Official Protocol Title:	Phase IIb, Double-Blinded, Multicenter, Randomized Study to Assess the Effect on Central Nervous System (CNS) Toxicity of Switching from ATRIPLA™ (Efavirenz, Tenofovir, Emtricitabine) to MK-1439A (Doravirine, Tenofovir, Lamivudine) in Virologically-Suppressed Subjects
NCT Number:	NCT02652260
Document Date:	31-Oct-2022

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This protocol amendment is applicable only to South Africa.

SPONSOR:
Merck Sharp & Dohme LLC
(hereafter referred to as the Sponsor or MSD)
126 East Lincoln Avenue
P.O. Box 2000
Rahway, NJ 07065 USA

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

TITLE:

Phase IIb, Double-Blinded, Multicenter, Randomized Study to Assess the Effect on Central Nervous System (CNS) Toxicity of Switching from ATRIPLA™ (Efavirenz, Tenofovir, Emtricitabine) to MK-1439A (Doravirine, Tenofovir, Lamivudine) in Virologically-Suppressed Subjects

IND NUMBER: [124, 997]
EudraCT NUMBER: [2015-003617-18]

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DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 05	31-OCT-2022	This is a country-specific amendment for South Africa to inform regarding the Sponsor's name and address change and updates that were made to the Code of Conduct in the previous amendment. Note: Amendment 05 supersedes Amendment 04.
Amendment 04	26-AUG-2022	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address. Amendment 04 was not released to sites.
Amendment 03	06-APR-2020	• Study extension 3 was added to (1) provide continued access to MK-1439A for participants who are deriving benefit from MK-1439A until the drug is available locally in the country participating in the trial or for an additional 2 years (whichever comes first), and (2) collect key safety information from participants who continue on MK-1439A in this study extension.
Amendment 02	08-JUN-2018	• Added open-label study extension 2 to provide continued access to MK-1439A until the drug is available locally in countries participating in the trial or for an additional 2 years (whichever comes first).
Amendment 01	30-SEP-2016	• Added open-label study extension 1 for 2 years to collect long-term efficacy and safety data. • Incorporated changes (including decreasing the number or subjects to be enrolled) to facilitate enrollment and ensure trial completion.
Original protocol	07-OCT-2015	• Not applicable.

SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
	Title Page	South Africa was added to the Title Page.	This is a country-specific amendment for South Africa to inform regarding the Sponsor's name and address change and updates that were made to the Code of Conduct in the previous amendment. Note: Amendment 05 supersedes Amendment 04.
The following changes were made in Amendment 04; however, Amendment 04 was not released to sites. These changes are summarized here for clarity and implementation in the current country-specific amendment.			
12.1 Throughout	Title Page Code of Conduct for Clinical Trials	Sponsor entity name and address change.	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.
12.1	Code of Conduct for Clinical Trials	The code of conduct was updated in Amendment 04.	To align with the current standard text for the Code of Conduct.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

No additional changes.

1.0 TRIAL SUMMARY

Abbreviated Title	Assess the effect of switching HIV-1 infected subjects with CNS toxicity (≥Grade 2) from ATRIPLA™ or its components to MK-1439A
Trial Phase	IIb
Clinical Indication	Exploratory trial to assess improvement in CNS toxicity (≥Grade 2) after a switch from ATRIPLA™ to MK-1439A
Trial Type	Interventional
Type of control	Active control (with double dummy placebo for blinding)
Route of administration	Oral
Trial Blinding	Double-blind
Treatment Groups	Base Study: Two treatment groups: Immediate Switch Group (ISG): Immediate Switch (at Study Day 1) from a baseline regimen of ATRIPLA™ or its components to MK-1439A (+ a placebo matched to ATRIPLA™ to maintain blinding) for 12 weeks followed by treatment with open-label MK-1439A for an additional 12 weeks. Deferred Switch Group (DSG): Subjects will receive ATRIPLA™ (+ a placebo matched to MK-1439A to maintain blinding) for the first 12 weeks of the study followed by treatment with open-label MK-1439A for 24 weeks. Study Extensions: All subjects: open-label MK-1439A
Number of trial subjects	Approximately 84 subjects will be enrolled.
Estimated duration of trial	The sponsor estimates that the trial will require approximately 103 months from the time the first subject signs the informed consent until the last subject's last study-related phone call or visit.
Duration of Participation	The study consists of a screening phase of up to 45 days (~6.5 weeks) followed by a double-blind base study of either 24 weeks ISG) or 36 weeks (DSG), 3 open-label study extensions (study extensions 1, 2, and 3), and a 14-day follow-up period. The treatment duration of study extension 1 is 96 weeks; and the treatment duration of study extensions 2 and 3 is up to 96 weeks for each, depending on when MK-1439A becomes locally available (whichever comes first). The approximate cumulative durations of participation in the trial (from informed consent through follow-up) are 32 (ISG) or 44 (DSG) weeks for subjects who complete the base study; 128 (ISG) or 140 (DSG) weeks for subjects who complete the base study and study extension 1; up to 224 (ISG) or up to 236 (DSG) weeks for subjects who complete the base study and study extensions 1 and 2; and up to 320 (ISG) or up to 332 (DSG) weeks for subjects who complete the base study and study extensions 1, 2, and 3.
Randomization Ratio	1:1.

A list of abbreviations used in this document can be found in Section 12.7.

2.0 TRIAL DESIGN

2.1 Trial Design

This is a multicenter, double-blind (with in-house blinding), randomized, active-controlled trial to evaluate a switch from ATRIPLA™, generic ATRIPLA™ or its components (EFV, TDF plus emtricitabine) to MK-1439A in virologically suppressed, human immunodeficiency virus type 1 (HIV-1)-infected subjects.

The study consists of a screening period of approximately 6.5 weeks, a base study of 24 weeks (ISG) or 36 weeks (DSG) followed by 3 consecutive 96-week open-label study extensions (study extensions 1, 2, and 3), and a 14-day post-study follow-up visit after the last treatment visit. The treatment duration of the first open-label study extension (study extension 1) is 96 weeks; and the treatment duration of the second and third open-label study extensions (study extensions 2 and 3, respectively) is up to 96 weeks for each, depending on when MK-1439A becomes locally available (whichever comes first).

The study is to be conducted in conformance with Good Clinical Practice.

MK-1439A is a single-tablet fixed-dose combination (FDC) that combines doravirine (also known as MK-1439), a non-nucleoside reverse transcriptase inhibitor (NNRTI), with lamivudine (3TC) and tenofovir disoproxil fumarate (TDF), 2 approved and marketed nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs). As of the date of issuance of this protocol amendment, MK-1439A has been approved in multiple markets including the US, EU, Canada, Switzerland and Australia for the treatment of HIV-1 infection in adult patients.

A single tablet of MK-1439A contains a full daily HIV treatment regimen of MK-1439 100 mg + 3TC 300 mg + TDF 300 mg (which is equivalent to 245 mg of tenofovir disoproxil). ATRIPLA™ is a single-tablet FDC that combines an approved and marketed NNRTI, efavirenz (EFV), with 2 approved and marketed NRTIs, emtricitabine (FTC) and TDF. A single tablet of ATRIPLA™ contains a full daily HIV treatment regimen of efavirenz 600 mg + FTC 200 mg + TDF 300 mg (which is equivalent to 245 mg of tenofovir disoproxil).

This study will investigate whether switching from ATRIPLA™ to MK-1439A leads to improvement in or resolution of CNS toxicity associated with EFV, as measured by the presence of Grade 2 or worse CNS AEs, an overall change in CNS toxicity score, and an improvement in sleep quality, neurocognitive function, anxiety/depression, and overall health-related quality of life. The study will also investigate whether switching from ATRIPLA™ to MK-1439A leads to continued virologic suppression and immunological reconstitution. In a Phase 2 study in treatment-naïve subjects initiating antiretroviral therapy, subjects treated with an MK-1439-based regimen had a significantly lower rate of treatment-emergent CNS events than those treated with an efavirenz-based regimen (26.9% vs. 46.3%, $p<0.001$) while the antiretroviral activity and immunological effect of the 2 regimens was comparable after 24 weeks of therapy [1]. Based on these data, subjects in this study are expected to benefit from the switch from ATRIPLA™ to MK-1439A.

Prior to enrolling in the base study and each of the study extensions, the subject must meet eligibility criteria (see Sec. 5.1.2) and provide consent.

Further detail for the base study and the 3 study extensions is provided below.

Base Study:

Approximately 84 subjects who meet eligibility criteria will be randomized to either switch immediately to MK-1439A (the ISG) or to continue the ATRIPLA™ regimen for 12 weeks and then switch to MK-1439A (the DSG). At Study Week 12, all subjects will be given open-label MK-1439A for the remainder of their study treatment period. At Study Week 24 (for ISG) or 36 (for DSG), subjects who meet the criteria defined in Section 5.1.2 will be eligible to enter study extension 1, which is approximately 2 years' duration, such that the total treatment period will be approximately 2.5 years.

The total duration of treatment with MK-1439A for subjects who complete the base study is 24 weeks, regardless of treatment group.

All subjects entering the study extensions will receive open-label treatment with MK-1439A (100 mg q.d.).

Study Extension 1:

At Study Week 24 (for ISG) or 36 (for DSG), eligibility into study extension 1 will be determined. Subjects who meet eligibility criteria may receive open-label MK-1439A for an additional 96 weeks; the total duration of treatment for subjects who continue into study extension 1 is 120 (ISG) or 132 (DSG) weeks.

Long-term efficacy and safety data will be collected during study extension 1 and summarized descriptively; an exploratory objective (efficacy and safety) is defined for study extension 1.

Study Extension 2:

At Study Week 120 (for ISG) or 132 (for DSG), eligibility into study extension 2 will be determined. Subjects who meet eligibility criteria and continue into study extension 2 may continue to receive treatment with MK-1439A until it becomes locally available or up to approximately 2 years beyond the first extension (whichever comes first). For subjects who continue into study extension 2, the total duration of treatment is dependent on when MK-1439A becomes locally available, with a maximum total duration of treatment of up to 216 weeks (ISG) or 228 weeks (DSG).

During study extension 2, pregnancy for female subjects and SAEs for all subjects will be monitored and collected. Efficacy data will not be collected for study extension 2.

Study Extension 3:

At Study Week 216 (for ISG) or 228 (for DSG), eligibility into study extension 3 will be determined. Subjects who meet eligibility criteria and continue into study extension 3 may continue to receive treatment with MK-1439A until it becomes locally available or up to

approximately 2 years beyond the second extension (whichever comes first). For subjects who continue into study extension 3, the total duration of treatment is dependent on when MK-1439A becomes locally available, with a maximum total duration of treatment of up to 312 weeks (ISG) or 324 weeks (DSG).

During study extension 3, pregnancy for female subjects and SAEs for all subjects will be monitored and collected. Efficacy data will not be collected for study extension 3.

Goals of the Study:

The primary goal of the study is to evaluate whether a switch from ATRIPLA™ to MK-1439A results in a lower proportion of subjects who have at least one CNS toxicity of at least Grade 2 intensity (according to the DAIDS Toxicity Criteria, Section 12.6) at Study Week 12 compared with continuation of ATRIPLA™. The initial double-blind period of the study will allow for a blinded comparison of the randomized treatment groups at the primary analysis time point, as well as a comparison of overall safety data. The unblinding to initial randomized treatment assignment that occurs at Study Week 16 will reduce complexity and allow continued observation of whether a switch from ATRIPLA™ to MK-1439A leads to within-subject improvement in or resolution of CNS toxicity associated with EFV at consistent timepoints following the switch (Weeks 4, 12, and 24) in both the ISG and DSG.

An additional exploratory goal of the study is to assess drug levels of both MK-1439 and EFV in the weeks following the switch to evaluate the decline in efavirenz plasma concentrations and the rise of MK-1439 plasma concentrations in HIV-1 infected subjects switching from EFV to MK-1439. The pharmacokinetic (PK) assessment will occur during the blinded period of the study and will require samples to be collected in both groups at Study Day 1 (day of randomization) and Study Weeks 1, 2, 3, and 4. Since sampling occurs during the blinded period of the study, plasma samples for PK analysis will be collected from both treatment groups, but only samples taken from the ISG will be analyzed.

Randomized subjects who meet virologic failure criteria during the base study or study extension 1 (see Section 4.2.3.2) will return to the site for repeat viral RNA testing between one and 4 weeks ($\geq$ 1 and $\leq$ 4 weeks) later (at a virologic failure confirmation visit). If virologic failure is confirmed and the viral load meets the threshold for resistance testing (HIV-1 RNA > 400 copies/mL), in the base study or study extension 1, 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 study extension 1, 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 discontinuation visit from subjects who discontinue, from either the base study or study extension 1, for reasons other than virologic failure, will be sent for testing. (Note that if a sample from the discontinuation visit is not available, a sample from the last available visit [if available] will be sent.)

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.

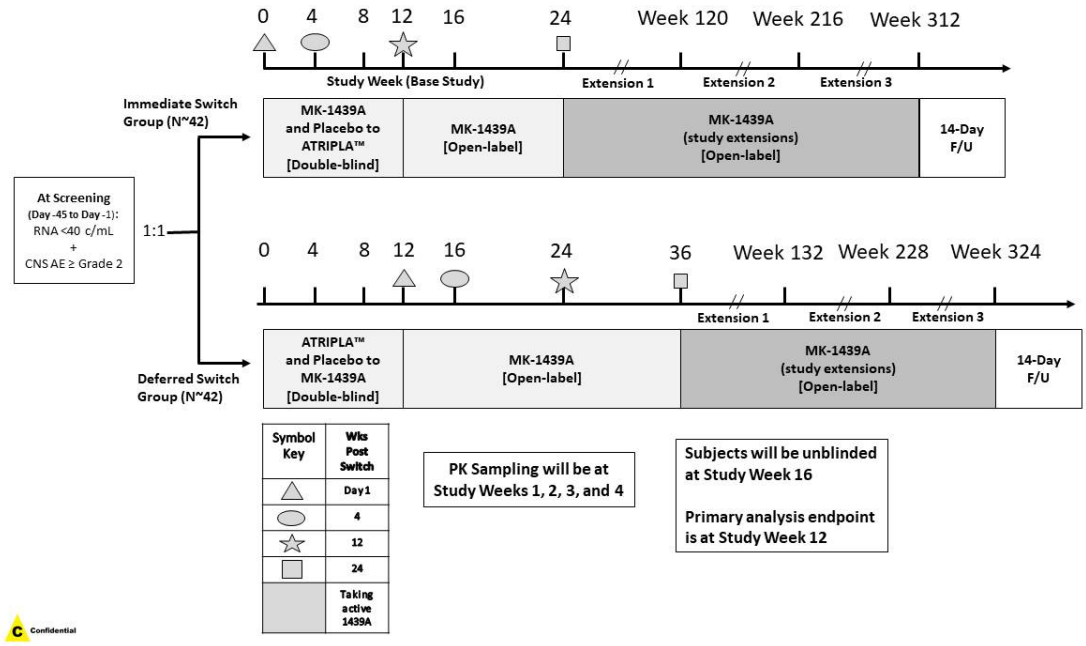

Figure 1 Trial Design: Base Study and Study Extensions

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

Base Study:

In HIV-1-positive subjects who are virologically suppressed on ATRIPLA™ and who, at both screening and randomization, are experiencing at least one Grade 2 or worse (according to the DAIDS Toxicity Criteria) CNS toxicity from the CNS toxicity questionnaire (ie, one of the following CNS toxicities: dizziness, depression/low mood, insomnia/sleeplessness, anxiety/nervousness, confusion, impaired concentration/attention, headache, somnolence/daytime sleepiness, aggressive mood/behavior and abnormal dreams).

3.1 Primary Objective(s) & Hypothesis(es)

1) Objective: To evaluate the effect of a switch to MK-1439A compared with continuation of ATRIPLA™ on the incidence of Grade 2 or worse CNS toxicity (defined as at least one toxicity listed on the CNS toxicity questionnaire) at Week 12.

   Hypothesis: Switching from ATRIPLA™) to MK-1439A results in a lower proportion of subjects with at least one CNS toxicity (from the CNS toxicity questionnaire) of at least Grade 2 intensity (according to the DAIDS Toxicity Criteria) at Week 12 than continuation of ATRIPLA™.

3.2 Secondary Objective(s) & Hypothesis(es)

1) Objective: To evaluate the effect of a switch from ATRIPLA™ to MK-1439A compared with continuation of ATRIPLA™ on the incidence of Grade 2 or worse CNS toxicity at Week 4.

2) Objective: To evaluate the change from baseline (the day of the switch from ATRIPLA™ to MK-1439A) in the incidence of Grade 2 or worse CNS toxicity in all subjects (combining both treatment groups) at 24 weeks after the switch.

3) Objective: To compare the change from baseline (Study Day 1) in CNS toxicity scores at Weeks 4 and 12 between subjects switching from ATRIPLA™ to MK-1439A at Study Day 1 and subjects continuing ATRIPLA™.

