of efficacy.

Time to Loss Of Virologic Response (TLOVR)

TLOVR will be estimated using Kaplan-Meier product-limit estimates and graphically displayed.

Protocol Defined Virologic Failure (PDVF)

The number of subjects with PDVF will be summarized.

Resistance

Genotypic and phenotypic resistance data from subjects with protocol defined virologic failure will be summarized.

Table 9 summarizes the key efficacy analyses.

Table 9 Analysis Strategy for Key Efficacy Variables

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach †	Statistical Method	Analysis Population	Missing Data Approach
Primary Objective				
Proportion of subjects achieving HIV-1 RNA <50 copies/mL at Week 48	P	Descriptive statistics overall and by mutant type	mFAS	OF approach
Proportion of subjects achieving HIV-1 RNA <50 copies/mL at Week 48	S	Descriptive statistics overall and by mutant type	mFAS	NC=F approach
Secondary Objectives				
Proportion of subjects achieving HIV-1 RNA <40 copies/mL at Week 48 and Week 96	P	Descriptive statistics overall and by mutant type	mFAS	OF approach
Proportion of subjects achieving HIV-1 RNA <40 copies/mL at Week 48 and Week 96	S	Descriptive statistics overall and by mutant type	mFAS	NC=F approach
Proportion of subjects achieving HIV-1 RNA <50 copies/mL at Week 96	P	Descriptive statistics overall and by mutant type	mFAS	OF approach

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach †	Statistical Method	Analysis Population	Missing Data Approach
Change from baseline in CD4 cell counts at Week 48 and Week 96	P	Descriptive statistics overall and by mutant type	mFAS	OF approach assuming baseline-carried-forward
Time-to-Loss-Of- Virologic-Failure (TLOVR)	P	Kaplan-Meier product limit estimates and graph overall and by mutant type	mFAS	Not applicable
† P=Primary approach; S=Secondary approach. Descriptive statistics will be number and percent (95% CI) for binary endpoints and mean (95% CI) for continuous endpoints.				

The strategy to address multiplicity issues with regard to multiple efficacy endpoints, multiple timepoints, and/or interim analyses is described in Section 8.7, Interim Analyses and in Section 8.8, Multiplicity. As described in Section 8.8, no multiplicity adjustment is necessary as there are no statistical hypothesis tests for this protocol.

8.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse experiences (AEs), laboratory tests and vital signs. Descriptive statistics will be provided for these safety parameters. Summary statistics will be number and percent (95% CI) for incidence of adverse experiences and mean (SD) for change from baseline in laboratory test.

The proportions of patients with clinical or laboratory adverse experiences of the following types will be tabulated overall and by mutant type: (1) at least one adverse experience; (2) a drug-related adverse experience; (3) a serious adverse experience; (4) serious and drug-related adverse experiences; (5) adverse experience leading to discontinuation.

The percentage of patients with specific adverse experiences by system organ class and the number and percentage of patients with laboratory tests that exceed the Pre-Defined Limit of Change in laboratory tests will also be summarized in the same fashion.

Summary statistics for baseline, on-treatment, and change from baseline values in laboratory parameters will be provided overall and by mutant type.

8.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

8.6.3.1 Demographic and Baseline Characteristics

Baseline characteristics for all allocated and treated patients will be summarized by the use of descriptive statistics. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of patients screened, allocated, the primary reasons for screen failure, and the primary reason for discontinuation will be displayed. Demographic variables (e.g., age, gender and race, history of AIDS, mutant type), primary and secondary diagnoses, prior and concomitant therapies will be summarized using descriptive statistics for continuous or categorical variables, as appropriate.

Summary statistics for baseline efficacy measures such as HIV RNA and CD4 cell count will also be provided.

8.6.3.2 Population PK Analyses

Based on pharmacokinetic data obtained within this study, a separate population Pharmacokinetics (PK) analysis will be performed. The prospective details of this analysis will be specified in a separate population PK analysis plan.

8.7 Interim Analyses

Two interim futility analyses will be performed. Both analyses will be conducted and evaluated internally by the study team. No external data monitoring committee will be used in this study. If futility criteria are satisfied the study team will discuss the analysis results with management at the Sponsor to make a final determination for stopping the study.

1st Futility Analysis

Initially, the first futility analysis was planned that after the first 10 evaluable mFAS-allocated subjects complete their Week 4 visit and have HIV-1 RNA data available, an interim futility analysis would be performed. Given enrollment was halted at 10 subjects, this analysis will be performed using all evaluable subjects.

If the mean change from baseline in $\log_{10}$ HIV-1 RNA at Week 4 is not a decline of 1.5 or more, the study may stop for futility. If the viral load dynamics in this study are the same as those observed in Protocol 007, there is 0.1% chance to possibly stop for futility. Week 24 data from the MK-1439 100 mg treatment group in Protocol 007 were used to determine the expected log decline in HIV-1 RNA at Week 4. Based on an analysis of these data, the mean (SD) change from baseline ($\log_{10}$ HIV-1 RNA, Week 4 – Baseline) was -2.09 (0.53). Under a conservative assumption that the true mean is -2.04 (mean + 1SE), by simulation, the likelihood of stopping for futility (i.e. observing a mean $\geq$-1.5) at Week 4 is <0.1%.

2nd Futility Analysis

This analysis is an ongoing assessment of the number of subjects belonging to the mFAS population who fail to achieve HIV-1 RNA <200 copies/mL by Week 24 or who discontinue due to lack of efficacy (not attributed to non-compliance) at any time up to and including Week 24. The percentage of subjects in the MK-1439 100 mg treatment group of Protocol 007 who failed to achieve HIV-1 RNA <200 copies/mL by Week 24 or who discontinued due to lack of efficacy at any time up to and including Week 24 was 3.7% (4/108). Therefore, it is expected that 3.7% of 10 evaluable subjects (1 subject, rounding up), would meet this criterion in Protocol 030 if complete data on 10 subjects were available. Based on this expected number, simulation was used to determine the likelihood of stopping for futility using >1 subject out of 10 as the criterion. The criterion of >1 was chosen based on the low likelihood of stopping (5%) when the expected number is <1.

8.8 Multiplicity

No multiplicity adjustment is necessary as there are no statistical hypothesis tests for this protocol.

8.9 Sample Size and Power Calculations

8.9.1 Sample Size and Power for Efficacy Analyses

The primary objective will be assessed based on the proportion of subjects with HIV-1 RNA <50 copies/mL at Week 48. This is an estimation study only with no hypotheses. The expected response rate is ~80% based on previous treatment-naïve clinical trials. MK-1439A is expected to be similarly active against each of the mutant types. Subjects meeting screening criteria were allocated to receive MK-1439A until the 20 evaluable subject minimums are met for both the K103N and Y181C single mutations or until a total of 60 evaluable subjects are enrolled (whichever comes first). However, enrollment was stopped after only 10 subjects were enrolled. Assuming an observed response rate of 80%, a sample size of 10 would provide a 2-sided exact 95% CI of [44.4%, 97.5%].

8.9.2 Sample Size and Power for Safety Analyses

The probability of observing at least one of a particular type of adverse experience in this study depends on the number of subjects treated and the underlying percentage of subjects with that adverse experience in the study population. If the underlying incidence of a particular adverse experience is 1% (1 of every 100 subjects receiving the drug), there is a <10.0% chance of observing at least one adverse experience of that type among 10 subjects. If no adverse experience of that type is observed among the 10 subjects, this study will provide 95% confidence that the underlying percentage of subjects with that particular adverse experience is <31%.

8.10 Subgroup Analyses and Effect of Baseline Factors (Base Study)

To characterize the efficacy response across various subgroups, the primary endpoint will be summarized and plotted within each category of the following classification variables:

- Age category (≤median vs. >median)
- Gender (female, male)
- Region (North America, South America, Europe, Asia, Africa, etc.)
- Race (White, Black, Asian, Other)
- Ethnicity (Hispanic/Latino, not Hispanic/Latino)
- NNRTI mutation type (K103N, Y181C and G190A)
- Screening HIV-1 RNA categories (HIV-1 RNA ≤100,000 copies/mL, HIV-1 RNA >100,000 copies/mL)
- Baseline HIV-1 RNA categories (HIV-1 RNA ≤100,000 copies/mL, HIV-1 RNA >100,000 copies/mL)
- Chronic Hepatitis C status (HCV-infected or HCV-uninfected)
- Baseline CD4 categories (100-200, and >200 cells/mm^3)

The Observed Failure approach will be used to handle missing values in these subgroup analyses.

8.11 Compliance (Medication Adherence)

Study Medication Diary Cards will be used to ensure and document drug compliance.

Subjects are to take one pill of study medication once daily. For the main analysis of compliance in this study, a day within the study will be considered an "On-Therapy" day if the subject takes study drug.

For a subject who is followed for the entire study period, the "Number of Days Should be on Therapy" is the total number of days from Day 1 to the last scheduled day for treatment administration for that subject. For a subject who discontinued from the study permanently, the "Number of Days Should be on Therapy" is the total number of days from Day 1 to the date of the last dose of study medication.

For each subject, percent compliance will then be calculated using the following formula:

$$\text{Percent Compliance} = \frac{\text{Number of Days on Therapy}}{\text{Number of Days Should be on Therapy}} \times 100.$$

Summary statistics will be provided for percent compliance for the mFAS population.

Data from the study medication diary, rather than the returned pill count will serve as the primary data for compliance.

8.12 Extent of Exposure

The extent of exposure to study therapy for all treated subjects will be summarized. The number of subjects exposed to various doses (actual total daily dose) for defined periods of time will be listed, along with a summary of the mean (range) duration subjects were exposed to various doses.

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 10.

Table 10 Product Descriptions

Product Name & Potency	Dosage Form
MK-1439A 100 mg/Lamivudine 300 mg/Tenofovir Disoproxil Fumarate 300 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 monthly 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.

9.6 Standard Policies

Trial site personnel will have access to a central electronic treatment allocation/randomization system (IVRS/IWRS system) to allocate subjects, to assign treatment to subjects and to manage the distribution of clinical supplies. Each person accessing the IVRS system must be assigned an individual unique PIN. They must use only their assigned PIN to access the system, and they must not share their assigned PIN with anyone.

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 member 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/ERC review and regulatory authority inspection of trial-related documents and procedures and provide for direct access to all trial-related source data and documents.

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

The investigator shall prepare and maintain complete and accurate trial documentation in compliance with 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 CI during the anticipated review process, thorough understanding of clinical trial methods, appropriate enrollment of subject cohort, timely achievement of trial milestones). The Protocol CI must be a participating trial investigator.

10.4 Compliance with Trial Registration and Results Posting Requirements

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

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

10.5 Quality Management System

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

10.6 Data Management

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

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

10.7 Publications

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

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

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

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

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

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

11.0 LIST OF REFERENCES

1. Pham QD, Wilson DP, Law MG, Kelleher AD, Zhang L. Global burden of transmitted HIV drug resistance and HIV-exposure categories: a systematic review and meta-analysis. AIDS 2014; 28: 2751-2762.
2. Frentz D, van de Vijver D, Abecasis A, Albert J, Hamouda O, et al. Patterns of Transmitted HIV Drug Resistance in Europe Vary by Risk Group. PLoS ONE 2014; 9(4): e94495.
3. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. April 8, 2015; 1-288. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf.
4. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection - recommendations for a public health approach. Department of Health and Human Services. April 8, 2015; 1-11. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/aa_recommendations.pdf
5. Anderson M, Gilmartin J, Cilissen C, etc., Safety, Tolerability, and Pharmacokinetics of Single and Multiple Doses of MK-1439, a Novel HIV Non-Nucleoside Reverse Transcriptase Inhibitor, in Healthy Subjects, Abstract presented at Conference on Retroviruses and Opportunistic Infections, March 3 – 6, 2014, Boston, MA
6. Morales-Ramirez JO, Gatel JM, Hagins DP, Thompson M, Arasteh K, Hoffman C, C. Harvey C, Xu X, Teppler H. Safety and antiviral effect of MK-1439, a novel NNRTI, (+Truvada®) in ART-Naïve HIV infected patients. Presented at Conference on Retrovirus and Opportunistic Infections (CROI) March 3-6, 2014
7. Gatell JM, Morales-Ramirez JO, Hagins DP, Thompson M, Keikawus A, et al. Forty-eight-week efficacy and safety and early CNS tolerability of doravirine (MK-1439), a novel NNRTI, with TDF/FTC in ART-naïve HIV-positive patients. JIAS 2014; 17(Suppl 3): 19532.
8. Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of binomial. Biometrika 1934; 26: 404-13.

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 collected in this trial as outlined in Section 7.1.3.9 – Future Biomedical Research Sample Collection will be used to study various causes for how subjects may respond to a drug/vaccine. Future biomedical research specimen(s) will be stored to provide a resource for future trials conducted by the Sponsor focused on the study of biomarkers responsible for how a drug/vaccine enters and is removed by the body, how a drug/vaccine works, other pathways a drug/vaccine may interact with, or other aspects 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 Visit 1. If delayed, present consent at next possible Subject Visit. Informed consent must be obtained prior to collection of all Future Biomedical Research specimens. 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. Each consent will be assessed for appropriate specimen permissions.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of patient 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 Collections

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 for transfer to the storage facility. This first 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 first 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 Merck Biorepository 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 have their specimens and all derivatives destroyed. 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) and a form will be provided to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. Documentation will be sent to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for 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 specimen destruction can not 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 (e.g., ISO17799) 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 any exploratory results are definitively associated with clinical significance for subjects while the clinical trial is still ongoing, investigators will be contacted with information. After the clinical trial has completed, if any exploratory results are definitively associated with clinical significance, the Sponsor will endeavor to make such results available

through appropriate mechanisms (e.g., scientific publications and/or presentations). 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. Risks include those associated with venipuncture to obtain the whole blood specimen. This specimen will be obtained at the time of routine blood specimens drawn in the main trial.