4) Objective: To evaluate the change from baseline (the day of the switch from ATRIPLA™ to MK-1439A) in CNS toxicity scores in all subjects (combining both treatment groups) at 24 weeks after the switch.

5) Objective: To evaluate the effect of a switch from ATRIPLA™ to MK-1439A compared with continuation of ATRIPLA™ on fasting lipids (LDL, HDL, non-HDL cholesterol and triglycerides) as measured by the change from baseline (Study Day 1) in fasting lipids at Study Week 12.

6) Objective: To evaluate the effect of a switch from ATRIPLA™ to MK-1439A on fasting lipids (LDL, HDL, non-HDL cholesterol and triglycerides) as measured by the change from baseline (the day of the switch from ATRIPLA™ to MK-1439A) in fasting lipids at 24 weeks after the switch (combining both treatment groups).

7) Objective: To evaluate the effect of a switch from ATRIPLA™ to MK-1439A on virologic suppression as measured by the proportion of subjects with HIV-1 RNA below the limit of quantification (< 40 copies/mL) and <50 copies/mL at 24 weeks after the switch (combining both treatment groups).

8) Objective: To evaluate the effect of a switch from ATRIPLA™ to MK-1439A on continued immunologic restoration as measured by the change from baseline (the day of the switch from ATRIPLA™ to MK-1439A) in CD4 cell count at 24 weeks after the switch (combining both treatment groups).

9) Objective: To evaluate the safety and tolerability of a switch from ATRIPLA™ to MK-1439A compared with continuation of ATRIPLA™, as assessed by review of the accumulated safety data through Study Week 12.

10) Objective: To evaluate the safety and tolerability of a switch from ATRIPLA™ to MK-1439A, as assessed by review of the accumulated safety data 24 weeks after the switch (combining both treatment groups).

3.3 Exploratory Objectives

1) Objective: To compare subjects switching from ATRIPLA™ to MK-1439A and subjects continuing ATRIPLA™ with respect to the change from baseline (Study Day 1) to Study Weeks 4 and 12 in questionnaire scores assessing the following:
    - Sleep quality
    - Anxiety and depression
    - Health-related quality of life.

2) Objective: To evaluate the effect of a switch from ATRIPLA™ to MK-1439A on the change from baseline (the day of the switch from ATRIPLA™ to MK-1439A) to 24 weeks after the switch (combining both treatment groups) in questionnaire scores assessing the following:
    - Sleep quality
    - Anxiety and depression
    - Health-related quality of life.

3) Objective: To compare subjects switching from ATRIPLA™ to MK-1439A and subjects continuing ATRIPLA™ with respect to the change from baseline (Study Day 1) to Study Weeks 4 and 12 in neurocognitive function as assessed by Cogstate Brief Battery (CBB).

4) Objective: To evaluate the effect of a switch from ATRIPLA™ to MK-1439A on the change from baseline (the day of the switch from ATRIPLA™ to MK-1439A) to 24 weeks after the switch (combining both treatment groups) in neurocognitive function as assessed by CBB.

5) Objective: To evaluate MK-1439 and efavirenz plasma concentrations in the Immediate Switch Group weekly through 4 weeks following the switch from ATRIPLA™ to MK-1439A.

6) Objective: 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.

7) Objective (Study Extension 1): To assess long-term efficacy and safety of MK-1439A administered for up to 120 weeks for each treatment group, the Immediate Switch Group and the Deferred Switch Group.

4.0 BACKGROUND & RATIONALE

4.1 Background

Refer to the Investigator's Brochure (IB) 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 lifelong combination antiretroviral therapy (cART) also referred to as 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 5 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 cART is to suppress HIV to undetectable levels so that immune function is preserved or restored. Yet, while cART 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 non-compliance if the treatment regimen is difficult to adhere to (e.g. pill burden, frequency of treatment) and associated with intolerable side-effects. This can potentially lead to treatment failures with possible emergence of resistant virus. Additionally, there is currently still significant concern regarding toxicities of some widely-used antiretroviral agents, including neuropsychiatric toxicities associated with efavirenz (EFV, an NNRTI), gastrointestinal toxicities such as diarrhea associated with multiple protease inhibitors (PIs), and serum lipid abnormalities associated with multiple mechanistic classes. These toxicities can be bothersome enough to cause subjects to switch from effective therapies to seek more tolerable alternatives. Thus, potent treatment regimens that have an excellent safety and tolerability profile and are convenient to take are still highly desirable.

In a retrospective chart review of 276 patients initiating cART therapy, EFV was part of initial therapy in 61% [2]. In this series, EFV was later discontinued in 54% of patients, and the majority of these discontinuations (60%) were due to CNS toxicities such as dizziness, abnormal dreams, mood changes and anxiety. The incidence of discontinuation due to CNS toxicities with a non-EFV based regimen was 3% ($P< 0.0001$).

Clinical trials have been conducted to examine the effect on CNS toxicity of a switch from an EFV-based regimen to an alternative antiretroviral regimen and have demonstrated significant improvements in various CNS adverse events, sleep quality, and anxiety scores [3, 4]. One study in particular provides key data supporting the statistical approach used in this protocol. That double-blind study [3] randomized 38 patients with CNS toxicity who were virologically suppressed on ATRIPLA™ to either an immediate switch to an etravirine-based regimen at study entry or a delayed switch at Study Week 12. The primary endpoint was the percentage of subjects with Grade 2-4 CNS toxicity at Week 12. In the immediate switch group, Grade 2-4 CNS events were observed in 90% of subjects at baseline and 60% of subjects at Week 12 ($p=0.041$); in the delayed switch group, CNS Grade 2-4 events were observed in 88.9% of subjects at baseline and 81.3% of subjects at Week 12 (p=NS). In both arms combined, the decline in the proportion of subjects with Grade 2-4 CNS events 12

weeks after a switch to etravirine was significant for overall CNS events, insomnia, abnormal dreams and nervousness (p=0.009, 0.016, 0.001. and 0.046, respectively).

As of the date of issuance of this protocol amendment, both MK-1439 (DOR) and MK-1439A (DOR/3TC/TDF) have been approved in multiple markets including the US, EU, Canada, Switzerland, and Australia for the treatment of HIV-1 infection in adult patients.

MK-1439 is a potent inhibitor of HIV-1 replication in vitro and is active against both wild type virus and the most common NNRTI resistant variants at concentrations achieved with once-daily dosing. MK-1439 displays excellent potency against wild type virus with an IC_{50} of 12 nM in the presence of 100% normal human serum (NHS). Preclinical studies also indicate 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. The potency against viruses containing the double mutant K103N + Y181C is 33nM. The preclinical toxicity profile of MK-1439 is favorable following dosing in rats up to 6 months in duration at 3, 30, and 450 mg/kg/day, and in dogs up to 9 months in duration at 1, 10, and 1000 mg/kg/day. Clinical pharmacology studies indicate that MK-1439 can be dosed once daily, without regard to food, and MK-1439 is not a metabolic inducer or inhibitor, reducing the likelihood that it will cause significant drug-drug interactions. In an ongoing Phase 2 study, MK-1439 has been associated with a significantly lower rate of treatment-emergent CNS events after 24 weeks of therapy than EFV in treatment-naïve subjects initiating antiretroviral therapy (26.9% vs 46.3%, p<0.001)) while achieving similar antiretroviral activity and immunological effect [1, 5]. These data provide support for the expectation that a study in which subjects switch from ATRIPLA™ to MK-1439A that is based on the etravirine switch study design, as discussed above, will demonstrate improvement in CNS toxicity.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Although ATRIPLA™ has recently been reclassified from a recommended /preferred agent to an alternative agent for initial antiretroviral therapy in US-DHHS guidelines [6], UK – BHIVA guidelines [7], and in other national guidelines, it remains in common use at present.

While some HIV therapies have been shown in clinical trials to be superior to EFV-based therapies, these apparent efficacy differences have been due to EFV tolerability issues and are not caused by inadequate virologic effect, since most analyses consider discontinuations due to adverse experiences as efficacy failures. Efavirenz CNS toxicity is common within the first weeks of therapy and generally resolves. However, some individuals have longer term CNS toxicity which is the most common reason patients switch from EFV to alternative therapy.

Minimizing pill burden and managing toxicities are crucial to maintaining adherence and thereby minimizing future risk of virologic failure. Therefore, when switching a patient from ATRIPLA™ to an alternate regimen, maintaining a once-daily FDC with a third agent such

as doravirine (while continuing a similar dual N(t)RTI backbone) is likely to optimize adherence. Furthermore, as stated in Section 4.1.1, data from a comparative Phase 2 study of MK-1439 and EFV demonstrated a superior CNS toxicity profile for MK-1439 and support the hypothesis that subjects experiencing CNS toxicity on an EFV-based regimen may expect improvement in their CNS toxicity after switching to a MK-1439-based regimen.

Current UK and European guidelines for switching an ARV regimen due to EFV-associated toxicity recommend either within-class switches or switches to a boosted protease inhibitor (PI), an integrase inhibitor (InSTI) such as raltegravir (RAL), or maraviroc (MVC); US guidance is consistent with this in the setting of virologic suppression, provided antiretroviral history and antiretroviral resistance data has been considered (DHHS guidelines, February 2014). While switching to a boosted PI, RAL or MVC may occur in the presence of active viral replication, pill burden may become a limiting factor, particularly given the requirement for twice-daily dosing with RAL or MVC. Furthermore, introduction of MVC in the setting of recent EFV therapy requires an increase in the dose of MVC to 600 mg bid for the first week post switch due to clinically significant induction of MVC metabolism. Within-class switches are best performed in the setting of virologic suppression due to the CYP3A4 enzyme-inducing effects of EFV and consequent risk of subtherapeutic drug concentrations of the new NNRTI.

Although MK-1439 is not expected to cause drug-drug interactions, it is metabolized by CYP3A4 and, thus, can be a victim of drug-drug interaction with agents that significantly induce or inhibit this enzyme, such as rifampin and ritonavir, respectively [4]. EFV is known to be a modest inducer of cytochrome metabolism, and therefore, in anticipation of the present study, a drug-drug interaction study was performed to examine the effect of switching from EFV to MK-1439 on the metabolism of MK-1439 in healthy volunteers [8]. This was an open-label, 3-period, fixed-sequence, multiple-dose study. In Period 1, MK-1439 100 mg q.d. was administered for 5 consecutive days, followed by 7 days of washout between the last dose of MK-1439 in Period 1 and the first dose of EFV in Period 2. In Period 2, EFV 600 mg q.d. was administered for 14 consecutive days. There was no washout between Periods 2 and 3. In Period 3, MK-1439 100 mg q.d. was administered for 14 consecutive days.

Following cessation of EFV treatment, MK-1439 C_{24} on Days 1 and 14 of q.d. dosing with MK-1439 decreased by 85% and 50%, respectively, relative to the MK-1439 C_{24} observed when MK-1439 was given without EFV pre-treatment. Following pre-treatment with EFV, MK-1439 C_{24} was 93.5 nM on Day 1 and increased to 449 nM on Day 14 compared to single dose and steady state C_{24} values of 625 nM and 902 nM for MK-1439 100 mg administered without prior efavirenz treatment. EFV plasma concentrations declined from 3180 ng/mL on Day 1 to 139 ng/mL on Day 15 after cessation of EFV treatment. The MK-1439 AUC and C_{max} were also significantly decreased on Day 1, but less of an effect was seen on Day 14, consistent with induction of CYP3A4 and resolution of induction during EFV washout. While MK-1439 and EFV plasma concentrations on Days 4 – 7 post-switch both fall below those evaluated for efficacy in the clinic for either compound, this drug interaction is not anticipated to be clinically meaningful considering the PK targets for both compounds based on in vitro potency, the additivity of MK-1439 and EFV antiviral activity and the population

being studied (ie, patients that are virologically suppressed and receiving combination antiretroviral therapy).

These data suggest no dose adjustment is warranted in the present study at the time of switch. However, this will be confirmed by obtaining additional sparse sampling from study subjects in the ISG over the first 4 weeks following the switch from ATRIPLA™ to MK-1439A. Note that in the present study, subjects will have received efavirenz for at least 6 months in contrast to 14 days in the Phase 1 study described above.

The goal of this study is to demonstrate that a switch from ATRIPLA™ to MK-1439A leads to improvement in EFV-associated CNS toxicity. Since all patients who enter the study will eventually switch to MK-1439A, the 12-week delay before the switch in the DSG is considered acceptable, as patients with intolerable (for example, Grade 4 which can be judged potentially life threatening) CNS toxicity will likely have had their regimens modified promptly during routine clinical care and will not be enrolled in this study.

Standard safety monitoring for treatment-emergent adverse experiences in this study will be conducted as per standard MSD safety monitoring. However, the standard tools to detect treatment-emergent signals focus on new or worsening signs and symptoms of toxicity. These tools are neither appropriate nor adequate for capturing improvement of toxicity already present at baseline, which is the overall objective of this study. Therefore a number of other instruments will be used, such as the CNS toxicity questionnaire (see Section 12.5). This questionnaire is based upon the widely used DAIDS Toxicity Grading Criteria (DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS, PUBLISH DATE: AUGUST 2009 Version 1, Section 12.6), and, while not validated, has been used as the standard Toxicity Grading Scale in many, if not most, studies in the field of HIV-1 infection for more than a decade. The specific terms contained in this tool are those commonly associated with EFV toxicity. Furthermore, this tool has been effectively used in studies conducted by the St. Stephens AIDS Trust network to show improvement in CNS toxicity following a switch from an EFV-based regimen (generally ATRIPLA™) to other anchor agents including etravirine [9] and raltegravir (unpublished). Thus, this network has extensive experience with the CNS toxicity questionnaire and has been collaboratively involved with the design of this study.

To characterize the exploratory outcomes of the study, a number of additional patient-reported outcomes will be assessed by questionnaire. These questionnaires will assess sleep quality, anxiety/depression, health-related quality of life and neurocognitive function. These tools will be administered at multiple time points to examine both between-group changes (up to Week 12) and within-patient changes (pre-switch to 24 weeks post switch in both groups combined).

4.2.2 Rationale for Dose Selection/Regimen/Modification

The FDC, MK-1439A, contains 100 mg of MK-1439, a potent NNRTI, and standard doses of 2 commercially-available 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 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) [1]. 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).

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 Y190A 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.

ATRIPLA™, the active comparator in this study will be administered at the standard approved dose of one tablet once daily. Each tablet contains 600 mg of efavirenz, 200 mg of FTC and 300 mg of TDF (which is equivalent to 245 mg of tenofovir disoproxil).

4.2.3 Rationale for Endpoints

4.2.3.1 CNS Toxicity Questionnaire

The CNS toxicity questionnaire (Section 12.5) will be used to solicit for CNS toxicity and will include the following events:

1) Dizziness
2) Depression/low mood
3) Insomnia/sleeplessness
4) Anxiety/nervousness
5) Confusion

6) Impaired concentration/attention
7) Headache
8) Somnolence/daytime sleepiness
9) Aggressive mood/behavior
10) Abnormal dreams

The primary endpoint is the proportion of subjects with at least one CNS toxicity of at least Grade 2 intensity (according to the DAIDS Toxicity Criteria) at Week 12. Based on a similarly designed study of a switch from ATRIPLA™ to an etravirine-based regimen that had the same primary endpoint [3] it was determined that the proportion of subjects with at least one CNS toxicity of at least Grade 2 intensity was deemed to be a more clinically relevant and statistically powerful an endpoint versus the CNS toxicity score.

Subjects are asked to rate the intensity for each of the events as none (Grade 0), mild (Grade 1), moderate (Grade 2), or severe (Grade 3). Mild, moderate and severe are generally defined as follows: mild = symptom is noticeable but does not interfere with normal activities; moderate = symptom has some impact on normal activities; severe = symptom prevents conduct of normal activities. The CNS toxicity questionnaire will be completed by each subject at screening, Study Day 1, and Study Weeks 4 and 12 during the blinded period for all subjects in both treatment groups. During the open-label period of the base study, CNS toxicity assessments will also be completed by subjects in the ISG at Study Week 24 and by subjects in the DSG at Study Weeks 16, 24 and 36 (which correspond to Weeks 4, 12 and 24 post-switch); during study extension 1, the CNS toxicity questionnaire will be completed at each treatment visit and, if applicable, at the early discontinuation visit.

The change from baseline in CNS toxicity scores is a secondary endpoint in the study. The CNS toxicity score is a measure of overall CNS toxicity and is calculated from the same CNS questionnaire as is used for the primary endpoint. The ACTG adverse event scale (None=0, Mild=1, Moderate=2, Severe=3) is applied to the intensity rating for each of the 10 CNS toxicities on the questionnaire, and a CNS toxicity score will be calculated for each subject at baseline and at each post-baseline visit by summing across all 10 CNS toxicities and converting the sum to a percentage of the maximum possible sum of intensities (10 x 3 = 30).