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

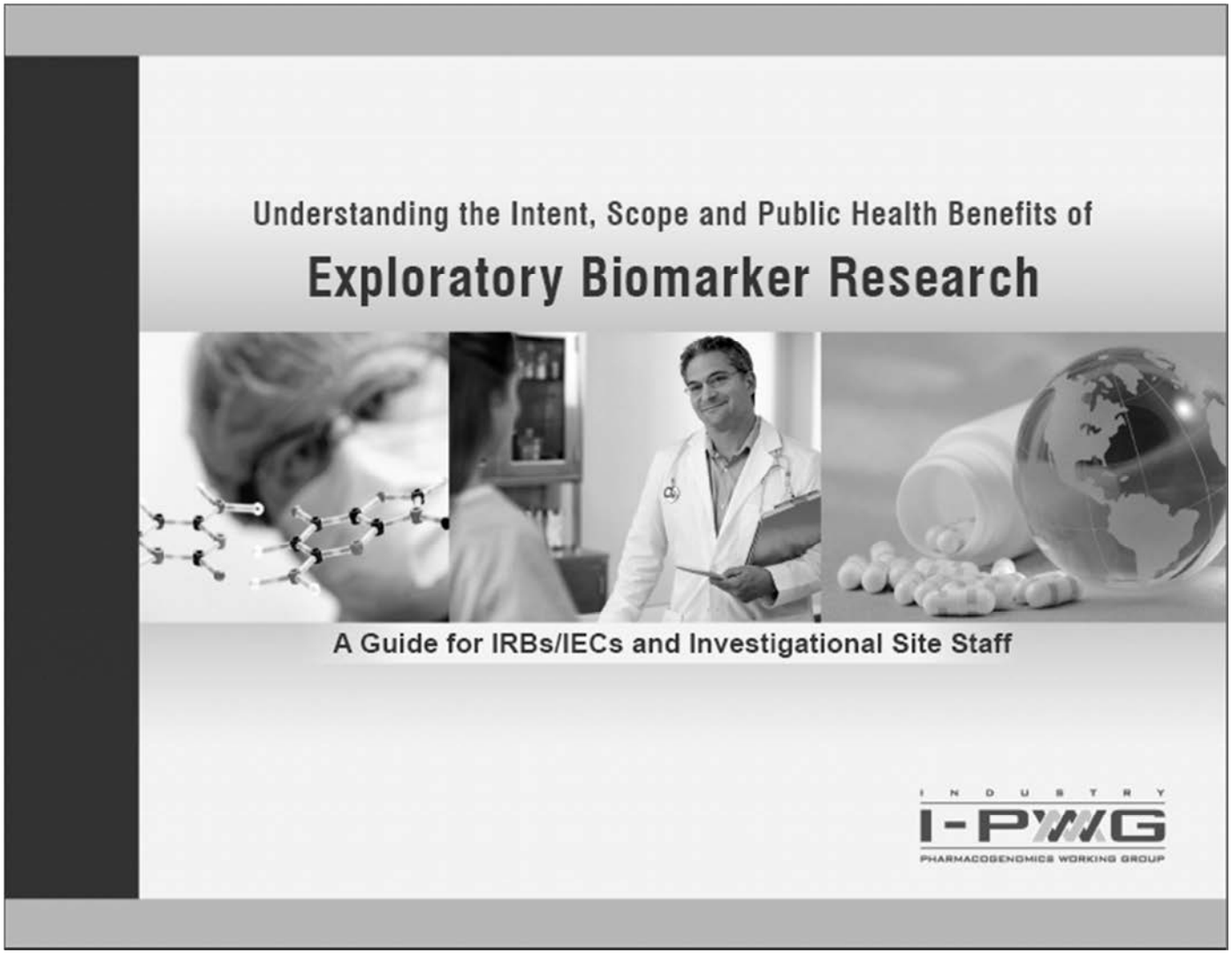
12. Questions

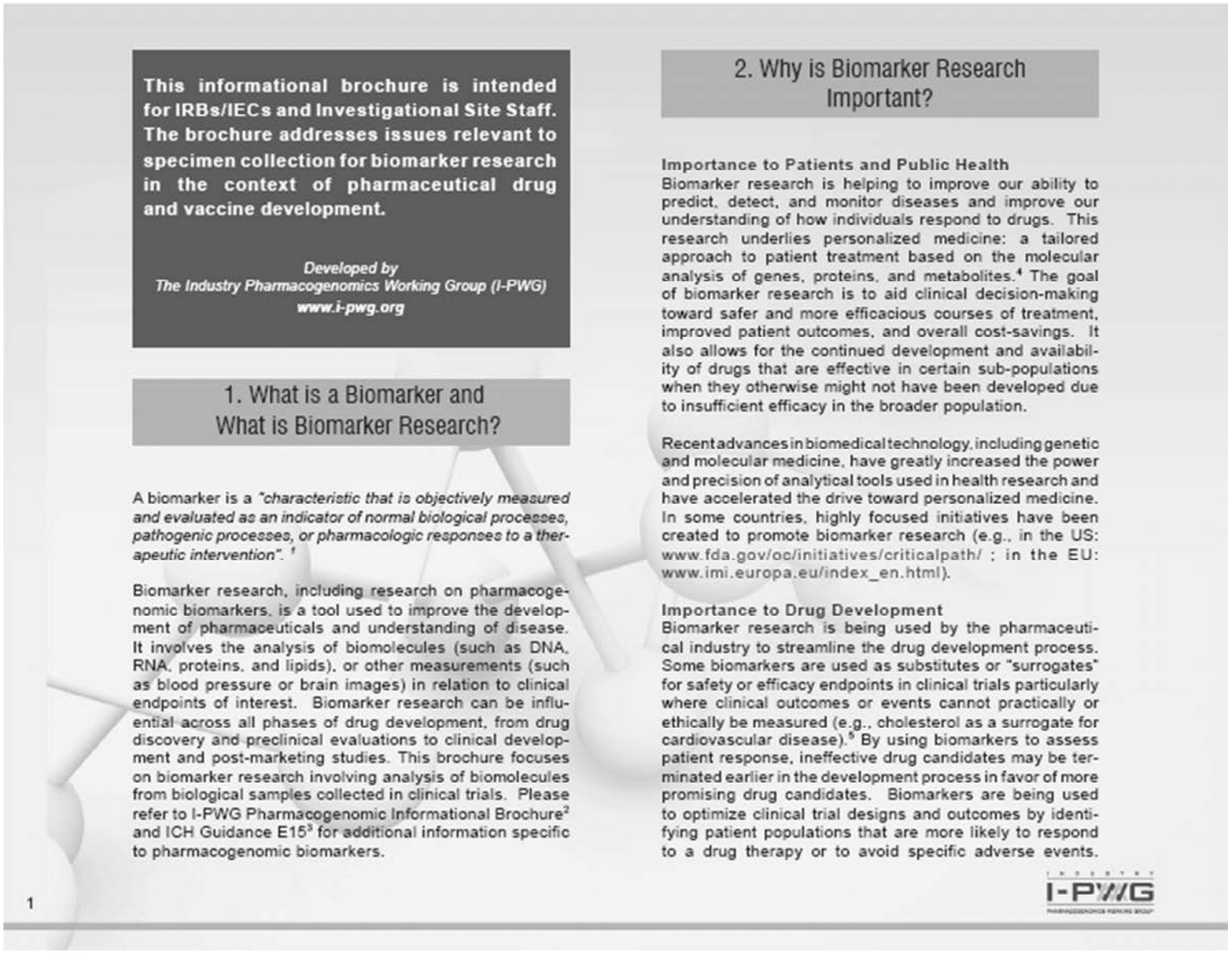
Any questions related to the future biomedical research should be e-mailed directly to clinical.specimen.management@merck.com.

13. References

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

12.3 Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff





This informational brochure is intended for IRBs/IECs and Investigational Site Staff. The brochure addresses issues relevant to specimen collection for biomarker research in the context of pharmaceutical drug and vaccine development.

Developed by
The Industry Pharmacogenomics Working Group (I-PWG)
www.i-pwg.org

1. What is a Biomarker and What is Biomarker Research?

A biomarker is a *"characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention".* [1]

Biomarker research, including research on pharmacogenomic biomarkers, is a tool used to improve the development of pharmaceuticals and understanding of disease. It involves the analysis of biomolecules (such as DNA, RNA, proteins, and lipids), or other measurements (such as blood pressure or brain images) in relation to clinical endpoints of interest. Biomarker research can be influential across all phases of drug development, from drug discovery and preclinical evaluations to clinical development and post-marketing studies. This brochure focuses on biomarker research involving analysis of biomolecules from biological samples collected in clinical trials. Please refer to I-PWG Pharmacogenomic Informational Brochure[2] and ICH Guidance E15[3] for additional information specific to pharmacogenomic biomarkers.

2. Why is Biomarker Research Important?

Importance to Patients and Public Health
Biomarker research is helping to improve our ability to predict, detect, and monitor diseases and improve our understanding of how individuals respond to drugs. This research underlies personalized medicine: a tailored approach to patient treatment based on the molecular analysis of genes, proteins, and metabolites.[4] The goal of biomarker research is to aid clinical decision-making toward safer and more efficacious courses of treatment, improved patient outcomes, and overall cost-savings. It also allows for the continued development and availability of drugs that are effective in certain sub-populations when they otherwise might not have been developed due to insufficient efficacy in the broader population.

Recent advances in biomedical technology, including genetic and molecular medicine, have greatly increased the power and precision of analytical tools used in health research and have accelerated the drive toward personalized medicine. In some countries, highly focused initiatives have been created to promote biomarker research (e.g., in the US: www.fda.gov/oc/initiatives/criticalpath/ ; in the EU: www.imi.europa.eu/index_en.html).

Importance to Drug Development
Biomarker research is being used by the pharmaceutical industry to streamline the drug development process. Some biomarkers are used as substitutes or "surrogates" for safety or efficacy endpoints in clinical trials particularly where clinical outcomes or events cannot practically or ethically be measured (e.g., cholesterol as a surrogate for cardiovascular disease).[5] By using biomarkers to assess patient response, ineffective drug candidates may be terminated earlier in the development process in favor of more promising drug candidates. Biomarkers are being used to optimize clinical trial designs and outcomes by identifying patient populations that are more likely to respond to a drug therapy or to avoid specific adverse events.

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Biomarker research is also being used to enhance scientific understanding of the mechanisms of both treatment response and disease processes, which can help to identify future targets for drug development. Depending on the clinical endpoints in a clinical trial, biomarker sample collection may either be a required or optional component of the trial. However, both mandatory and optional sample collections are important for drug development.

3. Importance of Biomarkers to Regulatory Authorities

Regulatory health authorities are increasingly aware of the benefits of biomarkers and how they may be used for drug approval, clinical trial design, and clinical care. Biomarkers have been used to establish risk:benefit profiles. For example, the FDA has modified the US warfarin (Coumadin®) label to include the analysis of *CYP2C9* and *VKORC1* genes to guide dosing regimens. Health authorities such as the FDA (USA), EMEA (European Union), MHLW (Japan), and ICH (International) are playing a key role in advancing this scientific field as it applies to pharmaceutical development by creating the regulatory infrastructure to facilitate this research. Numerous regulatory guidances and concept papers have already been issued, many of which are available through www.i-pwg.org. Global regulatory authorities have highlighted the importance of biomarker research and the need for the pharmaceutical industry to take the lead in this arena.[3, 6-24]

4. How are Biomarkers Being Used in Drug/Vaccine Development?

Biomarker research is currently being used in drug/vaccine development to:

- Explain variability in response among participants in clinical trials
- Better understand the mechanism of action or metabolism of investigational drugs
- Obtain evidence of pharmacodynamic activity (i.e., how the drug affects the body) at the molecular level
- Address emerging clinical issues such as unexpected adverse events
- Determine eligibility for clinical trials to optimize trial design
- Optimize dosing regimens to minimize adverse reactions and maximize efficacy
- Develop drug-linked diagnostic tests to identify patients who are more likely or less likely to benefit from treatment or who may be at risk of experiencing adverse events
- Provide better understanding of mechanisms of disease
- Monitor clinical trial participant response to medical interventions

Biomarker research, including research on banked samples, should be recognized as an important public health endeavor for the overall benefit of society, whether by means of advancement of medical science or by development of safer and more effective therapies.[7] Since the value of collected samples may increase over time as scientific discoveries are made, investment in long-term sample repositories is a key component of biomarker research.

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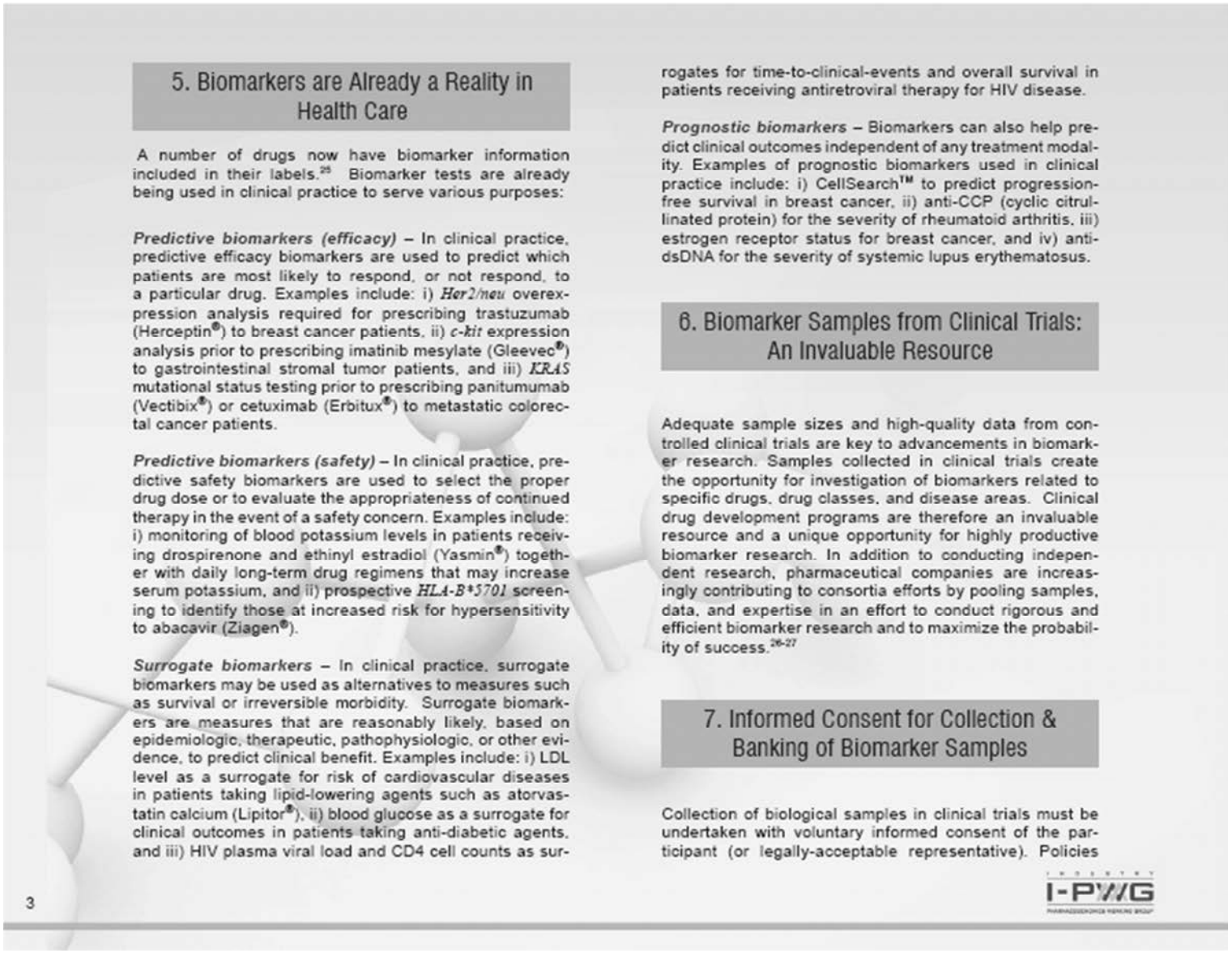

5. Biomarkers are Already a Reality in Health Care

A number of drugs now have biomarker information included in their labels.[25] Biomarker tests are already being used in clinical practice to serve various purposes:

Predictive biomarkers (efficacy) – In clinical practice, predictive efficacy biomarkers are used to predict which patients are most likely to respond, or not respond, to a particular drug. Examples include: i) *Her2/neu* overexpression analysis required for prescribing trastuzumab (Herceptin®) to breast cancer patients, ii) *c-kit* expression analysis prior to prescribing imatinib mesylate (Gleevec®) to gastrointestinal stromal tumor patients, and iii) *KRAS* mutational status testing prior to prescribing panitumumab (Vectibix®) or cetuximab (Erbitux®) to metastatic colorectal cancer patients.

Predictive biomarkers (safety) – In clinical practice, predictive safety biomarkers are used to select the proper drug dose or to evaluate the appropriateness of continued therapy in the event of a safety concern. Examples include: i) monitoring of blood potassium levels in patients receiving drospirenone and ethinyl estradiol (Yasmin®) together with daily long-term drug regimens that may increase serum potassium, and ii) prospective *HLA-B*5701* screening to identify those at increased risk for hypersensitivity to abacavir (Ziagen®).

Surrogate biomarkers – In clinical practice, surrogate biomarkers may be used as alternatives to measures such as survival or irreversible morbidity. Surrogate biomarkers are measures that are reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit. Examples include: i) LDL level as a surrogate for risk of cardiovascular diseases in patients taking lipid-lowering agents such as atorvastatin calcium (Lipitor®), ii) blood glucose as a surrogate for clinical outcomes in patients taking anti-diabetic agents, and iii) HIV plasma viral load and CD4 cell counts as surrogates for time-to-clinical-events and overall survival in patients receiving antiretroviral therapy for HIV disease.

Prognostic biomarkers – Biomarkers can also help predict clinical outcomes independent of any treatment modality. Examples of prognostic biomarkers used in clinical practice include: i) CellSearch™ to predict progression-free survival in breast cancer, ii) anti-CCP (cyclic citrullinated protein) for the severity of rheumatoid arthritis, iii) estrogen receptor status for breast cancer, and iv) anti-dsDNA for the severity of systemic lupus erythematosus.

6. Biomarker Samples from Clinical Trials: An Invaluable Resource

Adequate sample sizes and high-quality data from controlled clinical trials are key to advancements in biomarker research. Samples collected in clinical trials create the opportunity for investigation of biomarkers related to specific drugs, drug classes, and disease areas. Clinical drug development programs are therefore an invaluable resource and a unique opportunity for highly productive biomarker research. In addition to conducting independent research, pharmaceutical companies are increasingly contributing to consortia efforts by pooling samples, data, and expertise in an effort to conduct rigorous and efficient biomarker research and to maximize the probability of success.[26-27]

7. Informed Consent for Collection & Banking of Biomarker Samples

Collection of biological samples in clinical trials must be undertaken with voluntary informed consent of the participant (or legally-acceptable representative). Policies

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and regulations for legally-appropriate informed consent vary on national, state, and local levels, but are generally based on internationally recognized pillars of ethical conduct for research on human subjects.[28-31]

Optional vs. Required Subject Participation

Depending on the relevance of biomarker research to a clinical development program at the time of protocol development, the biomarker research may be a core required component of a trial (e.g., key to elucidating the drug mechanism of action or confirming that the drug is interacting with the target) or may be optional (e.g., to gain valuable knowledge that enhances the understanding of diseases and drugs). Informed consent for the collection of biomarker samples may be presented either in the main clinical informed consent form or as a separate informed consent form, with approaches varying somewhat across pharmaceutical companies. The relevance of biomarker research to a clinical development program may change over time as the science evolves. The samples may therefore increase in value after a protocol is developed.

Consent for Future Research Use

While it can be a challenge to specify the details of the research that will be conducted in the future, the I-PWG holds the view that future use of samples collected for exploratory biomarker research in clinical trials should be permissible when i) the research is scientifically sound, ii) participants are informed of the scope of the intended future research, even if this is broadly defined (see potential uses in Section 4 above), iii) autonomy is respected by providing the option to consent separately to future use of samples or by providing the option to terminate further use of samples upon request (consent withdrawal / sample destruction), and iv) industry standards for confidentiality protection per Good Clinical Practice guidelines are met.[3, 31] Importantly, any research using banked samples should be consistent with the original informed consent, except where otherwise permitted by local law or regulation.

Important elements of informed consent for **future use** of samples include, but are not limited to:[39]

The scope of research – Where the scope of the potential future research is broad, participants should be informed of the boundaries of the research. While it may not be possible to describe the exact analytical techniques that will be used, or specific molecules that will be analyzed, it is possible to clearly articulate in reasonable detail the type of research to be conducted and its purpose. Information regarding whether stored samples may be shared with other parties or utilized for commercialization purposes should also be addressed.

Withdrawal of consent / sample destruction – The informed consent form should inform participants of their right to withdraw their consent / request destruction of their samples. This should include the mechanisms for exercising that right and any limitations to exercising that right. For example, participants should be informed that it is not possible to destroy samples that have been anonymized.[3] In addition, according to industry standards and regulatory guidance, participants should be informed that data already generated prior to a consent withdrawal request are to be maintained as part of the study data.[38]

The duration of storage – The permissible duration of storage may vary according to the nature and uses of the samples and may also vary on national, state, and local levels. The intended duration of storage, including indefinite storage, should be specified.