4.2.3.2 Efficacy Endpoints

Efficacy endpoints being used to address the study objectives are commonly accepted endpoints in this type of trial. Maintaining HIV-1 RNA suppression is considered the key efficacy endpoint for switch studies of this type. Secondary and exploratory measurements for efficacy include the proportion of subjects maintaining HIV-1 RNA <50 copies/mL 24 weeks after the switch to MK-1439A, the proportion of subjects maintaining HIV-1 RNA <40 copies/ mL 24 weeks after the switch to MK-1439A, the change in CD4 cell counts from baseline (immediately pre-switch) to 24 weeks after the switch to MK-1439A, and viral resistance for subjects who meet the virologic failure criteria and whose virus can be amplified. Plasma HIV RNA and samples for resistance testing will be collected at all study visits (except the post-study follow-up visit and Study Weeks 1, 2 and 3 in both treatment

groups). For all confirmed virologic failures, the plasma sample collected for resistance testing from the virologic failure visit will be sent for resistance testing provided the viral load meets the criteria for resistance testing (HIV-1 RNA > 400 copies/mL); otherwise, the plasma sample collected at the confirmation visit will be sent for resistance testing (if HIV-1 RNA > 400 copies/mL).

Protocol-defined virologic failure (PDVF) is defined as subjects who have 2 consecutive measurements of HIV-1 RNA ≥200 copies/mL at least one week apart. Subjects should be discontinued if they meet the protocol-defined virologic failure criteria. The choice of subsequent antiretroviral therapy will be at the discretion of the study investigator or subject's physician.

4.2.3.3 Safety Endpoints

Safety evaluations and data collected are generally typical of this type of trial. There is special emphasis on subject-reported outcomes and other assessments used to assess non-efficacy related advantages anticipated of the ISG versus the DSG (see Section 4.2.3.1 and Section 4.2.3.4). General safety evaluations in the base study will include physical examinations (and vital signs) and laboratory tests (including fasting lipids at designated visits) performed at all scheduled study visits (except Study Weeks 1, 2 and 3 since only PK samples are being collected at these timepoints and for subjects in the ISG at Study week 16), and, for subjects who do *not* enter study extension 1, a 14-day follow-up visit. For subjects who continue into study extension 1, safety evaluations will be performed at each of the study visits in the extension (for subjects in the ISG group, at Study Weeks 40, 56, 72, 88, 104 and 120 and in the DSG group, at Study Weeks 52, 68, 84, 100, 116 and 132) and, if applicable, an early discontinuation visit and/or a virologic failure confirmation visit and at a 14-day follow-up visit. Adverse experiences will be evaluated at each visit and assessed according to the guidelines in Section 7.2. Subjects may be asked to return for unscheduled visits in order to perform additional safety monitoring.

During study extension 2, SAEs and pregnancy test results will be collected at each study visit (Week 136, 152, 168, 184, 200, and 216 for ISG and Week 148, 164, 180, 196, 212, and 228 for DSG, as applicable, depending on when MK-1439A is available locally, and, if applicable, at early discontinuation visit).

During study extension 3, SAEs and pregnancy test results will be collected at each study visit (Week 232, 248, 264, 280, 296, and 312 for ISG and Week 244, 260, 276, 292, 308, and 324 for DSG, as applicable, depending on when MK-1439A is available locally, and, if applicable, at early discontinuation visit).

4.2.3.4 Exploratory Endpoints

Exploratory endpoints, assessed in the base study only, include the changes from baseline in sleep quality scores, neurocognitive function as assessed by CBB, anxiety and depression scores, and health-related quality of life scores. The Pittsburgh Sleep Quality Index (PSQI) will be used to assess sleep quality. Neurocognitive function will be assessed using CBB tests. The anxiety and depression assessment will be done using the Hospital Anxiety and

Depression Scale (HADS), and general health-related quality of life will be assessed using the EQ-5D-5L. The questionnaires are further described in 7.1.1.9. All 5 questionnaires will be administered at Study Day 1, and Study Weeks 4 and 12 during the blinded period for all subjects in both treatment groups. During the open-label period, all 5 questionnaires will also be administered in subjects in the ISG at Study Week 24 and in subjects in the DSG at Study Weeks 16, 24 and 36 (which correspond to Weeks 4, 12 and 24 post-switch).

Pharmacokinetic samples will be collected at Study Day 1 (predose) and Study Weeks 1, 2, 3, and 4 in all subjects in both treatment groups. Although samples will be collected from subjects in both treatment groups to maintain blinding, only samples from subjects in the ISG will be analyzed. These samples will be assayed for MK-1439 and efavirenz plasma concentrations and used to evaluate the decline of efavirenz plasma concentrations and the rise of MK-1439 plasma concentrations in the 4 weeks post-switch.

4.2.3.5 Planned Exploratory Biomarker Research

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.

4.2.3.6 Future Biomedical Research

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

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main study) and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for future biomedical research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that participants receive the correct dose of the correct drug/vaccine at the correct time. The details of future biomedical research are presented in Appendix 12.2. Additional informational material for institutional review boards/ethics committees (IRBs/ECs) and investigational site staff is provided in Appendix 12.3.

4.2.4 Rationale for Amendment 01

The main reasons for the amendment are to provide a study extension to collect long-term safety and efficacy data on MK-1439A; to update the inclusion criteria as well as the protocol-specific definition of virologic failure to reflect current medical practice and HIV

treatment guidelines; and to update the inclusion criteria and revise the sample size to facilitate timely completion of the trial.

Because HIV infection is a chronic disease, with treatment generally lasting for years, collection of long-term safety and efficacy data on MK-1439A will provide useful information; these data will be summarized descriptively and will not be used to test hypotheses.

Subjects who are virologically suppressed on ATRIPLA™ for at least 12 weeks are very unlikely to have drug resistance mutations to NRTIs or efavirenz, since complete viral suppression would require fully active efavirenz and NRTIs with no resistance. Therefore, the absence of baseline genotype information for subjects switching from an NNRTI-based regimen (ie, ATRIPLA™) would not increase the risk of failure on MK-1439A due to NRTI resistance. This justifies the removal of the requirement for genotyping results prior to the start of subject's initial antiretroviral regimen; inclusion criterion #5 (criterion #6 in the original protocol, version 00) has been modified such that genotyping is no longer required, but if it has been done and documentation is available, it must show no resistance mutations to any study drug.

The inclusion criteria are also broadened to include subjects whose initial regimen was not ATRIPLA™ or its components, as long as complete viral suppression is demonstrated prior to screening. This is to acknowledge that there are subjects who had to switch from their initial antiretroviral therapy to ATRIPLA™ due to tolerability or other reasons.

For consistency with the definition for viral blips in the US Department of Health & Human Services (DHHS) 'Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents' and to prevent unnecessary discontinuation of trial subjects, protocol-defined virologic failure (PDVF) is defined as subjects who have 2 consecutive measurements of HIV-1 RNA ≥200 instead of ≥ 50 copies/mL at least one week apart.

Due to slower than expected enrollment, the number of subjects is being reduced from 106 to 84 to allow timely completion of the trial, with the power thus reduced from 90% to 80%. A power of 80% is sufficient to test the trial's primary objective.

4.2.5 Rationale for Study Extensions

Because HIV infection is chronic, with treatment generally life long, collection of long-term safety and efficacy data will provide useful information on MK-1439A. Thus, after the 96-week double-blind period to evaluate the key primary and secondary objectives and hypotheses, there will be an open-label study extension ("study extension 1") for an additional 96-week period where all eligible subjects can continue to receive an open-label MK-1439A regimen.

Study extensions 2 and 3 were added to avoid interruption of treatment with MK-1439 for eligible subjects who are deriving benefit from treatment, until MK-1439 becomes locally available. This will also reduce the well-recognized, but small, risk of treatment failure associated with a change from a successfully suppressive and tolerated cART regimen.

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) and thus may offer improvement of CNS toxicity associated with EFV. 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.

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, who have had documentation of HIV-1 RNA < 50 copies/mL for at least 12 weeks prior to screening while on ATRIPLA™, generic versions of ATRIPLA™, or the components of ATRIPLA™ (EFV, TDF plus emtricitabine), and at study entry have undetectable HIV-1 RNA, and who have at least one EFV-associated CNS toxicity of Grade 2 or worse intensity at the time of screening and Study Day 1 (randomization visit) 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. have had documentation of HIV-1 RNA < 50 copies/mL for at least 12 weeks prior to screening while on ATRIPLA™, as evidenced by

   at least one HIV-1 RNA < 50 copies/mL between 3 and 15 months prior to screening.

   Note: Any subsequent HIV-1 RNA values (if performed) before screening must be < 50 copies/mL.

4. have plasma HIV-1 RNA levels BLoQ (< 40 copies/mL by the Abbott RealTime HIV-1 Assay as determined by the central laboratory) at the screening visit.

5. if genotyping was performed at any point prior to screening and the results are available, the subject must have no known resistance mutations to any of the study agent components (MK-1439, tenofovir, lamivudine, EFV, or emtricitabine).

6. have at least one EFV-associated CNS toxicity of Grade 2 or worse intensity both at the time of screening and at Study Day 1 (BL); at least one of the Grade 2 or worse intensity CNS toxicity present at screening must also be present at Study day 1 with Grade 2 or worse intensity. EFV-associated CNS toxicity is defined as one of the following conditions listed on the CNS toxicity questionnaire: dizziness, depression/low mood, insomnia/sleeplessness, anxiety/nervousness, confusion, impaired concentration/attention, headache, somnolence/daytime sleepiness, aggressive mood/behavior, abnormal dreams. See examples below:

   a. Screen – Grade 2 dizziness, BL – Grade 2 dizziness = eligible

   b. Screen – Grade 3 dizziness, BL – Grade 2 dizziness = eligible

   c. Screen – Grade 2 dizziness, BL - Grade 1 dizziness = not eligible

   d. Screen – Grade 2 dizziness, BL - Grade 1 dizziness and Grade 2 insomnia = not eligible

7. have the following laboratory values at screening:

   a) Alkaline phosphatase ≤ 3.0 x upper limit of normal (ULN)

   b) AST (SGOT) and ALT (SGPT) ≤ 5.0 x ULN

   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:

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

$$\text{For Women: } Cl_{cr}\,(\text{mL/min}) = \frac{(140\text{-age}) \times \text{weight (in kg)}}{72 \times \text{serum creatinine (mg/dL)}} \times 0.85$$

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 (ie, 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, for 12 weeks after the last dose of ATRIPLA™ on study (this applies to the last dose of ATRIPLA™ prior to the switch to MK-1439A in both treatment groups), and for 14 days following the last dose of MK-1439A on study (if subjects discontinue prior to receiving 10 weeks of MK-1439A, they will still need to agree to follow aforementioned ATRIPLA™ requirements) 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 2 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

[†]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.

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

In order to be eligible for participation in study extension 1, the subject must:

11. have completed the Study Week 24 (for ISG) or Study Week 36 (for DSG) visit.

12. be considered, in the opinion of the investigator, to have derived benefit from study participation through Study Week 24 (for ISG) or Study Week 36 (for DSG).

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 study extension 1 and provide written informed consent to enter study extension 1, thus continuing for approximately 2 years (96 weeks) beyond the base study.

In order to be eligible to continue receiving MK-1439A in study extension 2, the subject must:

15. have completed the Study Week 120 (for ISG) or Study Week 132 (for DSG) visit.

16. be considered, in the opinion of the investigator, to have derived benefit from MK-1439A by Study Week 120 (for ISG) or Study Week 132 (for DSG).

17. 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.

18. understand the procedures in the study extension and provide written informed consent to enter study extension 2, thus continuing treatment with MK-1439A until it is locally available or for up to approximately 2 years (whichever comes first) beyond study extension 1.

In order to be eligible to continue receiving MK-1439A in study extension 3, the subject must:

19. have completed the Study Week 216 (for ISG) or Study Week 228 (for DSG) visit.

20. be considered, in the opinion of the investigator, to have derived benefit from MK-1439A by Study Week 216 (for ISG) or Study Week 228 (for DSG).

21. 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.

22. understand the procedures in the study extension and provide written informed consent to enter study extension 3, thus continuing treatment with MK-1439A until it is locally available or for up to approximately 2 years (whichever comes first) beyond study extension 2.

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 the 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 ongoing Grade 4 CNS toxicity during screening period that requires a prompt change in ART.

4. 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, emtricitabine, entecavir, lamivudine or tenofovir.

   Note: Subjects may be enrolled if treatment occurred prior to the diagnosis of HIV or in the context of their treatment with ATRIPLA™.

5. has documented or known resistance to study drugs including MK-1439, EFV, lamivudine, emtricitabine, and/or tenofovir (based on genotyping performed prior to the initiation of treatment with ATRIPLA™) as defined below:

    a. Resistance to MK-1439 or Efavirenz for the purpose of this study includes the following NNRTI mutations: L100I, K101E, K101P, K103N, K103S, V106A, V106I, V106M, V108I, E138A, E138G, E138K, E138Q, E138R, V179L, Y181C, Y181I, Y181V, Y188C, Y188H, Y188L, G190A, G190S, H221Y, L234I, P225H, F227C, F227L, F227V, M230L, M230I

    b. Resistance to lamivudine, emtricitabine and tenofovir includes the following mutations: K65R, M41L, T69S (insertion complex), Q151M, M184I, M184V, L210W, T215F, T215Y, K219E, K219Q, D67N, K70R, K70E.

6. 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 this study.

7. has used systemic immunosuppressive therapy or immune modulators within 30 days prior to treatment in this study or is anticipated to need them during the course of the study.

    Note: Short courses of corticosteroids (e.g., as for asthma exacerbation) will be allowed

8. requires or is anticipated to require any of the prohibited medications noted in the protocol (refer to Section 5.5).

9. has significant hypersensitivity or other contraindication to any of the components of the study drugs as determined by the investigator

10. has a current (active) diagnosis of acute hepatitis due to any cause.

    Note: Subjects with chronic hepatitis B and 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).

11. 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 is pregnant, breastfeeding, or expecting to conceive (at any time during the study).

12. is pregnant, breastfeeding, or expecting to conceive.

13. is female and is 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).

    Note: Investigators should provide appropriate guidance to the subjects regarding egg and sperm donation after completion of the study treatment. Consistent with the recommendations for contraceptive use, it is recommended that all subjects refrain from egg or sperm donation for 12 weeks following their last dose of study treatment.

14. is or has an immediate family member (e.g., spouse, parent/legal guardian, sibling or child) who is investigational site or sponsor staff directly involved with this trial.

5.2 Trial Treatment(s)

The 2 treatment regimens to be used in the base trial are outlined below in Table 1, and the treatment regimen to be used in the trial extension is shown in Table 2. To maintain blinding, both drugs will be administered with a placebo matched to the other active drug in the study. Sites should not call IVRS/IWRS for drug administration until the subject has met all criteria for the study and is ready to receive the first dose of study medication on Day 1. All subjects in this study will switch from ATRIPLA™ to MK-1439A and receive MK-1439A for 24 weeks. The 2 treatment groups differ in the timing of the switch and the treatment they will receive for the first 12 weeks of the study. The Immediate Switch Group will switch to MK-1439A on Study Day 1. This group will receive MK-1439A with a placebo matched to ATRIPLA™ during the first 12 weeks of the trial (the blinded treatment period) and will receive MK-1439A alone for 12 additional weeks in the open-label period of the trial. The Deferred Switch Group will receive ATRIPLA™ with a placebo matched to MK-1439A during the first 12 weeks of the trial (the blinded period) and will receive MK-1439A alone for 24 weeks in the open-label period of the trial. Blinded trial treatment should begin on the day of randomization in both treatment groups. At Study Week 12, all subjects will be given open-label MK-1439A for the remainder of their study treatment period. No further ATRIPLA™ or placebo matched to either agent will be used beyond the Week 12 visit. At Study week 16, all subjects will be unblinded to their initial treatment assignment.

Table 1 Treatment Regimens During Base Study

Groups	**Blinded Period (Study day 1 – Week 12)**	**Open-Label Period (Duration)**
Immediate Switch N = ~ 42	MK-1439A Placebo# matched to ATRIPLA™	MK-1439A (Week 12-24)
Deferred Switch N = ~ 42	ATRIPLA™ Placebo# matched to MK-1439A	MK-1439A (Week 12-36)
MK-1439A is a single-tablet FDC containing MK-1439 100 mg, lamivudine 300 mg and TDF 300 mg (which is equivalent to 245 mg of tenofovir disoproxil). ATRIPLA™ is a single tablet FDC containing efavirenz 600 mg, emtricitabine 200 mg, and TDF 300 mg (which is equivalent to 245 mg of tenofovir disoproxil). # Placebos are used to maintain blinding		

Table 2 Treatment Regimen During Study Extensions

Groups	Open-Label Period (Duration)
Immediate Switch	MK-1439A (Study Week 24-312)
Deferred Switch	MK-1439A (Study Week 36-324)
MK-1439A is a single-tablet FDC containing MK-1439 100 mg, lamivudine 300 mg and TDF 300 mg (which is equivalent to 245 mg of tenofovir disoproxil).	

Subjects will receive study medication at the Day 1 visit and should take the first dose of medication from each bottle (Bottle A and Bottle B) on the same day.