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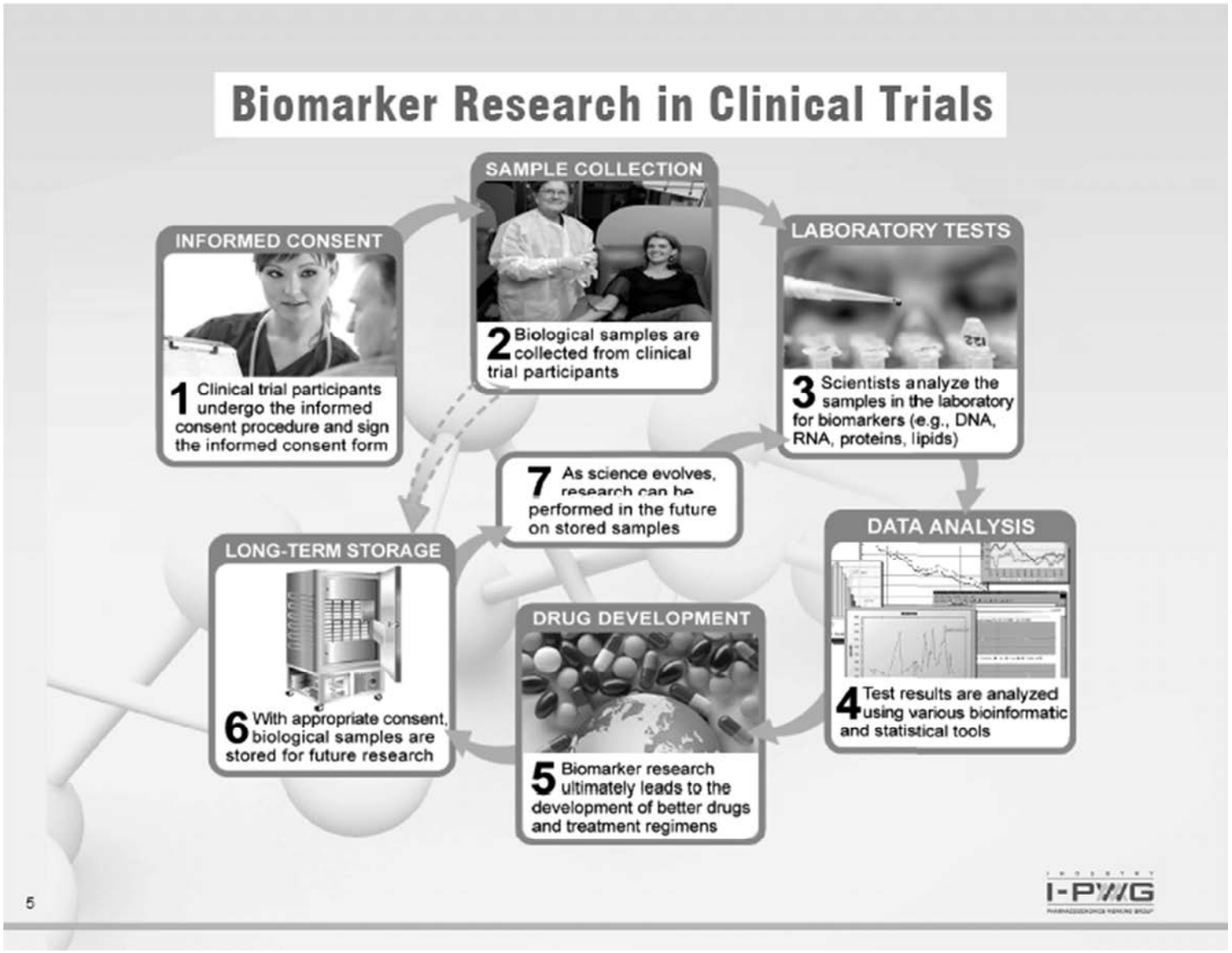
Biomarker Research in Clinical Trials
SAMPLE COLLECTION
2 Biological samples are collected from clinical trial participants
INFORMED CONSENT
1 Clinical trial participants undergo the informed consent procedure and sign the informed consent form
LABORATORY TESTS
3 Scientists analyze the samples in the laboratory for biomarkers (e.g., DNA, RNA, proteins, lipids)
7 As science evolves, research can be performed in the future on stored samples
DATA ANALYSIS
4 Test results are analyzed using various bioinformatic and statistical tools
LONG-TERM STORAGE
6 With appropriate consent, biological samples are stored for future research
DRUG DEVELOPMENT
5 Biomarker research ultimately leads to the development of better drugs and treatment regimens
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8. Biomarker Sample Collection in Different Countries

Collection of biological samples for biomarker research is straightforward in most jurisdictions. Some countries have specific laws and regulations regarding collection, labeling, storage, export, and/or use of exploratory samples. In addition, some regulations distinguish between DNA and non-DNA samples or between samples used for diagnostic purposes and samples collected for scientific research. Processes for the collection, labeling, storage, export, and/or use of biomarker samples should always adhere to the laws and regulations of the country/region in which those samples are collected.

9. Return of Research Results to Study Participants

Policies for the return of biomarker research results to study participants who request them vary among pharmaceutical companies. There are many considerations that pharmaceutical companies weigh when determining their policy regarding the return of biomarker research results to study participants. These include:

i) the conditions under which biomarker research results were generated (i.e., exploratory research laboratory versus accredited diagnostic laboratory)

ii) whether the results will have an impact on the medical care of the participant or on a related person, if applicable

iii) whether genetic counseling is recommended (for genetic results)

iv) the ability to accurately link the result to the individual from whom the sample was collected

v) international, national, and local guidelines, policies, legislation, and regulations regarding participants' rights to access data generated on them

Renegar *et al*. 2008 and Article 29 Data Protection Working Party (an advisory committee to the European Commission on the European Data Protection Directive) have addressed these considerations in detail in relation to pharmacogenomic research data and provided a list of documents addressing the general issue of return of research results.[34-35]

10. Benefits and Risks Associated with Biomarker Research

Benefits

While it may not always directly benefit the study participant who is providing the samples, biomarker research can improve overall understanding of disease and treatment of future patients receiving therapies developed from such research. Patients are now benefiting from retrospective biomarker research conducted on samples collected from clinical trials and stored for exploratory research. One example is the recent label update to the EGFR antibody drugs cetuximab (Erbitux®) and panitumumab (Vectibix®) which highlights the value of *KRAS* status as a predictive biomarker for treatment of metastatic colorectal cancer with this class of drug.

The humanitarian benefit of human research is recognized by the Nuremberg Code.[28,33] Provided that the degree of risk does not exceed that determined by the humanitarian importance of the problem to be solved, research participants should not be denied the right to contribute to the greater common good.[28,32]

Risks

Risks associated with biomarker research are primarily related to the physical aspects of obtaining the sample and to patient privacy concerns.

Physical risks associated with biomarker sample collection in clinical trials can be characterized in two ways: i) negligible additional risk when the biomarker sample is collected as part of a procedure conducted to support

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other core trial objectives, and ii) some added risk where the sampling procedure would otherwise have not been performed as a core component of a trial. Risks are also determined by the invasiveness of the sample collection procedure.

Privacy risks are generally those associated with the inappropriate disclosure and misuse of data. Pharmaceutical companies have policies and procedures for confidentiality protection to minimize this risk for all data collected and generated in clinical trials. These may vary across companies, but are based on industry standards of confidentiality and privacy protection highlighted in the following section. Importantly, privacy risks inherent to biomarker data are no greater than other data collected in a clinical trial.

11. Privacy, Confidentiality, and Patient Rights

Maintaining the privacy of study participants and the confidentiality of information relating to them is of paramount concern to industry researchers, regulators, and patients. Good Clinical Practice (GCP), the standard adhered to in pharmaceutical clinical research, is a standard that

"...provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected",

where confidentiality is defined as, *"The prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a subject's identity."*

This standard dictates that *"the confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with applicable regulatory requirements."* [31]

Exploratory biomarker research in pharmaceutical development is commonly conducted in research laboratories that are not accredited to perform diagnostic tests used for healthcare decision-making. Therefore, results from exploratory biomarker research usually are not appropriate for use in making decisions about a trial participant's health. In addition, exploratory research data should not be included as part of a participant's medical record accessible for use by insurance companies. Legislation and policies to protect individuals against discrimination based on genetic information continually evolve based on social, ethical, and legal considerations. Examples of such legislation include the Human Tissue Act 2004 (UK) and the Genetic Information Nondiscrimination Act (GINA) 2008 (USA).[36-37]

12.Where to Get More Information?

Educational resources related to biomarker and pharmacogenomic research that caters to health care professionals, IRBs/IECs, scientists, and patients are continually being created and are publicly available. Links to many of these resources are available through the I-PWG website: www.i-pwg.org.

13. What is I-PWG?

The Industry Pharmacogenomics Working Group (I-PWG) (formerly the Pharmacogenetics Working Group) is a voluntary association of pharmaceutical companies engaged in pharmacogenomic research. The Group's activities focus on non-competitive educational, informational, ethical, legal, and regulatory topics. The Group provides information and expert opinions on these topics and sponsors educational/informational programs to promote better understanding of pharmacogenomic and other biomarker research for key stakeholders. The I-PWG interacts with regulatory author-

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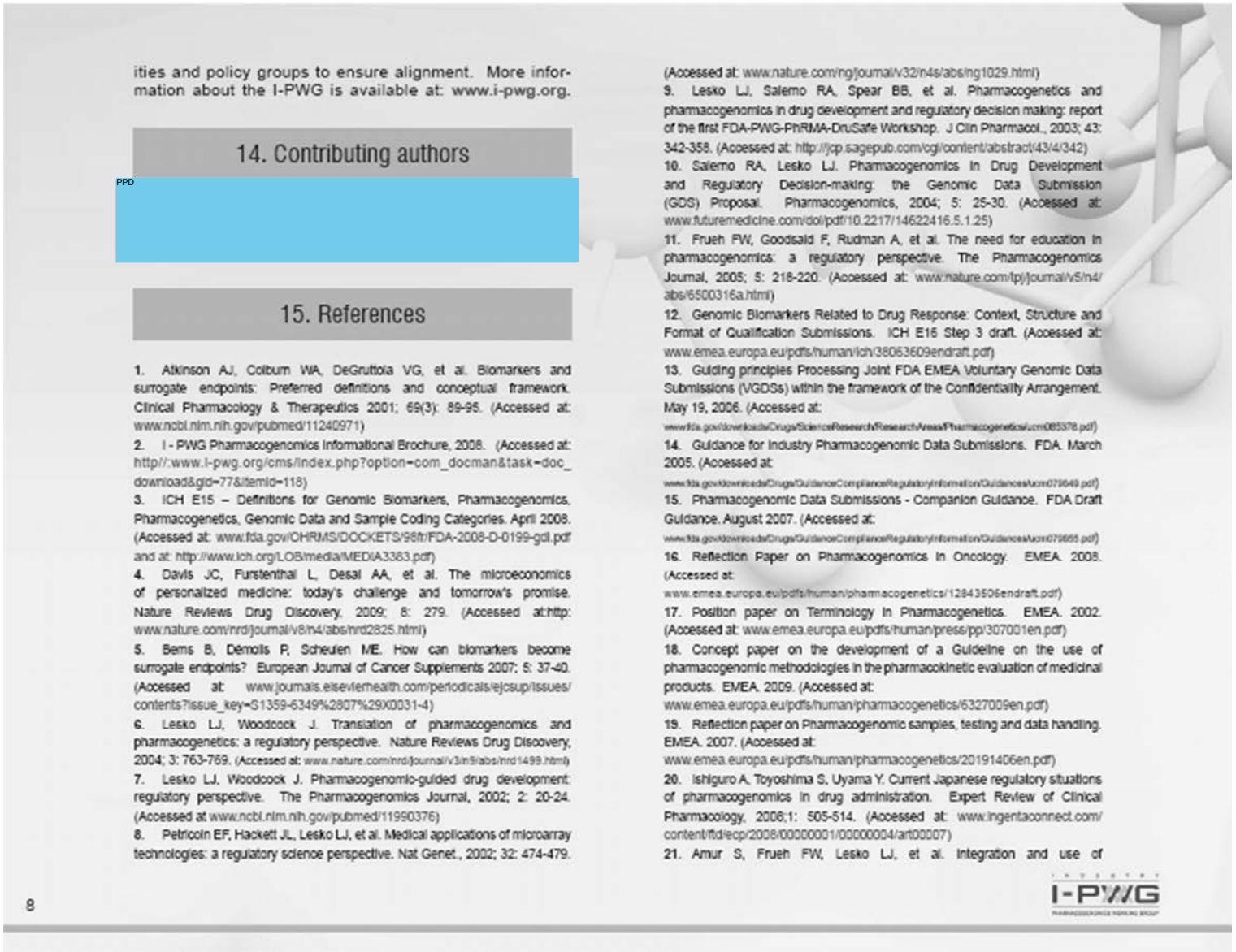

ities and policy groups to ensure alignment. More information about the I-PWG is available at: www.i-pwg.org.

14. Contributing authors

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

Table A: Approximate Blood Volume Drawn From Screening Through Week 96 Plus 14 Days Follow-up (Base Study)

Trial Period:	Screening		Treatment												Post-treatment			
Visit Number/Title:	1 Screen -ing	2	3	4	5	6	7	8	9	10	11	12	13	14	U (Virologic Failure Confirmation)	U (Early Discon-tinuation)	99	
Scheduled Weeks/Days:	-45 to -1	Day 1	WK 2	WK 4	WK 8	Fasting WK 12[a]	WK 16	WK 24	WK 36	Fasting WK 48[a]	WK 60	WK 72	WK 84	Fasting WK 96[a]	≥ 1 to ≤ 4 weeks after initial virologic failure	At time of Discon	Post study 14 day follow up	
Laboratory Procedures/Assessments																		Total Volume (mL)
Hematology	2	2	2	2	2	2	2	2	2	2	2	2	2	2		2	2	32
Serum Pregnancy Test[c]	29																	-137.5
Chemistry		7	7	7	7	7	7	7	7	7	7	7	7	7	3.5	7	7	
HIV/Hepatitis Screen[b]																		
Hemostatic Function Test[d]	4.5																	4.5
Virology Test Plasma HIV RNA quantification test (Abbott Real Time HIV-1)	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	170
Collect Blood for CD4 Cell Count	2	2						2		2		2		2				12
Collect Blood for MK-1439 PK		4		4	4			8		8								28
Collect Plasma for Viral Resistance Test	14			14	14	14	14	14	14	14	14	14	14	14[g]	14	14		196
Collect Blood for Genetic Analysis		8.5																8.5
Collect Blood for Deep Sequencing Analysis		10													10			20

Trial Period:	Screening		Treatment												Post-treatment			
Visit Number/Title:	1 Screen -ing	2	3	4	5	6	7	8	9	10	11	12	13	14	U (Virologic Failure Confirmation)	U (Early Discon- tinuation)	99	
Scheduled Weeks/Days:	-45 to -1	Day 1	WK 2	WK 4	WK 8	Fasting WK 12[a]	WK 16	WK 24	WK 36	Fasting WK 48[a]	WK 60	WK 72	WK 84	Fasting WK 96[a]	≥ 1 to ≤ 4 weeks after initial virologic failure	At time of Discon	Post study 14 day follow up	
Laboratory Procedures/Assessments																		Total Volume (mL)
Collect Plasma for Future Biomedical Research		10								10				10				30
Total (mL)	61.5	53.5	19	37	37	33	33	43	33	53	33	35	33	45	37.5	33	19	638.5
Total (tablespoons)[f]	4.1	3.6	1.3	2.5	2.5	2.2	2.2	2.9	2.2	3.5	2.2	2.3	2.2	3.0	2.3	2.2	1.3	~42.3

a. Fasting is required at these visits.
b. Includes Enzyme Immunoassay HIV Antibody Screen, Serum Hepatitis B Surface Antigen, Serum Hepatitis B Surface Antibody, Serum Hepatitis B e-Antigen and Serum Hepatitis C Antibody. A plasma Hepatitis C virus PCR quantitative test (an additional ~6 ml= 0.4 tablespoon of blood) will be performed if the Hepatitis C antibody test is positive.
c. For women of childbearing potential.
d. Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT) and International Normalized Ratio (INR).
e. At Study Day 1 and Study Week 4, sample must be collected predose. At Study Week 8, the sample may be collected irrespective of time of dose. At Study Weeks 24 and 48, samples must be collected predose, and within 0.5 to 2 hours postdose (subjects should remain fasting until postdose PK sample is collected at Week 48).
f. One Tablespoon = 15 mL.
g. If viral failure or relapse is confirmed (with a confirmatory HIV-1 RNA at least one week later), and the decision is made to discontinue the subject, plasma for resistance need not be collected again at the discontinuation visit.

Table B: Approximate Blood Volume Drawn From Week 112 Through Week 144 Plus 14 Days Follow-up (Study Extension)

Week (Visit)	WK 112 (V15)	WK 128 (V 16)	WK 144 (V 17)	WK 160 (V 18)	WK 176 (V 19)	WK 192 (V 20)	Virologic Failure Confirmation (U)	Extension Early Discontinuation (U)	14 Day Follow-up (Post Treatment) (99)	Total Volume
Hematology	2	2	2	2	2	2	2	2	2	**18**
Chemistry	7	7	7 [a]	7	7	7 [a]	7	7	7	**63**
Plasma for HIV Viral RNA	10	10	10	10	10	10	10	10	10	**90**
CD4 Cell Count			2			2				**4**
Plasma for Viral Resistance							14	14 [b]		**28**
TOTAL (mL)	**19**	**19**	**21**	**19**	**19**	**21**	**33**	**33**	**19**	**203**
Total (tablespoons) [c]	**1.3**	**1.3**	**1.4**	**1.3**	**1.3**	**1.4**	**2.2**	**2.2**	**1.3**	**~13.5**

a. Fasting is required at these visits for lipids measurement.
b. If viral failure or relapse is confirmed (with a confirmatory HIV-1 RNA at least one week later), and the decision is made to discontinue the subject, plasma for resistance need not be collected again at the early discontinuation visit.
c. One tablespoon = 15 mL.

12.5 Plasma Assay – Sample Collection, Handling, Labeling, Storage, and Shipment

See Laboratory Manual.