During the double-blind period, MK-1439A and the placebo matched to MK-1439A (Bottle A) are to be taken once daily without regard to food at approximately the same time each day.

During the double-blind period, ATRIPLA™ and the placebo matched to ATRIPLA™ (Bottle B) are to be taken once daily at bedtime on an empty stomach.

During the open-label period of the base study and during the study extensions, MK-1439A (Bottle C) should be taken once daily without regard to food at approximately the same time each day.

All study medications as indicated in Table 1 and Table 2 above (ATRIPLA™, ATRIPLA™-matched placebo, MK-1439A and MK-1439A-matched placebo) for the base study and for the study extensions (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

Dose Modification:

No dose modification of study therapy is allowed during the base study or the study extensions.

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

From Study Day 1 to the Study Week 12 visit (Blinded Treatment Period):

Bottle A (MK-1439A or placebo):

Subjects will be instructed to take one tablet from Bottle A 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 drug from Bottle A 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.

Bottle B (ATRIPLA™ or placebo):

Subjects will be instructed to take one tablet from Bottle B once a day (q.d.) orally, on an empty stomach at bedtime.

If a subject misses a dose of drug from Bottle B 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.

From Study Week 12 to the end of study treatment (Open-Label Treatment Period).

Bottle C (open label MK-1439A):

Subjects will be instructed to take one tablet from Bottle C 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 drug from Bottle C 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

A double-blind/masking technique will be used. MK-1439A, ATRIPLA™ and their respective placebos will be packaged so that blind/masking is maintained. The subject, the investigator and Sponsor personnel or delegate(s) who are involved in the treatment or clinical evaluation of the subjects are unaware of the group assignments.

Unblinding Procedures:

A subject will not be unblinded until Study Week 16 visit. All adverse event data through the first 12 weeks of treatment for that subject must be cleaned and reconciled prior to unblinding.

See Section 7.1.4.2, Blinding/Unblinding, for a description of the method of unblinding a subject during the trial, should such action be warranted.

5.3 Randomization

Treatment allocation/randomization will occur centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). There are 2 treatment arms. Subjects will be assigned randomly in a 1:1 ratio to either an immediate switch to MK-1439A on Study Day 1 (Immediate Switch Group) or to continued treatment with ATRIPLA™ for 12 weeks in the base study followed by switch to open label MK-1439A (Deferred Switch Group). With ~84 subjects enrolled, ~42 subjects will be randomized to each group.

5.4 Stratification

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

5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

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 prior to the start of treatment in this 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 Medication/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 and ATRIPLA™.

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 MSD 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, including interferon-based treatment for hepatitis, 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 randomization, 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.

Antiretroviral therapies other than MK-1439A and ATRIPLA™ are not permitted for use by subjects during the course of the study.

Investigational agents must be discontinued for 30 days prior to treatment in this study and are also 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 CYP3A (cytochrome)-mediated oxidation.

The medications and/or substances below are prohibited in this study because they are moderate or potent inducers of CYP3A, and their co-administration 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.

Table 3 Prohibited Medication/Therapy Due to MK-1439 Interaction During the Base Study and Study Extensions

Carbamazepine
Oxcarbazepine
Enzalutamide
Mitotane
Rifapentine
Phenobarbital
Phenytoin
Rifabutin
Rifampin
St. John's Wort
Modafinil
Bosentan
Nafcillin

Prohibited Concomitant Therapy Due to Potential Interactions with ATRIPLA™ (applicable during the blinded treatment period + 4 weeks: Study Day 1 to Study Week 16)

Efavirenz induces CYP3A4 metabolism and may significantly reduce the exposure of CYP3A4 substrates. In addition, there are some medications that may significantly alter the metabolism of efavirenz. In some cases, co-administration of certain drugs with ATRIPLA™ may lead to significant safety risks. The following medications are prohibited in this study because they: (1) are contraindicated for concomitant use with ATRIPLA™ (according to one or more available ATRIPLA™ package circulars), (2) may alter the plasma concentration of one or more of the ATRIPLA™ components and/or (3) may have significant changes in their plasma concentrations when co-dosed with ATRIPLA™ that would require additional monitoring or dose adjustment, which is not feasible in the setting of a double-blind trial.

Table 4 Prohibited Medication/Therapy Due to ATRIPLA™ Interactions

Artermether
Astemiazole
Bepridil
Boceprevir
Carbamazepine
Cisapride
Clarithromycin
Cyclosporine
Dihydroatenisinin
Ergot derivatives
Itraconazole
Ketoconazole
Lumefantrine
Midazolam
Phenobarbital
Phenytoin
Pimozide
Rifabutin
Rifampin
Simeprevir
Sirolimus
St. John's Wort
Tacrolimus
Telaprevir
Terfenadine
Triazolam
Voriconazole

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

Concomitant Therapy to be used With Caution

For complete information, please refer to the ATRIPLA™ package circular available locally for drugs that are permitted in the protocol but that should be used with caution, since they have established drug interactions with ATRIPLA™.

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

ATRIPLA™/placebo should be taken once daily at bedtime on an empty stomach.

Alcohol/Substance Abuse:

Subjects should be questioned about their estimated daily intake of alcohol and about substance abuse during the screening evaluation of eligibility. Any subject who, in the opinion of the investigator has an excessive intake of any of these substances must be excluded from the study

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 (electronic case record form).

- 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).
    - severe rash associated with blistering, desquamation, mucosal involvement or fever

- severe depression, psychosis or suicidal ideation

- 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.

- The subject has a creatinine clearance of <50 mL/min (confirmed by repeat measurement) based on the following Cockcroft-Gault equation:

  Male:

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

  Female:

  $$Cl_{cr}\,(mL/min) = \frac{(140\text{-age}) \times \text{weight (in kg)}}{72 \times \text{serum creatinine (mg/dL)}} \times 0.85$$

  or subject has serum phosphorous <0.32 mmol/l.

  Note: Subjects with serum phosphorous <0.48 mmol/l should be closely monitored.

- Subject requires interferon-based treatment for hepatitis.

- Subjects who participate in study extension 2 or study extension 3 should be discontinued at next scheduled visit after MK-1439A becomes locally available.

Subjects should be discontinued regardless of compliance with study therapy if they meet the protocol-defined virologic failure criteria in Section 4.2.3.2.

Subjects who require discontinuation of any component of the study therapy must be discontinued from the trial.

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

Due to the potential for severe acute exacerbations of hepatitis B following discontinuation with ATRIPLA™, lamivudine and tenofovir, subjects who are co-infected with hepatitis B who stop their assigned study therapy at or prior to the end of the study must be closely

monitored for such exacerbations for at least 6 months. This requirement applies to subjects in both treatment arms. 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 study extension 1. Note that a subject who completes the base study and does not elect to participate in study extension 1 is considered to have completed the study. Once discontinued from study extension 1, a subject is not eligible to enter study extension 2; and once discontinued from study extension 2, a subject is not eligible to enter study extension 3.

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:

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

The flow chart in Section 6.1 applies to the base study from screening through follow-up after the Week 24 or 36 visit. The flow charts in Sections 6.2 and 6.3 apply to ISG and DSG subjects, respectively, continuing into study extension 1, from Week 24 (ISG) or Week 36 (DSG) through follow-up after the Week 120 (ISG) or Week 132 (DSG) visit. The flow charts in Sections 6.4 and 6.5 apply to ISG and DSG subjects, respectively, continuing into study extension 2. The flow charts in Sections 6.6 and 6.7 apply to ISG and DSG subjects, respectively, continuing into study extension 3.

6.1 Base Study Flow Chart: Screening Through Week 24 (ISG) or 36 (DSG) Plus 14-Day Follow-up

Visit number/Title	**1**	**2 Random-ization**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**U (Virologic Failure Confirma-tion)**	**U (Early Discontin-uation)**	**99**
Trial Period	**Screening**		**Double-Blind Treatment Period[n] (Both Groups)**					**Open-Label Treatment Period[n] (By Group)**					**Post treatment[o]**
TRIAL PROCEDURES by STUDY WEEK	**Screen (45 days)**	**Fasting Day 1[a]**	**WK 1**	**WK 2**	**WK 3**	**WK 4**	**Fasting WK 12**	**WK 16[s]**	**Fasting WK 24**	**Fasting WK 36 (DSG ONLY)**	**≥ 1 to ≤ 4 weeks after initial virologic failure**	**At time of Discontin-uation**	**14-Day Follow-up**
	Timing relative to switch to MK-1439A												
Immediate Switch Group (ISG)		Day 1 of Switch	WK 1 Post Switch	WK 2 Post Switch	WK 3 Post Switch	WK 4 Post Switch	WK 12 Post Switch	WK 16 Post Switch	WK 24 Post Switch	NA			
Deferred Switch Group (DSG)		-12 WKs (Prior to Switch)	-11 WKs (Prior to Switch)	-10 WKs (Prior to Switch)	-9 WKs (Prior to Switch)	-8 WKs (Prior to Switch)	Day 1 of Switch	WK 4 Post Switch	WK 12 Post Switch	WK 24 Post Switch			
Administrative Procedures													
Informed Consent	x												
Informed Consent ISG (For subjects entering study extension only)									x[u]				
Informed Consent DSG (For subjects entering study extension only)										x[u]			
Informed Consent for Future Biomedical Research[b]	x												

Visit number/Title	**1**	**2 Random-ization**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**U (Virologic Failure Confirma-tion)**	**U (Early Discontin-uation)**	**99**
Trial Period	**Screening**		**Double-Blind Treatment Period[n] (Both Groups)**					**Open-Label Treatment Period[n] (By Group)**					**Post treatment[o]**
TRIAL PROCEDURES by STUDY WEEK	**Screen (45 days)**	**Fasting Day 1[a]**	**WK 1**	**WK 2**	**WK 3**	**WK 4**	**Fasting WK 12**	**WK 16[s]**	**Fasting WK 24**	**Fasting WK 36 (DSG ONLY)**	**≥ 1 to ≤ 4 weeks after initial virologic failure**	**At time of Discontin-uation**	**14-Day Follow-up**
	Timing relative to switch to MK-1439A												
Immediate Switch Group (ISG)		Day 1 of Switch	WK 1 Post Switch	WK 2 Post Switch	WK 3 Post Switch	WK 4 Post Switch	WK 12 Post Switch	WK 16 Post Switch	WK 24 Post Switch	NA			
Deferred Switch Group (DSG)		-12 WKs (Prior to Switch)	-11 WKs (Prior to Switch)	-10 WKs (Prior to Switch)	-9 WKs (Prior to Switch)	-8 WKs (Prior to Switch)	Day 1 of Switch	WK 4 Post Switch	WK 12 Post Switch	WK 24 Post Switch			
Inclusion/Exclusion Criteria	x	x											
Medical History[c]	x												
Provide Subject Identification Card	x												
Concomitant Medication Review	x	x				x	x	x	x	x		x	x
Treatment Allocation/Randomization		x											
Register Study Visit via Interactive Voice/Web Response System (IVRS/IWRS)	x	x				x	x	x	x	x		x	
Dispense Study Therapy[d]		x				x	x	x	x[q]	x[t]			
Provide/Review Study Medication Diary		x	x	x	x	x	x	x	x	x		x	
Unblinding via IVRS/IWRS[p]								x					
Clinical Procedures /Assessments													
Full Physical Examination	x												

Visit number/Title	1	2 Random-ization	3	4	5	6	7	8	9	10	U (Virologic Failure Confirma-tion)	U (Early Discontin-uation)	99
Trial Period	**Screening**		**Double-Blind Treatment Period[n] (Both Groups)**					**Open-Label Treatment Period[n] (By Group)**					**Post treatment[o]**
TRIAL PROCEDURES by STUDY WEEK	**Screen (45 days)**	**Fasting Day 1[a]**	**WK 1**	**WK 2**	**WK 3**	**WK 4**	**Fasting WK 12**	**WK 16[s]**	**Fasting WK 24**	**Fasting WK 36 (DSG ONLY)**	**≥ 1 to ≤ 4 weeks after initial virologic failure**	**At time of Discontin-uation**	**14-Day Follow-up**
	Timing relative to switch to MK-1439A												
Immediate Switch Group (ISG)		Day 1 of Switch	WK 1 Post Switch	WK 2 Post Switch	WK 3 Post Switch	WK 4 Post Switch	WK 12 Post Switch	WK 16 Post Switch	WK 24 Post Switch	NA			
Deferred Switch Group (DSG)		-12 WKs (Prior to Switch)	-11 WKs (Prior to Switch)	-10 WKs (Prior to Switch)	-9 WKs (Prior to Switch)	-8 WKs (Prior to Switch)	Day 1 of Switch	WK 4 Post Switch	WK 12 Post Switch	WK 24 Post Switch			
Directed Physical Examination		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
Adverse Events Monitoring		x	x	x	x	x	x	x	x	x		x	x
Birth Control Confirmation	x	x				x	x	x	x	x		x	x
12-Lead Electrocardiogram (ECG) (local)	x [e m]												
CNS toxicity questionnaire	x	x				x	x	x	x	x		x	
Neurocognitive function (Cogstate brief battery - CBB)[f]		x				x	x	x	x	x		x	
Patient-Reported Outcomes[f]		x				x	x	x	x	x		x	

Visit number/Title	1	2 Random-ization	3	4	5	6	7	8	9	10	U (Virologic Failure Confirma-tion)	U (Early Discontin-uation)	99
Trial Period	**Screening**		**Double-Blind Treatment Period[n] (Both Groups)**					**Open-Label Treatment Period[n] (By Group)**					**Post treatment[o]**
TRIAL PROCEDURES by STUDY WEEK	**Screen (45 days)**	**Fasting Day 1[a]**	**WK 1**	**WK 2**	**WK 3**	**WK 4**	**Fasting WK 12**	**WK 16[s]**	**Fasting WK 24**	**Fasting WK 36 (DSG ONLY)**	**≥ 1 to ≤ 4 weeks after initial virologic failure**	**At time of Discontin-uation**	**14-Day Follow-up**
	Timing relative to switch to MK-1439A												
Immediate Switch Group (ISG)		Day 1 of Switch	WK 1 Post Switch	WK 2 Post Switch	WK 3 Post Switch	WK 4 Post Switch	WK 12 Post Switch	WK 16 Post Switch	WK 24 Post Switch	NA			
Deferred Switch Group (DSG)		-12 WKs (Prior to Switch)	-11 WKs (Prior to Switch)	-10 WKs (Prior to Switch)	-9 WKs (Prior to Switch)	-8 WKs (Prior to Switch)	Day 1 of Switch	WK 4 Post Switch	WK 12 Post Switch	WK 24 Post Switch			
Assess Subject Eligibility for Study Extension 1 (ISG)									x[u]				
Assess Subject Eligibility for Extension Study 1 (DSG)										x[u]			
Laboratory Procedures/ Assessments													
Collect Blood for Safety Laboratory Tests (Hematology/ Chemistry)[g]	x	x				x	x	x	x	x	x	x	x
Serum Pregnancy Test[h]	x												
Urine Pregnancy Test (if applicable)[h]		x[e]				x	x	x	x	x		x	x
Hemostatic Function Test[i]	x												
HIV/Hepatitis Screen[j]	x												
Virology Test Plasma HIV viral RNA quantification test (Abbott Real Time HIV-1)	x	x				x	x	x	x	x	x	x	x

Visit number/Title	**1**	**2 Random-ization**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**U (Virologic Failure Confirma-tion)**	**U (Early Discontin-uation)**	**99**
Trial Period	**Screening**		**Double-Blind Treatment Period[n] (Both Groups)**					**Open-Label Treatment Period[n] (By Group)**					**Post treatment[o]**
TRIAL PROCEDURES by STUDY WEEK	**Screen (45 days)**	**Fasting Day 1[a]**	**WK 1**	**WK 2**	**WK 3**	**WK 4**	**Fasting WK 12**	**WK 16[s]**	**Fasting WK 24**	**Fasting WK 36 (DSG ONLY)**	**≥ 1 to ≤ 4 weeks after initial virologic failure**	**At time of Discontin-uation**	**14-Day Follow-up**
	Timing relative to switch to MK-1439A												
Immediate Switch Group (ISG)		Day 1 of Switch	WK 1 Post Switch	WK 2 Post Switch	WK 3 Post Switch	WK 4 Post Switch	WK 12 Post Switch	WK 16 Post Switch	WK 24 Post Switch	NA			
Deferred Switch Group (DSG)		-12 WKs (Prior to Switch)	-11 WKs (Prior to Switch)	-10 WKs (Prior to Switch)	-9 WKs (Prior to Switch)	-8 WKs (Prior to Switch)	Day 1 of Switch	WK 4 Post Switch	WK 12 Post Switch	WK 24 Post Switch			
Collect Blood for CD4 Cell Count		x					x		x	x			
Viral Resistance Test (Plasma)		x				x	x	x	x	x	x	x[k]	
Collect Blood for Genetic Analysis[b]		x											
Collect Plasma for Future Biomedical Research[r]		x											
Collect Blood for MK-1439 and Efavirenz PK[l]		x	x	x	x	x							

a. Prior to the first dose on Day 1.
b. 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.
c. Includes smoking history, historical genotype (if available) and pretreatment HIV RNA.
d. IVRS/IWRS will be used to allocate drug and to manage distribution of study drugs.
e. Results of test must be available prior to randomization and prior to the subject's first dose of medication.
f. Patient-Reported Outcomes including, for subjects enrolled under the original protocol (version 00), the CBB, will be done on Study Day 1 and Study Weeks 4, 12, and 24 for the ISG, on Study Day 1 and Study Weeks 4, 12, 16, 24 and 36 for the DSG and at discontinuation (if applicable) for all subjects (Immediate and Deferred Switch Treatment Groups). CBB at Study Day 1 will also include a practice. NOTE: Subjects enrolled under Amendment 01 will not use the CBB. Subjects enrolled under the original protocol (version 00) are required to complete the CBB at specified visits in the base study per the study flow chart. All other PRO questionnaires (CNS Toxicity questionnaire, Pittsburgh Sleep Quality Index [PSQI], Hospital Anxiety and Depression Scale [HADS], and the EuroQol Five Dimensional Descriptive System, Five Level Version [EQ-5D-5L]) are mandatory for all subjects.
g. Refer to Table 5 for listing of specific blood safety tests.
h. For women of childbearing potential.
i. Hemostatic Function Test includes: Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT) and International Normalized Ratio (INR).
j. HIV/Hepatitis Screening Tests include: 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 will be performed if the Hepatitis C antibody test is positive.
k. 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 does not need to be collected again at the discontinuation visit. All other early discontinuation tests should be performed at the early discontinuation visit.
l. Blood samples will be collected from subjects in both treatment groups due to the blinded nature of the study, even though samples will only be analyzed for subjects randomized to the Immediate Switch Group.
m. A local ECG should be performed prior to the subject's first dose of study medication (at either the Screening visit or the Study Day 1 visit).
n. Visit window periods are approximately: +/- 1 day for the Week 1, 2, and 3 visits; +/- 3 days for the Week 4, 12, 16, 24, and 36 visits. The timing of each visit is relative to the randomization (Day 1) visit. Every attempt must be made to keep subjects on schedule.
o. The visit window period for the Post-study 14 day follow-up visit is approximately – 2 to 0 days. 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 adverse events have occurred since the post-study clinic visit. This follow-up assessment applies only to subjects who complete (or discontinue from) the base study and do not enter study extension 1.
p. All adverse events data through the first 12 weeks of treatment for that subject will be cleaned and reconciled prior to unblinding.
q. At Week 24, subjects in the ISG entering study extension 1 will be dispensed a 16-week supply of study drug (open-label MK-1439A) and subjects in the DSG participating in the base study will be dispensed a 12-week supply of study drug (open-label MK-1439A).
r. Plasma samples for Future Biomedical Research should be collected at Study Day 1 if the subject consents to future biomedical research.
s. For subjects in the ISG only assessments required are AE, concomitant medication and study medication diary review at this visit in addition to unblinding via IVRS/IWRS. Subjects in the DSG will have all assessments listed at this visit in addition to unblinding via IVRS/IWRS.
t. Subjects in the DSG entering the study extension at Week 36 will be dispensed a 16-week supply of study drug (open-label MK-1439A).
u. If the subject is eligible (based on the inclusion criteria relevant to the study extension) and elects to enter the study extension, he/she will be considered to have completed the base study and will, after providing informed consent (signed an ICF for the extension), immediately enter the study extension and be dispensed MK-1439A.

NA: Not applicable

6.2 Study Extension 1 Flow Chart for Immediate Switch Group (ISG): Weeks 40 Through 120 Plus 14-Day Follow-up

Visit Number	**11**	**12**	**13**	**14**	**15**	**16**			
TRIAL PROCEDURES by STUDY WEEK	**WK 40**	**WK 56**	**Fasting WK 72**	**WK 88**	**WK 104**	**Fasting WK 120**	**U (Virologic Failure Confirmation)**	**U (Extension 1 Early Discontinuation)**	**99**
Trial Period:	**Study Extension: Treatment[a,b]**						**≥ 1 to ≤ 4 after initial virologic failure**	**At time of Discontinuation**	**Post treatment**
Weeks post base study	**16 WKs**	**32 WKs**	**48 WKs**	**64 WKs**	**80 WKs**	**96 WKs**			**14-Day Follow-up[c]**
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	x[e]			
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
CNS toxicity questionnaire	x	x	x	x	x	x		x	
Assess Subject Eligibility for Study Extension 2						x[f]			
Informed Consent for Study Extension 2						x[f]			
Laboratory Procedures/Assessments									
Collect Blood for Safety Laboratory Tests (Hematology/Chemistry)[g]	x	x	x[h]	x	x	x[h]	x	x	x
Urine Pregnancy Test (if applicable)[i]	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
Collect Blood for CD4 Cell Count			x			x			
Viral Resistance Test (Plasma)							x	x[j]	

a. Subjects who enter study extension 1 are considered enrolled in the extension upon providing written informed consent at the Week 24 study visit.
b. The visit windows are approximately +/- 14 days for all visits from Week 40 through Week 120. The timing of each visit is relative to the randomization (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. Study drug for extension 2 will be dispensed at Week 120, if subject is continuing into extension 2.
f. If the subject is eligible and elects to enter study extension 2, he/she will be considered to have completed study extension 1 and will, after providing informed consent, immediately enter study extension 2 and be dispensed MK-1439A.
g. Refer to Table 5 for listing of specific blood safety tests.
h. Fasting for at least 8 hours.
i. For women of childbearing potential.
j. 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. All other early discontinuation tests should be performed at the early discontinuation visit.

6.3 Study Extension 1 Flow Chart for Deferred Switch Group (DSG): Weeks 52 Through 132 Plus 14-Day Follow-up

Visit Number	11	12	13	14	15	16			
TRIAL PROCEDURES by STUDY WEEK	**WK 52**	**WK 68**	**Fasting WK 84**	**WK 100**	**WK 116**	**Fasting WK 132**	**U (Virologic Failure Confirmation)**	**U (Extension 1 Early Discontinuation)**	**99**
Trial Period:	**Study Extension: Treatment[a,b]**						**≥1 to ≤4 weeks after initial virologic failure**	**At time of Discontinuation**	**Post treatment**
Weeks post base study	**16 WKs**	**32 WKs**	**48 WKs**	**64 WKs**	**80 WKs**	**96 WKs**			**14 Day Follow-up[c]**
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	x[e]			
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
CNS toxicity questionnaire	x	x	x	x	x	x		x	
Assess Subject Eligibility for Study Extension 2						x[f]			
Informed Consent for Study Extension 2						x[f]			
Laboratory Procedures/Assessments									
Collect Blood for Safety Laboratory Tests (Hematology/Chemistry)[g]	x	x	x[h]	x	x	x[h]	x	x	x
Urine Pregnancy Test (if applicable)[i]	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
Collect Blood for CD4 Cell Count			x			x			
Viral Resistance Test (Plasma)							x	x[j]	

a. Subjects who enter study extension 1 are considered enrolled in the extension upon providing written informed consent at the Week 36 study visit.
b. The visit windows are approximately +/- 14 days for all visits from Week 52 through Week 132. The timing of each visit is relative to the randomization (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. Study drug for extension 2 will be dispensed at Week 132, if subject is continuing into extension 2
f. If the subject is eligible and elects to enter study extension 2, he/she will be considered to have completed study extension 1 and will, after providing informed consent, immediately enter study extension 2 and be dispensed MK-1439A.
g. Refer to Table 5 for listing of specific blood safety tests.
h. Fasting for at least 8 hours.
i. For women of childbearing potential.
j. 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. All other early discontinuation tests should be performed at the early discontinuation visit.

6.4 Study Extension 2 Flow Chart for Immediate Switch Group (ISG): Weeks 136 Through 216 Plus 14-Day Follow-up

Visit Number	**17**	**18**	**19**	**20**	**21**	**22**		
TRIAL PROCEDURES by STUDY WEEK[a]	**WK 136[b, c]**	**WK 152**	**WK 168**	**WK 184**	**WK 200**	**WK 216**	**U (Extension 2 Early Discontinuation)**	**99**
Trial Period:	**Study Extension 2: Treatment**						**At time of Discontinuation**	**Post treatment[d]**
Weeks post study extension 1	**16 WKs**	**32 WKs**	**48 WKs**	**64 WKs**	**80 WKs**	**96 WKs**		**14-Day Follow-up**
Administrative Procedures								
Register Study Visit via Interactive Voice/Web Response System (IVRS/IWRS)	x	x	x	x	x	x	x	
Dispense Study Therapy [e]	x	x	x	x	x	x[f]		
Assess Subject Eligibility for Study Extension 3						x[g]		
Informed Consent for Study Extension 3						x[g]		
Clinical Procedures/Assessments								
Serious 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								
Urine Pregnancy Test (if applicable)[h]	x	x	x	x	x	x	x	x

a. The total duration is dependent on when MK-1439A becomes locally available, with a maximum total duration of treatment of 216 weeks. Subjects should discontinue at the next scheduled visit after MK-1439A becomes locally available in the market.
b. Subjects who enter study extension 2 are considered enrolled in the extension upon providing written informed consent at the Week 120 study visit.
c. The visit windows are approximately +/- 14 days for all visits from Week 136 through Week 216. The timing of each visit is relative to the randomization (Day 1) visit. Every attempt must be made to keep subjects on schedule.
d. The visit window for the post-study 14-day follow-up visit is approximately – 2 to 0 days.
e. IVRS/IWRS will be used to allocate drug and to manage distribution of MK-1439A.
f. Study drug for extension 3 will be dispensed at Week 216, if subject is continuing into extension 3.
g. If the subject is eligible and elects to enter study extension 3, he/she will be considered to have completed study extension 2 and will, after providing informed consent, immediately enter study extension 3 and be dispensed MK-1439A.
h. For women of childbearing potential.

6.5 Study Extension 2 Flow Chart for Deferred Switch Group (DSG): Weeks 148 Through 228 Plus 14-Day Follow-up

Visit Number	17	18	19	20	21	22		
TRIAL PROCEDURES by STUDY WEEK[a]	WK 148[b, c]	WK 164	WK 180	WK 196	WK 212	WK 228	U (Extension 2 Early Discontinuation)	99
Trial Period:	Study Extension 2: Treatment						At time of Discontinuation	Post treatment[d]
Weeks post study extension 1	16 WKs	32 WKs	48 WKs	64 WKs	80 WKs	96 WKs		14-Day Follow-up
Administrative Procedures								
Register Study Visit via Interactive Voice/Web Response System (IVRS/IWRS)	x	x	x	x	x	x	x	
Dispense Study Therapy [e]	x	x	x	x	x	x[f]		
Assess Subject Eligibility for Study Extension 3						x[g]		
Informed Consent for Study Extension 3						x[g]		
Clinical Procedures/Assessments								
Serious 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								
Urine Pregnancy Test (if applicable)[h]	x	x	x	x	x	x	x	x

a. The total duration is dependent on when MK-1439A becomes locally available, with a maximum total duration of treatment of 228 weeks. Subjects should discontinue at the next scheduled visit after MK-1439A becomes locally available in the market.
b. Subjects who enter study extension 2 are considered enrolled in the extension upon providing written informed consent at the Week 132 study visit.
c. The visit windows are approximately +/- 14 days for all visits from Week 148 through Week 228. The timing of each visit is relative to the randomization (Day 1) visit. Every attempt must be made to keep subjects on schedule.
d. The visit window for the post-study 14-day follow-up visit is approximately – 2 to 0 days.
e. IVRS/IWRS will be used to allocate drug and to manage distribution of MK-1439A.
f. Study drug for extension 3 will be dispensed at Week 228, if subject is continuing into extension
g. If the subject is eligible and elects to enter study extension 3, he/she will be considered to have completed study extension 2 and will, after providing informed consent, immediately enter study extension 3 and be dispensed MK-1439A.
h. For women of childbearing potential.

6.6 Study Extension 3 Flow Chart for Immediate Switch Group (ISG): Weeks 232 Through 312 Plus 14-Day Follow-up

Visit Number	**23**	**24**	**25**	**26**	**27**	**28**		
TRIAL PROCEDURES by STUDY WEEK [a]	**WK 232 [b, c]**	**WK 248**	**WK 264**	**WK 280**	**WK 296**	**WK 312**	**U (Extension 3 Early Discontinuation)**	**99**
Trial Period:	**Study Extension 3: Treatment**						**At time of Discontinuation**	**Post treatment[d]**
Weeks post Study Extension 2	**16 WKs**	**32 WKs**	**48 WKs**	**64 WKs**	**80 WKs**	**96 WKs**		**14-Day Follow-up**
Administrative Procedures								
Register Study Visit via Interactive Voice/Web Response System (IVRS/IWRS)	x	x	x	x	x	x	x	
Dispense Study Therapy[e]	x	x	x	x	x			
Clinical Procedures/Assessments								
Serious 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								
Urine Pregnancy Test (if applicable)[f]	x	x	x	x	x	x	x	x

a. The total duration is dependent on when MK-1439A becomes locally available, with a maximum total duration of treatment of 312 weeks. Subjects should discontinue at the next scheduled visit after MK-1439A becomes locally available in the market.
b. Subjects who enter study extension 3 are considered enrolled in the extension upon providing written informed consent at the Week 216 study visit.
c. The visit windows are approximately +/- 14 days for all visits from Week 232 through Week 312. The timing of each visit is relative to the randomization (Day 1) visit. Every attempt must be made to keep subjects on schedule.
d. The visit window for the post-study 14-day follow-up visit is approximately – 2 to 0 days.
e. IVRS/IWRS will be used to allocate drug and to manage distribution of MK-1439A.
f. For women of childbearing potential.

6.7 Study Extension 3 Flow Chart for Deferred Switch Group (DSG): Weeks 244 Through 324 Plus 14-Day Follow-up

Visit Number	**23**	**24**	**25**	**26**	**27**	**28**		
TRIAL PROCEDURES by STUDY WEEK[a]	**WK 244[b, c]**	**WK 260**	**WK 276**	**WK 292**	**WK 308**	**WK 324**	**U (Extension 3 Early Discontinuation)**	**99**
Trial Period:	**Study Extension 3: Treatment**						**At time of Discontinuation**	**Post treatment[d]**
Weeks post extension 2	**16 WKs**	**32 WKs**	**48 WKs**	**64 WKs**	**80 WKs**	**96 WKs**		**14-Day Follow-up**
Administrative Procedures								
Register Study Visit via Interactive Voice/Web Response System (IVRS/IWRS)	x	x	x	x	x	x	x	
Dispense Study Therapy[e]	x	x	x	x	x			
Clinical Procedures/Assessments								
Serious 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								
Urine Pregnancy Test (if applicable)[f]	x	x	x	x	x	x	x	x

a. The total duration is dependent on when MK-1439A becomes locally available, with a maximum total duration of treatment of 324 weeks. Subjects should discontinue at the next scheduled visit after MK-1439A becomes locally available in the market.
b. Subjects who enter study extension 3 are considered enrolled in the extension upon providing written informed consent at the Week 228 study visit.
c. The visit windows are approximately +/- 14 days for all visits from Week 244 through Week 324. The timing of each visit is relative to the randomization (Day 1) visit. Every attempt must be made to keep subjects on schedule.
d. The visit window for the post-study 14-day follow-up visit is approximately – 2 to 0 days.
e. IVRS/IWRS will be used to allocate drug and to manage distribution of MK-1439A.
f. For women of childbearing potential.

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 Future Biomedical Research. 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 Study Day 1 visit (prior to randomization). For subjects who wish to continue into study extension 1, the additional inclusion criteria (11 to 14, Section 5.1.2) are to be reviewed at the Study Week 24 or Study Week 36 study visit (according to the assigned initial treatment group). For subjects who wish to continue into study extension 2, the additional inclusion criteria (Section 5.1.2, 15 through 18) are to be reviewed at the Study Week 120 (ISG) or Study Week 132 (DSG) study visit; and for subjects who wish to continue into study extension 3, the additional inclusion criteria (Section 5.1.2, 19 through 22) are to be reviewed at the Study Week 216 (ISG) or Study Week 228 (DSG) 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 at the Screening visit. The medical history should include information pertaining to the diagnosis of HIV infection and Acquired Immunodeficiency Syndrome (if applicable) and the year diagnosed. If the subject has been previously diagnosed with any Acquired Immunodeficiency Syndrome (AIDS) defining conditions or a CD4 cell count < 200, the condition as well as a corresponding medical history of Acquired Immunodeficiency Syndrome must be reported. Additionally, the subject's pre-treatment HIV viral load (RNA), historical genotype and history of smoking 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 all medication taken by the subject within 30 days before starting the trial and all prior antiretroviral agents taken for the treatment of HIV infection.

Investigational agents must be discontinued for 30 days prior to receiving study therapy.

7.1.1.5.2 Concomitant Medications

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

7.1.1.6 Assignment of Screening Number

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

Any subject who is rescreened will retain the original screening number assigned at the initial screening visit.