12.6 List of Abbreviations and Acronyms

3TC	lamivudine
β-hCG	β-human chorionic gonadotropin
AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase
AMA	American Medical Association
APaT	All Patients as Treated
APTT	Activated partial thromboplastin time
ART	Antiretroviral therapy
AST	Aspartate aminotransferase
BLoQ	Below the limit of quantification
CCR5	Chemokine Receptor Type 5
CI	Confidence Interval
Clcr	Creatinine clearance
CSR	Clinical study report
CYP	cytochrome
DAIDS	Division of acquired immunodeficiency syndrome
DNA	Deoxyribonucleic acid
ECG	electrocardiogram
ECI	Event of clinical interest
eCRF	Electronic case report form
EFV	efavirenz
ERC	Ethical review committee
EU	European union
FAS	Full analysis set
FBR	Future Biomedical Research
FDA	Food & Drug Administration
FDAAA	Food & Drug Administration Amendments Act
FDAMA	Food & Drug Administration Modernization Act
FDC	Fixed dose combination
GCP	Good clinical practice
HAART	Highly active antiretroviral therapy
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDL-C	High-density lipoprotein cholesterol
HIV-1	Human immune deficiency virus type 1
IB	Investigator's brochure
ICF	Informed consent form
ICH	International conference on harmonization
IDU	Injection drug users
IEC	Independent ethics committee
INR	International normalized ratio
InSTI	Integrase strand transfer inhibitors
IQ	Inhibitory Quotient
IRB	Institutional Review board
IRIS	Immune reconstitution syndrome
IUD	Intrauterine device

IVRS/IWRS	Interactive voice response system/Integrated web response system
LDL-C	Low-density lipoprotein cholesterol
LOQ	Lower limit of reliable quantification
mFAS	Modified full analysis set
MSM	Men who have sex with men
NC=F	Non-completer = failure
NHS	Normal human serum
NNRTI	Non-nucleotide reverse transcriptase inhibitor
NRTI	Nucleotide reverse transcriptase inhibitor
N(t)RTI	Nucleotide reverse transcriptase inhibitor
OF	Observed failure
PCR	Polymerase chain reaction
PDLC	Predefined limit of change
PDVF	Protocol defined virologic failure
PI	Protease inhibitor
PIN	Personal Identification number
PK	pharmacokinetics
PO	Per oral
PT	Prothrombin time
PWID	People who inject drugs
q.d.	Once daily
RNA	Ribonucleic acid
SAE	Serious adverse event
siDMC	Standing internal data monitoring committee
SOP	Standard operating procedure
sSAP	Supplemental statistical analysis plan
TDF	Tenofovir disoproxil fumarate
TDF/FTC	Tenofovir disoproxil fumarate/Emtricitabine (TRUVADA™)
TDR	Transmitted drug resistance
TLOVR	Time to loss of virologic response
vRNA	Viral ribonucleic acid
WT	Wild Type

12.7 Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
HEMATOLOGY ***Standard International Units are listed in italics***				
Absolute CD4+ count **– Adult and Pediatric > 13 years** (HIV NEGATIVE ONLY)	300 – 400/mm3 *300 – 400/µL*	200 – 299/mm3 *200 – 299/µL*	100 – 199/mm3 *100 – 199/µL*	< 100/mm3 < *100/µL*
Absolute lymphocyte count **– Adult and Pediatric > 13 years** (HIV NEGATIVE ONLY)	600 – 650/mm3 *0.600 x 10⁹ – 0.650 x 10⁹/L*	500 – 599/mm3 *0.500 x 10⁹ – 0.599 x 10⁹/L*	350 – 499/mm3 *0.350 x 10⁹ – 0.499 x 10⁹/L*	< 350/mm3 < *0.350 x 10⁹/L*
Comment: Values in children ≤ 13 years are not given for the two parameters above because the absolute counts are variable.				
Absolute neutrophil count (ANC)				
Adult and Pediatric, > 7 days	1,000 – 1,300/mm3 *1.000 x 10⁹ – 1.300 x 10⁹/L*	750 – 999/mm3 *0.750 x 10⁹ – 0.999 x 10⁹/L*	500 – 749/mm3 *0.500 x 10⁹ – 0.749 x 10⁹/L*	< 500/mm3 < *0.500 x 10⁹/L*
Fibrinogen, decreased	100 – 200 mg/dL *1.00 – 2.00 g/L* OR 0.75 – 0.99 x LLN	75 – 99 mg/dL *0.75 – 0.99 g/L* OR 0.50 – 0.74 x LLN	50 – 74 mg/dL *0.50 – 0.74 g/L* OR 0.25 – 0.49 x LLN	< 50 mg/dL < *0.50 g/L* OR < 0.25 x LLN OR Associated with gross bleeding
† Use age and sex appropriate values (e.g., bilirubin).				

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Hemoglobin (Hgb)				
Comment: The Hgb values in mmol/L have changed because the conversion factor used to convert g/dL to mmol/L has been changed from 0.155 to 0.6206 (the most commonly used conversion factor). For grading Hgb results obtained by an analytic method with a conversion factor other than 0.6206, the result must be converted to g/dL using the appropriate conversion factor for that lab.				
Adult and Pediatric ≥ 57 days (HIV POSITIVE ONLY)	8.5 – 10.0 g/dL *5.24 – 6.23 mmol/L*	7.5 – 8.4 g/dL *4.62–5.23 mmol/L*	6.50 – 7.4 g/dL *4.03–4.61 mmol/L*	< 6.5 g/dL < *4.03 mmol/L*
Adult and Pediatric ≥ 57 days (HIV NEGATIVE ONLY)	10.0 – 10.9 g/dL *6.18 – 6.79 mmol/L* OR Any decrease 2.5 – 3.4 g/dL *1.58 – 2.13 mmol/L*	9.0 – 9.9 g/dL *5.55 - 6.17 mmol/L* OR Any decrease 3.5 – 4.4 g/dL *2.14 – 2.78 mmol/L*	7.0 – 8.9 g/dL *4.34 - 5.54 mmol/L* OR Any decrease ≥ 4.5 g/dL > *2.79 mmol/L*	< 7.0 g/dL < *4.34 mmol/L*
Comment: The decrease is a decrease from baseline				
International Normalized Ratio of prothrombin time (INR)	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 3.0 x ULN	> 3.0 x ULN
Methemoglobin	5.0 – 10.0%	10.1 – 15.0%	15.1 – 20.0%	> 20.0%
Prothrombin Time (PT)	1.1 – 1.25 x ULN	1.26 – 1.50 x ULN	1.51 – 3.00 x ULN	> 3.00 x ULN
Partial Thromboplastin Time (PTT)	1.1 – 1.66 x ULN	1.67 – 2.33 x ULN	2.34 – 3.00 x ULN	> 3.00 x ULN
Platelets, decreased	100,000 – 124,999/mm^3 *100.000 x 10^9 – 124.999 x 10^9/L*	50,000 – 99,999/mm^3 *50.000 x 10^9 – 99.999 x 10^9/L*	25,000 – 49,999/mm^3 *25.000 x 10^9 – 49.999 x 10^9/L*	< 25,000/mm^3 < *25.000 x 10^9/L*
WBC, decreased	2,000 – 2,500/mm^3 *2.000 x 10^9 – 2.500 x 10^9/L*	1,500 – 1,999/mm^3 *1.500 x 10^9 – 1.999 x 10^9/L*	1,000 – 1,499/mm^3 *1.000 x 10^9 – 1.499 x 10^9/L*	< 1,000/mm^3 < *1.000 x 10^9/L*
∗ Values are for term infants. Preterm infants should be assessed using local normal ranges. † Use age and sex appropriate values (e.g., bilirubin).				

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
CHEMISTRIES ***Standard International Units are listed in italics***				
Acidosis	NA	pH < normal, but ≥ 7.3	pH < 7.3 without life-threatening consequences	pH < 7.3 with life-threatening consequences
Albumin, serum, low	3.0 g/dL – < LLN *30 g/L – < LLN*	2.0 – 2.9 g/dL *20 – 29 g/L*	< 2.0 g/dL < *20 g/L*	NA
Alkaline Phosphatase	1.25 – 2.5 x ULN†	2.6 – 5.0 x ULN†	5.1 – 10.0 x ULN†	> 10.0 x ULN†
Alkalosis	NA	pH > normal, but ≤ 7.5	pH > 7.5 without life-threatening consequences	pH > 7.5 with life-threatening consequences
ALT (SGPT)	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN
AST (SGOT)	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN
Bicarbonate, serum, low	16.0 mEq/L – < LLN *16.0 mmol/L – < LLN*	11.0 – 15.9 mEq/L *11.0 – 15.9 mmol/L*	8.0 – 10.9 mEq/L *8.0 – 10.9 mmol/L*	< 8.0 mEq/L < *8.0 mmol/L*
Comment: Some laboratories will report this value as Bicarbonate (HCO_3) and others as Total Carbon Dioxide (CO_2). These are the same tests; values should be graded according to the ranges for Bicarbonate as listed above.				
Bilirubin (Total)				
Adult and Pediatric > 14 days	1.1 – 1.5 x ULN	1.6 – 2.5 x ULN	2.6 – 5.0 x ULN	> 5.0 x ULN
Calcium, serum, high				
Adult and Pediatric ≥ 7 days	10.6 – 11.5 mg/dL *2.65 – 2.88 mmol/L*	11.6 – 12.5 mg/dL *2.89 – 3.13 mmol/L*	12.6 – 13.5 mg/dL *3.14 – 3.38 mmol/L*	> 13.5 mg/dL > *3.38 mmol/L*
Calcium, serum, low				
Adult and Pediatric ≥ 7 days	7.8 – 8.4 mg/dL *1.95 – 2.10 mmol/L*	7.0 – 7.7 mg/dL *1.75 – 1.94 mmol/L*	6.1 – 6.9 mg/dL *1.53 – 1.74 mmol/L*	< 6.1 mg/dL < *1.53 mmol/L*
Comment: Do not adjust Calcium, serum, low or Calcium, serum, high for albumin				
† Use age and sex appropriate values (e.g., bilirubin).				