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

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

7.1.1.7 Assignment of Treatment/Randomization Number

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

The study medication diary will be used to document study drug compliance for the base study and study extension 1.

On Study Day 1, the investigator/study coordinator will give the subject a study medication diary to be completed during the study period. The investigator/study coordinator will be responsible for entering the subject's identification number (screening and randomization number) before giving the study medication diary to the subject. The subject should follow

the instructions on the study medication diary for recording all study drugs. Aside from the initial information entered by the investigator/study coordinator, only the subject should enter information on the study medication diary. The subject is to return the completed study medication diary at each scheduled visit. The investigator/study coordinator will be responsible for reviewing the study medication diary for completeness and accuracy with the subject. Only the subject shall make changes to the entries on the diary. The subject will initial the diary to confirm that the information is accurate. The investigator/study coordinator will be responsible for transferring the appropriate information from the diary onto the appropriate case report form.

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

The Subject Medication Diary will not be used during study extension 2 or study extension 3. Sites are responsible for source documentation for drug accountability.

Interruptions from the protocol specified treatment for 7 days or greater require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

7.1.1.9 Patient-Reported Outcomes

There are a total of 4 questionnaires to be completed by subjects in the base study (CNS toxicity questionnaire, PSQI, HADS and EQ-5D-5L); subjects enrolled under the original protocol (version 00) also complete a CBB questionnaire in the base study. Only the CNS toxicity questionnaire is administered in study extension 1.

Subjects will complete only the CNS toxicity questionnaire at Screening. However, subjects will complete all questionnaires at Study Day 1, Study Weeks 4, 12, 16 (DSG only), 24, and 36 (DSG only) and the Early Discontinuation visit, if applicable.

1) <u>CNS Toxicity questionnaire</u>

   The CNS toxicity questionnaire is a self-administered questionnaire developed to assess CNS toxicities. A 7 day recall period will be used.

2) <u>Cogstate Brief Battery (CBB)</u>

   The Cogstate Brief Battery, while not formally a PRO, has been validated for use in HIV-infected patients where it has been shown to offer specificity for identifying neurocognitive function and provides a measure of 4 core cognitive domains: processing speed, attention/vigilance, visual recognition memory and working memory [10, 11]. NOTE: Subjects enrolled under Amendment 01 will not be administered the CBB. Subjects enrolled under the original protocol (version 00) are required to complete the CBB at specified visits in the base study per the study flow chart. All other PRO questionnaires are mandatory for all subjects.

3) Pittsburgh Sleep Quality Index (PSQI)

The PSQI is a validated 19-item questionnaire that was developed to provide a reliable, valid, and standardized measure of sleep quality [12]. The PSQI discriminates between "good" and "poor" sleepers and provides a brief, clinically useful assessment of a variety of sleep disturbances that might affect sleep quality. The instrument can be self-administered and has a four-week recall period. The PSQI has been used in studies of HIV-infected patients.

4) Hospital Anxiety and Depression Scale (HADS)

The Hospital Anxiety and Depression Scale (HADS) measures depression and anxiety in and outside of the hospital and in community settings [13, 14]. The HADS is a 14-item self-administered instrument that takes 2 to 5 minutes to complete. It has been widely used to measure depression and anxiety in adults. Although the term 'hospital' refers to the setting in which the instrument was first developed, many studies conducted throughout the world have confirmed that it is valid when used in community settings and primary care medical practice. The 2 subscales, anxiety and depression, are independent measures and can be scored and mapped to 4 ranges: normal, mild, moderate and severe.

5) EuroQol Five Dimensional Descriptive System, Five Level Version (EQ-5D-5L)

The EuroQol EQ-5D-5L is a validated, standardized 5-item health-state questionnaire applicable to a wide range of health conditions and treatments and used to assess health outcomes [15, 16]. The 5 health state dimensions include: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems.

Administration

Subjects are to complete the questionnaires on their own at the site at the beginning of the appropriate study visit (see study flow charts). On Study Day 1, every attempt should be made to have the subjects complete the questionnaires prior to receiving study treatment, prior to discussing any medical conditions with the study personnel, and prior to receiving any medical results. In the base study, the CNS toxicity questionnaire should always be administered first and the rest of the questionnaires should be administered in the following order: PSQI, HADS, EQ-5D-5L, and, for subjects enrolled under the original protocol (version 00), CBB. During study extension 1, the CNS toxicity questionnaire will be completed at each treatment visit and, if applicable, at the early discontinuation visit.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Physical Examination

All physical examinations should be performed as indicated in the study flow charts (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 [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 Study Day 1 visits should be noted on the Medical History eCRF on Study Day 1. Any significant changes in the physical examination after receiving study therapy at Study Day 1 must be reported as adverse events and entered on the adverse event eCRF. If the subject is discontinued from the study during the treatment period for any reason, 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 study flow charts (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 adverse event on the eCRF.

7.1.2.3 Vital Signs and Weight

Vital signs including pulse rate, respiratory rate, blood pressure and body temperature, should be assessed as indicated in the study 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.

Weight will be collected at all study visits except at Study weeks 1, 2 and 3.

After the screening visit, the site should indicate whether or not the results are clinically significant and document this in the subject's chart. If any result is clinically significant, it should be captured as an adverse event on the eCRF.

7.1.2.4 12-Lead ECG (performed locally)

As indicated in the flow chart for the base study (Section 6.1), a local 12-Lead electrocardiogram (ECG) should be performed prior to the subject's first dose of study medication (at either the Screening visit or the Study Day 1 visit), and any abnormality should be documented. Results must be available prior to subject randomization and prior to the subject's first dose of 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 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 subject is on study treatment or during the follow-up period, any clinically significant change compared with the ECG performed prior to the first dose of study medication must be captured as an AE on the eCRF and documented in the subject's chart.

7.1.2.5 Adverse Events

If a subject is diagnosed with an AIDS-defining condition following randomization, the condition must be reported as an AE.

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

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

7.1.2.6 Toxicity Management

Guidelines for grading the severity of laboratory adverse events are based on Division of Acquired Immunodeficiency Syndrome (DAIDS) criteria for grading severity of adverse events (Appendix 12.6). 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 adverse events 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 rechallenge must be approved in advance by the MSD Clinical Director or Designee and, if required, by the Independent Ethics Committee/Institutional Review Board, and a rechallenge consent is needed prior to re-initiation of study therapy. If advance approval of rechallenge is not required by local regulations, the Independent Ethics Committee/Institutional Review Board will receive notification for information only. If, after re-initiation of study therapy, there is a recurrence of the laboratory abnormality or clinical adverse event, consideration should be given to permanently discontinuing all study therapy. In general, when a clinical or laboratory adverse event occurs which requires interruption of study therapy, all study drugs should be interrupted to avoid having a subject receive suboptimal therapy which may predispose them to the development of resistance. In general, all study medications should be restarted concomitantly at full dose. **Whenever study drugs are interrupted, the MSD 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 male subjects when the female partners are of childbearing potential.

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, a serum pregnancy test is to be done at the screening visit, and a urine pregnancy test is to be done at the Study Day 1 visit prior to randomization. Urine pregnancy tests must also be subsequently done at the Week 4 visit and at each subsequent study visit, including the discontinuation and Follow-Up visits in both the base study and the study extensions. Results must be documented in the subject's chart. A subject who is pregnant must be discontinued from the study.

7.1.3.2 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests (hematology, chemistry and other) that are to be performed during the base study and study extension 1 of the trial are specified in Table 5.

Table 5 Laboratory Tests

Hematology	Chemistry	Other
Hematocrit	Aspartate aminotransferase (AST, SGOT)	Prothrombin time (PT)[3]
Hemoglobin	Alanine aminotransferase (ALT, SGPT)	Activated partial thromboplastin time (APTT)[3]
Platelet count	Alkaline phosphatase	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]
CD4% and Absolute CD4/ Lymphocytes	Direct Bilirubin	Hepatitis B e-Antigen [3]
CD8% and Absolute CD8/Lymphocytes	Indirect Bilirubin	Hepatitis C Antibody [3]
CD4/CD8 ratio	Amylase	Plasma hepatitis C virus PCR quantitative[4]
White Blood cell Count	Lipase	Enzyme immunoassay HIV antibody (with confirmation WB)[3]

Hematology	Chemistry	Other
WBC Differential Leukocytes	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]
	Calcium	
	Phosphorus	
	Magnesium	
	Protein	
	Albumin	
	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 Randomization (Study Day 1), Study Weeks 12, 24 and 36 (DSG only) and, for subjects who continue into study extension 1, at the Week 72 (ISG) or 84 (DSG) and Week 120 (ISG) or 132 (DSG) visits. Subjects should be fasting for at least 8 hours.
2. Perform at the screening visit and Study Weeks 4 and 16 (DSG only) and, in study extension 1, at the Study Week 40 (ISG) or 52 (DSG), 56 (ISG) or 68 (DSG), 88 (ISG) or 100 (DSG), and 104 (ISG) or 116 (DSG) visits.
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. The serum β hCG test at the screening visit to be performed by central laboratory.
6. The urine β hCG test is to be performed at the investigator site at Study Day 1 and every study visit thereafter.
7. Perform at Study Day 1, all applicable study visits (except Screening, Study Weeks 1, 2, and 3 and Post-Treatment 14-Day Follow-Up), the Virologic Failure Confirmation visit and the Early Discontinuation visit (if not collected at Virologic Failure Confirmation 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, in the base study and study extension 1, except Study Weeks 1, 2, and 3 for all subjects and Study Week 16 for subjects in the ISG. 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 HIV viral resistance testing at Study Day 1, Study Weeks 4, 12, 16 (DSG only), 24, and 36 (DSG only), and, in both the base study and study extension 1, at the Virologic Failure Confirmation visit or the Early Discontinuation Visit (if not already obtained at Virologic Failure Confirmation visit). Baseline (Study Day 1) samples will be analyzed in cases of virologic failure and/or discontinuation, provided the viral load meets the criterion for resistance testing (>400 copies/mL). All resistance testing in the base study and in study extension 1 will be performed by a central laboratory. Amplifiable virus to screen for resistance would not be expected for subjects whose viral load was BLoQ at entry.

7.1.3.6 CD4 Cell Counts

CD4 cell count (absolute and percentage) will be determined at Study Day 1 and at Study Weeks 12 and 24. CD4 cell count (absolute and percentage) will also be determined at Study Week 36 for subjects in the DSG only. For subjects who continue into study extension 1, CD4 cell count will also be determined at the Study Week 72 and 120 visits in the ISG and at the Study Week 84 and 132 visits in the DSG. Testing will be performed at the central laboratory using a commercially-available assay.

7.1.3.7 Pharmacokinetic/Pharmacodynamic Evaluations

7.1.3.7.1 Blood Collection for Plasma MK-1439 and Efavirenz

Samples for MK-1439 and efavirenz PK will be collected from all subjects as outlined in Table 6. The exact time the dose of MK-1439A and efavirenz were taken prior to the sample collection will be recorded on the appropriate eCRF. On the day of any visit at which a PK sample will be collected, the sample must be collected before the subject takes the study drug.

Table 6 Pharmacokinetic Sampling Timepoints

Visit Number	**Study Day/Week** (for all subjects)	**Time Relative to MK-1439A dose**
2	Day 1	2 samples to be collected predose
3	Week 1	2 samples to be collected predose
4	Week 2	2 samples to be collected predose
5	Week 3	2 samples to be collected predose
6	Week 4	2 samples to be collected predose

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 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 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.

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@MSD.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

Procedures for blinding and unblinding apply only to the base study; treatment during the study extensions is open-label.

STUDY TREATMENT IDENTIFICATION INFORMATION IS TO BE UNMASKED ONLY IF NECESSARY FOR THE WELFARE OF THE SUBJECT. EVERY EFFORT SHOULD BE MADE NOT TO UNBLIND THE SUBJECT UNLESS NECESSARY.

For emergency situations where the investigator or sub-investigator needs to identify the drug used by a subject and/or the dosage administered in case of emergency, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or sub-investigator the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the sponsor. The emergency unblinding call center will make a record promptly however, the investigator or sub-investigator must enter the intensity/toxicity grade of the adverse experiences observed, their relation to study drug, the reason thereof, etc., in the medical chart etc., before unblinding is performed.

Additionally, the investigator must go into the IVRS system and perform the unblind in the IVRS system to update drug disposition. In the event that the emergency unblinding call center is not available for a given site in this trial, IVRS/IWRS should be used for emergency unblinding in the event that this is required for subject safety.

Study treatment identification information is to be unmasked ONLY if necessary for the welfare of the subject. Every effort should be made not to unblind the subject unless necessary.

In the event that unblinding has occurred, the circumstances around the unblinding (eg, date, reason and person performing the unblinding) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible. Once an emergency unblinding has taken place, the principal investigator, site personnel, and Sponsor personnel may be unblinded so that the appropriate follow-up medical care can be provided to the subject.

7.1.4.3 Calibration of Equipment

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

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 set forth in Section 5.1. The investigator will discuss the study, its requirements, and its restrictions with each potential subject. The study screening period is 30 days.

- All procedures listed for the screening visit (Visit 1) in the Study Flow Chart (Section 6.1) must be completed and the subjects eligibility confirmed by the investigator prior to the subject's randomization and drug administration on Study Day 1.

- Blood will be collected for safety laboratory evaluations, hemostatic function tests, an HIV/hepatitis screen, and HIV-1 RNA quantification. 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) conducted at the screening visit. Women who are pregnant will be excluded from the study.

- Subjects will be instructed to complete the CNS toxicity questionnaire, as noted in the Study Flow Chart (Section 6.1). Subjects are to complete the questionnaire on their own at the site.

- 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 Rescreening

Subjects who have previously completed the screening visit (Visit 1) and were deemed eligible for randomization into this study, but failed to be randomized within the 45 day window, may be rescreened to re-evaluate study eligibility. To reconfirm the subject's eligibility, safety evaluations and HIV RNA test should be repeated. In addition, the serum pregnancy test for female participants of childbearing potential should be repeated, Rescreening of a patient will require approval from the SPONSOR.

7.1.5.3 Treatment Visits

Randomization - Study Day 1 (Visit 2)

- Procedures listed for Study Day 1 (Visit 2) on the Study Flow Chart (Section 6.1) should be performed prior to the subject's randomization and drug administration on Study 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 eligibility criteria, the subject will be eligible for randomization and the remainder of the pretreatment (Study Day 1) testing/procedures will be performed. If the urine pregnancy test result is positive, the subject must not be randomized.

- Fasting blood will be collected for genetic analysis, safety laboratory evaluations, HIV-1 RNA quantification, CD4 cell counts, HIV viral resistance and PK measurements. Subjects will be required to fast for at least 8 hours prior to the study visit. These samples will be sent to the appropriate central laboratory(ies) following the procedure(s) set forth in the manual(s).

- Plasma samples for future biomedical research will be also collected from all subjects from whom appropriate consent has been obtained.

- Subjects will be instructed to complete the CNS toxicity questionnaire to confirm presence of at least one CNS toxicity noted at the screening visit as noted in the Study Flow Chart (Section 6.1). Subjects are to complete the questionnaire on their own at the site.

- Following completion of the Study Day 1 pretreatment procedures and confirmation of eligibility, the site staff will access the IVRS/IWRS for assignment of the drug to be administered. Site staff should not access 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.

- Subjects will be instructed to complete the CBB (including practice) and other PRO questionnaires, as noted in the Study Flow Chart (Section 6.0). Subjects are to complete the questionnaires on their own at the site.

- Subjects randomized to both treatment groups will receive a 4-week supply of study medication on Study Day 1 (Visit 2). Subjects will be instructed to take their first dose of study medication on the same day as the Study Day 1 visit.

- The investigator/study coordinator will give a study medication diary to all subjects in both treatment groups. Subjects will start the diary on Study Day 1 and continue to complete the diary throughout the treatment period. The site must ensure that the subject is properly trained and comfortable with completing the medication diary prior to the subject leaving the clinic.

Drug Administration

Subjects will be dispensed study drug as outlined in Table 7.

Table 7 Study Drug Bottle (A, B and C) Components

Bottle Label	Component
Bottle A	MK-1439A or placebo
Bottle B	ATRIPLA™ or placebo
Bottle C	MK-1439A (open label)

Subjects will be instructed to take the study medication as follows:

All Subjects will take one tablet once-daily from each of the bottles as follows:

Bottle A (MK-1439A or placebo):

Subjects will be instructed to take one tablet from Bottle A q.d. orally, with or without food at approximately the same time each day. Tablets from Bottle A must be kept in the bottle prior to taking study medication since the formulation being used in this study is moisture sensitive.

Bottle B (ATRIPLA™ or placebo):

Subjects will be instructed to take one tablet from Bottle B q.d. orally, at bedtime, on an empty stomach.

Note: Study medication should be taken directly from the study bottle.