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Cardiac troponin I (cTnI)	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the manufacturer
Cardiac troponin T (cTnT)	NA	NA	NA	≥ 0.20 ng/mL OR Levels consistent with myocardial infarction or unstable angina as defined by the manufacturer
Cholesterol (fasting)				
Adult ≥ 18 years	200 – 239 mg/dL *5.18 – 6.19 mmol/L*	240 – 300 mg/dL *6.20 – 7.77 mmol/L*	> 300 mg/dL > *7.77 mmol/L*	NA
Pediatric < 18 years	170 – 199 mg/dL *4.40 – 5.15 mmol/L*	200 – 300 mg/dL *5.16 – 7.77 mmol/L*	> 300 mg/dL > *7.77 mmol/L*	NA
Creatine Kinase	3.0 – 5.9 x ULN†	6.0 – 9.9 x ULN†	10.0 – 19.9 x ULN†	≥ 20.0 x ULN†
Creatinine	1.1 – 1.3 x ULN†	1.4 – 1.8 x ULN†	1.9 – 3.4 x ULN†	≥ 3.5 x ULN†

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Glucose, serum, high				
Nonfasting	116 – 160 mg/dL *6.44 – 8.88 mmol/L*	161 – 250 mg/dL *8.89 – 13.88 mmol/L*	251 – 500 mg/dL *13.89 – 27.75 mmol/L*	> 500 mg/dL > *27.75 mmol/L*
Fasting	110 – 125 mg/dL *6.11 – 6.94 mmol/L*	126 – 250 mg/dL *6.95 – 13.88 mmol/L*	251 – 500 mg/dL *13.89 – 27.75 mmol/L*	> 500 mg/dL > *27.75 mmol/L*
Glucose, serum, low				
Adult and Pediatric ≥ 1 month	55 – 64 mg/dL *3.05 – 3.55 mmol/L*	40 – 54 mg/dL *2.22 – 3.06 mmol/L*	30 – 39 mg/dL *1.67 – 2.23 mmol/L*	< 30 mg/dL < *1.67 mmol/L*
Infant∗†, < 1 month	50 – 54 mg/dL *2.78 – 3.00 mmol/L*	40 – 49 mg/dL *2.22 – 2.77 mmol/L*	30 – 39 mg/dL *1.67 – 2.21 mmol/L*	< 30 mg/dL < *1.67 mmol/L*
Lactate	ULN - < 2.0 x ULN without acidosis	≥ 2.0 x ULN without acidosis	Increased lactate with pH < 7.3 without life-threatening consequences	Increased lactate with pH < 7.3 with life-threatening consequences
Comment: Added ULN to Grade 1 parameter				
LDL cholesterol (fasting)				
Adult ≥ 18 years	130 – 159 mg/dL *3.37 – 4.12 mmol/L*	160 – 190 mg/dL *4.13 – 4.90 mmol/L*	≥ 190 mg/dL ≥ *4.91 mmol/L*	NA
Pediatric > 2 - < 18 years	110 – 129 mg/dL *2.85 – 3.34 mmol/L*	130 – 189 mg/dL *3.35 – 4.90 mmol/L*	≥ 190 mg/dL ≥ *4.91 mmol/L*	NA
Lipase	1.1 – 1.5 x ULN	1.6 – 3.0 x ULN	3.1 – 5.0 x ULN	> 5.0 x ULN
Magnesium, serum, low	1.2 – 1.4 mEq/L *0.60 – 0.70 mmol/L*	0.9 – 1.1 mEq/L *0.45 – 0.59 mmol/L*	0.6 – 0.8 mEq/L *0.30 – 0.44 mmol/L*	< 0.60 mEq/L < *0.30 mmol/L*
Pancreatic amylase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN
Phosphate, serum, low				
Adult and Pediatric > 14 years	2.5 mg/dL – < LLN *0.81 mmol/L – < LLN*	2.0 – 2.4 mg/dL *0.65 – 0.80 mmol/L*	1.0 – 1.9 mg/dL *0.32 – 0.64 mmol/L*	< 1.00 mg/dL < *0.32 mmol/L*
Pediatric 1 year – 14 years	3.0 – 3.5 mg/dL *0.97 –*	2.5 – 2.9 mg/dL *0.81 –*	1.5 – 2.4 mg/dL *0.48 –*	< 1.50 mg/dL < *0.48 mmol/L*

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
	1.13 mmol/L	*0.96 mmol/L*	*0.80 mmol/L*	
Pediatric < 1 year	3.5 – 4.5 mg/dL *1.13 – 1.45 mmol/L*	2.5 – 3.4 mg/dL *0.81 – 1.12 mmol/L*	1.5 – 2.4 mg/dL *0.48 – 0.80 mmol/L*	< 1.50 mg/dL < *0.48 mmol/L*
Potassium, serum, high	5.6 – 6.0 mEq/L *5.6 – 6.0 mmol/L*	6.1 – 6.5 mEq/L *6.1 – 6.5 mmol/L*	6.6 – 7.0 mEq/L *6.6 – 7.0 mmol/L*	> 7.0 mEq/L > *7.0 mmol/L*
Potassium, serum, low	3.0 – 3.4 mEq/L *3.0 – 3.4 mmol/L*	2.5 – 2.9 mEq/L *2.5 – 2.9 mmol/L*	2.0 – 2.4 mEq/L *2.0 – 2.4 mmol/L*	< 2.0 mEq/L < *2.0 mmol/L*
Sodium, serum, high	146 – 150 mEq/L *146 – 150 mmol/L*	151 – 154 mEq/L *151 – 154 mmol/L*	155 – 159 mEq/L *155 – 159 mmol/L*	≥ 160 mEq/L ≥ *160 mmol/L*
Sodium, serum, low	130 – 135 mEq/L *130 – 135 mmol/L*	125 – 129 mEq/L *125 – 129 mmol/L*	121 – 124 mEq/L *121 – 124 mmol/L*	≤ 120 mEq/L ≤ *120 mmol/L*
Triglycerides (fasting)	NA	500 – 750 mg/dL *5.65 – 8.48 mmol/L*	751 – 1,200 mg/dL *8.49 – 13.56 mmol/L*	> 1,200 mg/dL > *13.56 mmol/L*
† Use age and sex appropriate values (e.g., bilirubin).				

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Uric acid	7.5 – 10.0 mg/dL *0.45 – 0.59 mmol/L*	10.1 – 12.0 mg/dL *0.60 – 0.71 mmol/L*	12.1 – 15.0 mg/dL *0.72 – 0.89 mmol/L*	> 15.0 mg/dL > *0.89 mmol/L*
URINALYSIS ***Standard International Units are listed in italics***				
Hematuria (microscopic)	6 – 10 RBC/HPF	> 10 RBC/HPF	Gross, with or without clots OR with RBC casts	Transfusion indicated
Proteinuria, random collection	1 +	2 – 3 +	4 +	NA
Proteinuria, 24 hour collection				
Adult and Pediatric ≥ 10 years	200 – 999 mg/24 h *0.200 – 0.999 g/d*	1,000 – 1,999 mg/24 h *1.000 – 1.999 g/d*	2,000 – 3,500 mg/24 h *2.000 – 3.500 g/d*	> 3,500 mg/24 h > *3.500 g/d*
Pediatric > 3 mo - < 10 years	201 – 499 mg/m2/24 h *0.201 – 0.499 g/d*	500 – 799 mg/m2/24 h *0.500 – 0.799 g/d*	800 – 1,000 mg/m2/24 h *0.800 – 1.000 g/d*	> 1,000 mg/ m2/24 h > *1.000 g/d*
† Use age and sex appropriate values (e.g., bilirubin).				

Adapted from DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS, PUBLISH DATE: 28 Dec-04/Clarification Aug 09 DECEMBER.

12.8 Child-Pugh Score for Cirrhosis Mortality

Measure	1 point	2 points	3 points
Total bilirubin, µmol/l (mg/dl)	<34 (<2)	34-50 (2-3)	>50 (>3)
Serum albumin, g/dl	>3.5	2.8-3.5	<2.8
Prothrombin time, prolongation (secs)	<4.0	4.0-6.0	>6.0
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory

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 – 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	