Study Week 1 (Visit 3) to Study Week 3 (Visit 5)

- All procedures for Study Week 1 (Visit 3) to Study Week 3 (Visit 5) listed on the Study Flow Chart (Section 6.1) should be performed.
- Blood will be collected for PK measurements (see section 7.1.3.7.1 for details) at the time points specified on the Study Flow Chart. These samples will be sent to the appropriate central laboratory(ies) following the procedure(s) set forth in the manual(s).
- At each study visit, the study coordinator and subject will review the study medication diary information.

Study Week 4 (Visit 6) and Study Week 12 (Visit 7)

- All procedures for Study Week 4 (Visit 6) and Study Week 12 (Visit 7) listed on the Study Flow Chart (Section 6.1) should be performed.
- Blood will be collected for safety laboratory evaluations, HIV-1 RNA quantification and HIV viral resistance at the time points specified on the Study Flow Chart. Blood will be collected for the CD4 cell count at Study Week 12 (Visit 7) only. 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. If the urine pregnancy test result is positive, the subject must be discontinued.
- Subjects will be instructed to complete the CNS toxicity questionnaire, the CBB and the other PRO questionnaires, as listed on the Study Flow Chart (Section 6.0). Subjects are to complete the questionnaires on their own at the site.
- For all subjects, blood samples for PK measurements will be collected at Study Week 4 only (see section 7.1.3.7.1 for details).
- All bottles of study drug will be returned to the study coordinator at each study 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.
- At each study visit, the study coordinator and subject will review the study medication diary information.
- Site staff will access the IVRS/IWRS for assignment of the drug to be administered and for registration of visits.
- Subjects will receive an 8-week supply of study drug at Study Week 4 (Visit 6).
- Subjects will receive 4-week supply of open-label study drug (Bottle C) at Study week 12 (Visit 7).
- At Study Week 12, subjects will be assigned a new medication diary (for the open-label period) and the previous diary (for the blinded period) will be collected.

Study Week 16 (Visit 8)

- Subject Unblinding: All adverse events data through the first 12 weeks of treatment for that subject will be cleaned and reconciled prior to unblinding. Site should have received confirmation from the sponsor study team prior to calling IVRS/IWRS to unblind. Site staff will access IVRS/IWRS for assignment of the drug to be administered, for registration of the visit and unblinding.
- After unblinding, all subjects will receive an 8-week supply of study drug (Bottle C).
- For subjects in the ISG group, the only assessments required are AE, concomitant medication and study medication diary review.
- For subjects in the DSG group all procedures for Study Week 16 (Visit 8) listed on the Study Flow Chart (Section 6.1) should be performed.
- For subjects in the DSG group blood will be collected for safety laboratory evaluations, HIV-1 RNA quantification and HIV viral resistance at the time points specified on the

Study Flow Chart. These samples will be sent to the appropriate central laboratory(ies) following the procedure(s) set forth in the manual(s).

- For subjects in the DSG group for a female subject who is of childbearing potential, a urine pregnancy test will be performed. If the urine pregnancy test result is positive, the subject must be discontinued.
- Subjects in the DSG group will be instructed to complete the CNS toxicity questionnaire, the CBB and the other PRO questionnaires, as listed on the Study Flow Chart (Section 6.0). Subjects are to complete the questionnaires on their own at the site.
- All bottles of study drug will be returned to the study coordinator at the 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.

Study Week 24 (Visit 9)

- All procedures for Study Week 24 (Visit 9) listed on the Study Flow Chart (Section 6.1) should be performed.
- Subjects will be required to fast for at least 8 hours prior to the study visit. Blood will be collected for safety laboratory evaluations, HIV-1 RNA quantification, CD4 cell count and HIV viral resistance at the time points specified on the Study 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 instructed to complete the CNS toxicity questionnaire, the CBB and the other PRO questionnaires, as listed on the Study Flow Chart (Section 6.0). Subjects are to complete the questionnaires on their own at the site.
- All bottles of study drug will be returned to the study coordinator at the visit. 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 assignment of the drug to be administered and for registration of the visit. Only subjects assigned to the DSG will receive a 12-week supply of study drug at Study Week 24 (Visit 9). Subjects in the ISG who are considered eligible and elect to enter the study extension will receive a 16-week supply of study drug at Study Week 24 (Visit 9). For subjects in the ISG who do not enter the study extension, no study drug will be dispensed, as Study Week 24 (Visit 9) will be the last treatment visit for subjects in the ISG.
- The study coordinator and subject will review the study medication diary information

Study Week 36 (Visit 10) for DSG

- Only subjects assigned to the DSG will return for Study Week 36 (Visit 10).
- All procedures for Study Week 36 (Visit 10) listed on the Study Flow Chart (Section 6.1) should be performed.
- Subjects will be required to fast for at least 8 hours prior to the study visit. Blood will be collected for safety laboratory evaluations, HIV-1 RNA quantification, CD4 cell count and HIV viral resistance at the time points specified on the Study 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 instructed to complete the CNS toxicity questionnaire, the CBB and the other PRO questionnaires, as listed on the Study Flow Chart (Section 6.0). Subjects are to complete the questionnaires on their own at the sit
- All bottles of study drug will be returned to the study coordinator at the visit. 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 the visit. Subjects who are considered eligible and elect to enter the study extension will receive a 16-week supply of study drug at Study Week 36 (Visit 10). For subjects in the DSG who do not enter the study extension, no study drug will be dispensed as Study Week 36 (Visit 10) will be the last treatment visit.

Study Week 40 Through Week 120 for ISG

- All procedures for Study Week 40, Week 56, Week 72, Week 88, Week 104, and Week 120 listed on the flow chart for the study extension (Section 6.2) should be performed.
- Blood will be collected for safety laboratory evaluations and HIV-1 RNA quantification at the time points specified in the Study Flow Chart. Samples for CD4 counts will also be collected at the Study Week 72 and 120 visits. Subjects will be required to fast for at least 8 hours prior to the Study Week 72 and 120 visits. Samples for HIV viral resistance will be collected at the Virologic Failure Confirmation visit or at the discontinuation visit (if not already obtained at Virologic Failure Confirmation 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.
- Subjects will be instructed to complete the CNS toxicity questionnaire as listed on the Study Flow Chart (Section 6.0). Subjects are to complete the questionnaires on their own at the site.

- All bottles of study drug will be returned to the study coordinator at the visit. 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 104. Study drug for study extension 2 will be dispensed at Week 120 for subjects continuing into study extension 2.
- At each study visit the study coordinator and subject will review the study medication diary information.

Study Week 52 Through Week 132 for DSG

- All procedures for Study Week 52, Week 68, Week 84, Week 100, Week 116, and Week 132 listed on the flow chart for the study extension (Section 6.3) should be performed for the DSG.
- Blood will be collected for safety laboratory evaluations and HIV-1 RNA quantification at the time points specified in the Study Flow Chart.
- Samples for CD4 counts will be collected at the Study Week 84 and 132 visits. Subjects will be required to fast for at least 8 hours prior to the Study Week 84 and 132 visits. Samples for HIV viral resistance will be collected at the virologic failure confirmation visit or at the discontinuation visit (if not already obtained at Virologic Failure Confirmation 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.
- Subjects will be instructed to complete the CNS toxicity questionnaire, as listed on the Study Flow Chart (Section 6.0). Subjects are to complete the questionnaires on their own at the site.
- 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 116. Study drug for extension 2 will be dispensed at Week 132 for subjects continuing into extension 2.
- At each study visit the study coordinator and subject will review the study medication diary information.

Week 136 Through Week 216 for ISG

- All procedures for Study Week 136, Week 152, Week 168, Week 184, Week 200, and Week 216 listed on the Study Flow Chart (Section 6.4) should be performed.
- 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. Only first dose, last dose, overdose (if applicable) and study drug interruption (if applicable) due to any toxicity, ECI or (S)AE will be collected in the database.
- 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 200. Study drug for study extension 3 will be dispensed at Week 216 for subjects continuing into study extension 3.

Week 148 Through Week 228 for DSG

- All procedures for Study Week 148, Week 164, Week 180, Week 196, Week 212, and Week 228 listed on the Study Flow Chart (Section 6.5) should be performed.
- 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. Only first dose, last dose, overdose (if applicable) and study drug interruption (if applicable) due to any toxicity, ECI or (S)AE will be collected in the database.
- 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 212. Study drug for study extension 3 will be dispensed at Week 228 for subjects continuing into study extension 3.

Week 232 Through Week 312 for ISG

- All procedures for Study Week 232, Week 248, Week 264, Week 280, Week 296, and Week 312 listed on the Study Flow Chart (Section 6.6) should be performed.
- 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. Only first dose, last dose, overdose (if applicable) and study drug interruption (if applicable) due to any toxicity, ECI or (S)AE will be collected in the database.

- 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 296.

Week 244 Through Week 324 for DSG

- All procedures for Study Week 244, Week 260, Week 276, Week 292, Week 308, and Week 324 listed on the Study Flow Chart (Section 6.7) should be performed.
- 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. Only first dose, last dose, overdose (if applicable) and study drug interruption (if applicable) due to any toxicity, ECI or (S)AE will be collected in the database.
- 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 308.

Virologic Failure Confirmation Visit (Base Study and Study Extension 1)

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

  Note: Protocol-defined virologic failure (PDVF) is defined as subjects who have 2 consecutive measurements of HIV-1 RNA ≥200 copies/mL at least one week apart.

- The virologic failure confirmation visit should be done between 1 and 4 weeks (≥1 to ≤ 4) after the first measurement of HIV-1 RNA ≥200 copies/ml.

Subjects should be discontinued if they meet the protocol-defined virologic failure criteria. The choice of subsequent antiretroviral therapy will be at the discretion of the study investigator or subject's physician.

Early Discontinuation Visit (Base Study, Study Extensions 1, 2, and 3)

- When a subject discontinues/withdraws from participation in the trial, all procedures for the Early Discontinuation visit listed on the Study 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 (including serious adverse events) in the base study and study extension 1

- Only serious adverse events in study extension 2 and study extension 3

- 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.

- Subjects who discontinue early from the base study will be instructed to complete the CNS toxicity questionnaire, the CBB and the other PRO questionnaires, as listed on the Study Flow Chart (Section 6.1); subjects who discontinue early from study extension 1 will be instructed to complete the CNS toxicity questionnaire. Subjects are to complete the questionnaires on their own at the site.

- Subjects who discontinue early from the study are expected to return for a 14-day post-therapy follow-up visit.

7.1.5.4 Post-Trial

- Following the completion of study therapy (in the base study or study extensions) 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 Study 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 adverse events have occurred since the post-study clinic visit.

7.1.5.5 Trial Unblinding

For emergency unblinding please refer to Section 7.1.4.2.

For planned unblinding at study week 16, please refer to Section 5.2.3.

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 during the base study and study extension 1 as specified in Section 2. During study extension 2 and study extension 3, serious adverse events must be reported by the investigator as specified in Section 2; and if an investigator chooses to report a non-serious adverse event (NSAE), it should be submitted using the same process used to submit NSAEs in the base study and study extension 1. 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 8 for additional details regarding each of the above criteria.

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

For the time period beginning at treatment allocation/randomization through 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 8. The investigator's assessment of causality is required for each adverse event. Refer to Table 8 for instructions in evaluating adverse events.

Table 8 Evaluating Adverse Events

Maximum Intensity	**Mild**	awareness of sign or symptom, but easily tolerated (for pediatric trials, awareness of symptom, but easily tolerated)
	Moderate	discomfort enough to cause interference with usual activity (for pediatric trials, definitely acting like something is wrong)
	Severe	incapacitating with inability to work or do usual activity (for pediatric trials, extremely distressed or unable to do usual activities)
Seriousness	A serious adverse event (AE) is any adverse event occurring at any dose or during any use of Sponsor's product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred [Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.]; or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of an MSD 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 unblinding, will be documented in a supplemental SAP (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Separate analysis plans (ie, separate documents from the sSAP) may be developed to detail other planned analyses (e.g. analysis of PK data, subject - reported outcomes other than endpoints related to the CNS toxicity questionnaire, 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 to 8.12. Analysis of data from the study extensions does not require changes to the SAP. All data from study extension 1 will be summarized descriptively only. These data will be summarized separately from data generated from the base study; only data from the base study will be used to address the primary objectives and hypotheses. Serious adverse event data from study extension 2 and study extension 3 will be summarized separately from data for the base and study extension 1 portions of the study.

Study Design Overview	Phase IIb, Double-Blinded, Multicenter, Randomized Study to Assess the Effect on Central Nervous System (CNS) Toxicity of Switching from ATRIPLA™ (Efavirenz, Tenofovir, Emtricitabine) to MK-1439A (Doravirine, Tenofovir, Lamivudine) in Virologically-Suppressed Subjects
Treatment Assignment	Subjects will be randomized to either the Immediate Switch Group or Deferred Switch Group in a 1:1 ratio. A total of 84 subjects (42/group) are planned to be randomized. There will be no stratification in this study. Centralized randomization will be used and implemented via an interactive voice recognition system (IVRS).
Analysis Populations	Efficacy and CNS toxicity assessment: Full Analysis Set (FAS) Safety: All Subjects as Treated (ASaT)
Primary Endpoint(s)	The proportion of subjects with at least one CNS toxicity of at least Grade 2 intensity at Week 12.

Key Secondary Endpoints	1. Proportion of subjects with at least one CNS toxicity of at least Grade 2 intensity at Week 4 2. Change from baseline in the proportion of subjects with at least one CNS toxicity of at least Grade 2 intensity at 24 weeks post-switch 3. Change from baseline in CNS toxicity score at Weeks 4 and 12 4. Change from baseline in CNS toxicity score at 24 weeks post-switch 5. The proportion of subjects with HIV-1 RNA < 50 copies/mL (and <40 copies/mL) at 24 weeks post-switch 6. Change from baseline in fasting lipids at Week 12 7. Change from baseline in fasting lipids at 24 weeks post-switch 8. Change from baseline in CD4 cell count at 24 weeks post-switch 9. Overall safety and tolerability through Week 12 10. Overall safety and tolerability through 24 weeks post-switch
Statistical Methods for Primary Objective/Hypothesis	The treatment difference and the associated 95% confidence interval will be calculated for the proportion of subjects with at least 1 CNS toxicity of at least Grade 2 intensity at Week 12 using Miettinen and Nurminen's method (1985) [17], an unconditional, asymptotic method, and p-values based on this method will be provided. The immediate switch group will be considered to have a statistically significantly smaller proportion of subjects with at least one CNS toxicity of at least Grade 2 intensity at Week 12 if the upper bound of the 95% confidence interval for the treatment difference (immediate – deferred) is less than 0.
Statistical Methods for Key Efficacy/Immunogenicity/ Pharmacokinetic Analyses	<u>Proportion of Subjects Maintaining HIV-1 RNA <50 copies/mL and <40 copies/mL</u> The proportion of subjects achieving HIV-1 RNA < 50 copies/mL (and separately for < 40 copies/mL) will be summarized separately by treatment group at 4 and 12 weeks post-switch and for the combined treatment groups at 24 weeks post-switch (with primary interest in the combined analysis). At each time point of interest, the 95% confidence interval for the proportion will be calculated using the exact binomial method proposed by Clopper and Pearson (1934) [18]. Subjects who discontinue prior to the switch in the deferred switch group will be excluded from the combined analysis. <u>Change from Baseline in CD4 cell count</u> Change from baseline in CD4 cell counts will be summarized separately by treatment group at 4 and 12 weeks post-switch and for the combined treatment groups at 24 weeks post-switch (with primary interest in the combined analysis). The observed failure approach will be used for the calculations of change from baseline in CD4 cell count. Subjects who discontinue prior to the switch in the deferred switch group will be excluded from the combined analysis.

Statistical Methods for Key Safety Analyses	Overall 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 for both the base study and for the entire treatment period, ie, base study plus the 96-week study extension, in which all subjects receive open-label MK-1439A. The proportions of subjects with clinical or laboratory adverse experiences of the following types will be tabulated: (1) at least one adverse experience; (2) a drug-related adverse experience; (3) a serious adverse experience; (4) a serious and drug-related adverse experience; (5) an adverse experience leading to discontinuation. The percentage of subjects with specific adverse experiences by system organ class and the number and percentage of subjects with laboratory test results that exceed Pre-Defined Limit of Change will also be summarized in the same fashion. Safety data through Week 12 by treatment group and post switch combining treatment groups will be summarized. In the post switch summary, all accumulated safety data through the end of treatment + 14 days of follow-up post treatment will be included in the analyses of safety.
Interim Analyses	No interim analyses are planned.
Multiplicity	No multiplicity adjustment is planned as there is a single comparison of 2 treatments using 1 endpoint in the primary hypothesis. Other efficacy and safety analyses will be considered supportive and/or explanatory.
Sample Size and Power	All subjects will have at least one Grade 2 or worse CNS toxicity at baseline. It is anticipated that by Week 12, only 67.0% of the subjects in the Immediate Switch Group will have such a toxicity, while 91.5% of the subjects in the Deferred Switch Group will have at least one such event. The assumed proportions are based on a study of similar design [3]. With these assumed incidence rates and randomization of 42 subjects per group, there is 80% power to demonstrate a statistically significantly lower proportion of subjects with a Grade 2 or worse CNS toxicity in the Immediate Switch Group than in the Deferred Switch Group using a one-sided alpha level of 0.025.

8.2 Responsibility for Analyses/In-House Blinding

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

The official, final adverse event data for a subject for the double-blind period will not be unblinded until review has been performed and data are clean and final. Results of the open-label period will be presented along with those of the double-blind period in the CSR.

The Clinical Biostatistics department will generate the randomized allocation schedule for study treatment assignment. Randomization will be implemented in an interactive voice response system (IVRS).

8.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.0.

8.4 Analysis Endpoints

Efficacy, safety, subject-reported outcomes (including responses to the primary CNS toxicity questionnaire) and neurocognitive endpoints for the base study and study extension 1 that will be evaluated for within- and/or between-treatment differences are listed below followed by descriptions of the derivations of selected endpoints.

Due to the fact that the Immediate Switch Group will still be in the double-blind treatment phase at 4 and 12 weeks post-switch and the Deferred Switch Group will be in the open-label treatment phase at 4 weeks post-switch (Week 16) and 12 weeks post-switch (Week 24), the treatment groups will not be combined for the assessments at 4 and 12 weeks post-switch. The treatment groups will be combined for the evaluation of endpoints at 24 weeks post-switch (when both treatment groups are in the open-label treatment phase). No treatment group comparisons will be made at post-switch time points.

For analyses that compare the 2 treatment groups at Study Week 4 and Study Week 12, "baseline" for the change from baseline analyses will refer the measurements taken at Study Day 1. For analyses that combine the 2 treatment groups at 24 weeks post switch, "baseline" for the change from baseline analyses will refer to the measurements taken on the day of switch to MK-1439A (Study Day 1 for the Immediate Switch Group and Study Week 12 for the Deferred Switch Group).

8.4.1 CNS Toxicity Questionnaire

Section 4.2.3.1 provides an initial description of these measures.

A separate analysis plan will be developed for the subject-reported outcomes measuring sleep quality, anxiety and depression, neurocognitive function, and health-related quality of life. Therefore, these endpoints are described here with only limited detail.

Proportion of subjects with ≥1 CNS Toxicity of at least Grade 2 Intensity

CNS toxicity is measured using the CNS toxicity questionnaire (as described in Section 4.2.3.1). On the CNS toxicity questionnaire, the following 10 CNS toxicities are assessed by subjects with respect to whether or not they are present and the level of intensity of the toxicity using a scale of Grade 0 = none, Grade 1 = mild, Grade 2 = moderate, and Grade 3 = severe:

1. Dizziness
2. Depression/low mood
3. Insomnia/sleeplessness
4. Anxiety/nervousness
5. Confusion
6. Impaired concentration/attention
7. Headache

8. Somnolence/daytime sleepiness
9. Aggressive mood/behavior
10. Abnormal dreams

The questionnaire will be used to assess CNS toxicity at baseline and each subsequent visit. All enrolled subjects are required will have at least one Grade 2 or worse CNS toxicity at baseline. The primary efficacy endpoint is the proportion of subjects with at least one Grade 2 or worse CNS toxicity at Week 12. The proportion of subjects with at least one Grade 2 or worse CNS toxicity at Study Week 4 (comparing treatment groups) as well as at 4 weeks post-switch (by treatment group), 12 weeks post-switch (by treatment group), and 24 weeks post-switch (combining both treatment groups) will also be summarized.

Change from baseline in CNS Toxicity Score

A CNS toxicity score will be calculated for each subject at baseline and each post-baseline visit. Each of the 10 CNS toxicities will be assigned a number determined by the intensity reported (None=0, Mild=1, Moderate=2, Severe=3). Each subject will have a CNS toxicity score calculated as the sum across all 10 CNS toxicities expressed as a percentage of the maximum sum possible (10 x 3 = 30). Lower scores represent better CNS toxicity profiles. The change from baseline will be defined as the CNS toxicity score at the post-baseline time point of interest minus the CNS toxicity score at baseline. Negative numbers with a large magnitude indicate a substantial improvement in CNS toxicity relative to baseline. The median change from baseline will be summarized for the immediate versus deferred switch groups at Study Weeks 4 and 12 (primary time points of interest). The change from baseline to 4 weeks post-switch (by treatment group), 12 weeks post-switch (by treatment group), and 24 weeks post-switch (combining both treatment groups) will also be summarized.

8.4.2 Efficacy Endpoints

Section 4.2.3.2 provides an initial description of efficacy measures.

Proportions of Subjects Maintaining HIV-1 RNA < 50 (and <40) copies/mL (by the Abbott RealTime HIV-1 Assay)

The proportions of subjects maintaining HIV-1 RNA <50 (and <40) copies/mL will be estimated separately by treatment group at 4 and 12 weeks post-switch and for the combined treatment groups at 24 weeks post-switch (with primary interest in the combined analysis). 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.

Change from Baseline in CD4 Cell Count

Change from baseline in CD4 cell count will be estimated separately by treatment group at 4 and 12 weeks post-switch and for the combined treatment groups at 24 weeks post-switch (with primary interest in the combined analysis).

For the calculations of change from baseline, baseline measurements are defined as the values collected predose on the day of the switch to MK-1439A for each subject. In the rare event when data for this visit are missing, the value obtained at the most recent screening visit (Immediate Switch Group) or Week 4 (Deferred Switch Group) will be used as baseline. This rule will also be applied to define the baseline measurements for other laboratory tests.

Protocol-Defined Virologic Failure (PDVF)

Subjects with protocol-defined virologic failure (PDVF) as defined in Section 4.2.3.2 will be identified and summarized for each treatment group.

8.4.3 Safety Endpoints

Section 4.2.3.3 provides an initial description of safety measures.

All accumulated safety data through 14 days following the end of treatment will be included in the analysis of safety with the exception of the summary of safety data limited to the double-blind period of the study through the Week 12 visit. Because some safety data will be collected in an open-label manner post-switch these data should be interpreted with caution.

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 discontinued study therapy due to an adverse experience. The percentage of subjects with specific adverse experiences by system organ class will also be summarized.

Laboratory Parameters

The mean (SD) for the change from baseline in laboratory tests including the change from baseline in fasting lipids (LDL-C, non-HDL-C, total cholesterol, HDL-C, and triglycerides) will be summarized.

Pre-defined Limits of Change in Laboratory Parameters

Subjects must have both a baseline and post-randomization on-treatment measurement to be included in the summaries of laboratory tests. 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 (ie, more abnormal in the direction of interest) than at baseline. The PDLC grading 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 12.6). A listing of the subjects who meet the PDLC grading criteria will be provided.

8.5 Analysis Populations

8.5.1 Efficacy and CNS Toxicity Questionnaire Analysis Populations

The Full Analysis Set (FAS) population will serve as the primary population for the analysis of efficacy and the CNS toxicity questionnaire data in this study. The FAS population consists of all randomized subjects who:

- receive at least one dose of study treatment,
- have baseline data for those analyses that require baseline data.

Subjects will be included in the treatment group to which they are randomized for the analysis of efficacy and CNS toxicity data using the FAS population. Details on the approach to handling missing data are provided in Section 8.6 Statistical Methods.

Additionally, for the primary CNS endpoint a per-protocol population will be used which excludes subjects who discontinue prior to Week 12.

8.5.2 Safety Analysis Populations

The All Subjects as Treated (ASaT) population will be used for the analysis of safety data in this study. The ASaT population consists of all randomized subjects who received at least one dose of study treatment. Subjects will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the ASaT population. For most subjects this will be the treatment group to which they are randomized. Subjects who take incorrect study treatment for the entire treatment period will be included in the treatment group corresponding to the study treatment actually received. Otherwise, subjects will be included in their randomized treatment groups.

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

Statistical testing and inference for safety analyses are described in Section 8.6.3.

Unless otherwise stated, all statistical tests will be conducted at the α=0.025 (1-sided) level.

Time Window

Table 9 and Table 10 list the time windows and the target days for the scheduled visits in the study that will be used for all analyses. The measurement closest to the target date within a window will be used for analyses at a specific time point.

Table 9 Definition of Study Time Point – Immediate Switch Group

Treatment Phase	Treatment Period	Protocol Time Point	Day-Range Rules[1]	Target Day Post Switch	CSR Time Post Switch[2]
Pre-treatment	Baseline	Day 1 (Baseline)	≤1	1	Day 1
Treatment	Double-Blind	Week 4	>1 and ≤56	29	Week 4
		Week 12	≥57 and ≤last day of double-blind treatment period	85	Week 12
	Open-Label	Week 16	≥first day of open label treatment and ≤140	113	Week 16
		Week 24	≥141 and ≤ reported Week 24 visit date for subject completed Week 24 visit or last day of treatment period for subject discontinued before having Week 24 visit	169	Week 24
Treatment	Extension 1	Week 40	≥first day after reported Week 24 visit date and ≤337	281	Week 40
		Week 56	≥338 and ≤448	393	Week 56
		Week 72	≥449 and ≤561	505	Week 72
		Week 88	≥562 and ≤672	617	Week 88
		Week 104	≥673 and ≤789	729	Week 104
		Week 120	≥790 and ≤last day of Extension 1 treatment period	841	Week 120

[1] Relative days are counted from the first day of study medication at randomization.

[2] The clinical study report (CSR) time post-switch is the time label to be used in the post-switch analysis tables. Relative days are counted from the day of switch.

Note, PK only visits are not included (ie, Weeks 1, 2, and 3).

Table 10 Definition of Study Time Point – Deferred Switch Group

Treatment Phase	Treatment Period	Protocol Time Point	Day-Range Rules[1]	Target Day	Day-Range Rules Post Switch	Target Day Post Switch	CSR Time Post Switch[2]
Pre-treatment	Baseline	Day 1 (Baseline)	≤1	1			
Treatment	Double-Blind	Week 4	>1 and ≤56	29			
		Week 12	≥57 and ≤ last day of double-blind treatment period	85	≤1	1	Day 1
	Open-Label	Week 16			>1 and ≤56	29	Week 4
		Week 24			>57 and ≤126	85	Week 12
		Week 36			>127 and ≤ reported Week 36 visit date for subject completed Week 36 visit or last day of treatment period for subject discontinued before having Week 36 visit	169	Week 24
Treatment	Extension 1	Week 52			≥ first day after reported Week 36 visit date and ≤337	281	Week 40
		Week 68			≥338 and ≤448	393	Week 56
		Week 84			≥449 and ≤561	505	Week 72
		Week 100			≥562 and ≤672	617	Week 88
		Week 116			≥673 and ≤789	729	Week 104
		Week 132			≥790 and ≤ last day of study extension 1 treatment period	841	Week 120

[1] Relative days are counted from the first day of study medication at randomization.
[2] The clinical study report (CSR) time post-switch is the time label to be used in the post-switch analysis tables. Relative days are counted from the day of switch.
Note, PK only visits are not included (ie, Weeks 1, 2, and 3).

8.6.1 Statistical Methods for Subject-Reported Outcomes for CNS Toxicity

CNS Toxicity Questionnaire

Missing Data

All missing post-baseline data will be assigned the intensity score for the same item from the closest prior visit with non-missing data. For example, for a given questionnaire item, the

Week 4 data would be used at Week 12 if a subject's information at Week 12 was incomplete or completely missing.

All subjects who discontinue will be asked to complete the CNS toxicity questionnaire at the discontinuation visit. These data, which are potentially informative, would also be used to impute missing data.

An analysis of the per-protocol population will be performed as a sensitivity analysis which excludes subjects who discontinue prior to Week 12. No data will be carried forward for this analysis, and only those subjects who have completed the Week 12 CNS toxicity questionnaire will be included.

Methods of Analysis

Proportion of subjects with ≥1 CNS Toxicity of at least Grade 2 Intensity at Study Week 4 and Study Week 12 (Primary Endpoint)

The treatment difference and the associated 95% confidence interval will be calculated for the proportion of subjects with at least 1 CNS toxicity of at least Grade 2 intensity at Study Week 12 using the Miettinen and Nurminen's method (1985) [17], an unconditional, asymptotic method, and p-values based on this method will be provided. The immediate switch group will be considered to have a statistically significantly smaller proportion of subjects with at least one CNS toxicity of at least Grade 2 intensity at Week 12 if the upper bound of the 95% confidence interval for the treatment difference (immediate – deferred) is less than 0. Data from Study Week 4 will be summarized in a similar manner with no inferential test of hypothesis.

Change from baseline in CNS Toxicity Score

The mean and standard deviation (SD) for the change from baseline in CNS toxicity score will be summarized by treatment group at Study Weeks 4 and 12 (primary interest). The difference in mean scores between treatment groups and the associated 95% CI based on a t-distribution will be summarized at Study Weeks 4 and 12. The median change from baseline and interquartile range will also be provided.

Table 11 summarizes the key CNS toxicity questionnaire analyses.

Table 11 Analysis Strategy for CNS Toxicity Questionnaire Variables

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach	Statistical Method	Analysis Population	Missing Data Approach
Primary Objective				
The proportion of subjects with at least one CNS toxicity of at least Grade 2 intensity at Week 12.	Primary	Miettinen and Nurminen's method: 95% CI and associated p-value	FAS	Last observation carried forward
The proportion of subjects with at least one CNS toxicity of at least Grade 2 intensity at Week 12.	Supportive	Miettinen and Nurminen's method: 95% CI	Per-protocol	Data as observed
Secondary Objectives				
Proportion of subjects with at least one CNS toxicity of at least Grade 2 intensity at Week 4	Primary	Miettinen and Nurminen's method: 95% CI	FAS	Last observation carried forward
Change from baseline in the proportion of subjects with at least one CNS toxicity of at least Grade 2 intensity at 24 weeks post-switch	Primary	Descriptive Statistics	FAS	Last observation carried forward
Change from baseline in CNS toxicity score at Weeks 4 and 12	Primary	Descriptive Statistics 95% CI based on a t-distribution	FAS	Last observation carried forward
Change from baseline in CNS toxicity score at 24 weeks post-switch	Primary	Descriptive Statistics 95% CI based on a t-distribution	FAS	Last observation carried forward

8.6.2 Statistical Methods for Efficacy Analyses

Missing Data

Missing HIV-1 RNA Data

The Non-Completer=Failure (NC=F) approach as defined by the FDA "snapshot" approach will be used to handle missing HIV-1 RNA data. 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 9 and Table 10, and 3) subject has the measurement closest to the target date of the time point <50 copies/mL. Subjects with an HIV-1 RNA measurement ≥50 copies/mL or no virologic data within the time window due to intermittent missing data or premature discontinuation (regardless of the reason) will be considered failures in the analyses of the proportion of subjects maintaining HIV-1 RNA <50 copies/mL at that time point. The proportion of subjects maintaining HIV-1 RNA <40 copies/mL will be summarized in a similar fashion.

Missing CD4 Cell Count Data

The observed failure (OF) approach will be used for the analysis of the 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. Otherwise, subjects with missing data are excluded.

Methods of Analysis

Proportion of Subjects Maintaining HIV-1 RNA <50 copies/mL and <40 copies/mL

The proportion of subjects maintaining HIV-1 RNA < 50 copies/mL and <40 copies/mL will be summarized at each time point post-switch, with a primary interest at 24 weeks post-switch. At each time point, the 95% confidence interval for the proportion will be calculated using the exact binomial method proposed by Clopper and Pearson (1934) [18]. Subjects who discontinue prior to switching to MK-1439A in the deferred switch group will be excluded from this analysis.

The NC=F approach as defined by FDA "snapshot" approach will be used as the primary approach to analysis with respect to the proportion of subjects with virologic response (HIV-1 RNA <50 copies/mL). All subjects with missing data at the time point of interest will be treated as failures regardless of the reason for the missing data.

To provide a full picture of the virologic outcome at a given time point, subjects who are not classified as a virologic success will be further categorized as a virologic failure (HIV-1 RNA ≥50 copies/mL or ≥40 copies/mL depending on the endpoint) or as having no virologic data in the time window for reasons of 1) discontinuation from the study due to an AE, 2) discontinuation from the study for other reasons (includes withdrawal of consent, loss to follow-up, relocation, etc.), or 3) on study but missing data in the window. The full categorization of virologic outcome at 24 weeks post-switch will be summarized.

Change from Baseline in CD4 cell count

The change from baseline in CD4 cell counts will be summarized in the combined treatment groups at each time point post-switch at which the CD4 cell count is collected with a key interest at 24 weeks post-switch. The OF approach will be used for the analyses of the change from baseline in CD4 cell count. Subjects who discontinue prior to switching to MK-1439A in the deferred switch group will be excluded from this analysis.

Protocol-Defined Virologic Failure (PDVF)

The number of subjects with protocol-defined virologic failure will be summarized.

Table 12 summarizes the key efficacy analyses.

Table 12 Analysis Strategy for Key Efficacy Variables

Endpoint/Variable (Description, Time Point)	Statistical Method	Analysis Population	Missing Data Approach
Secondary Objectives			
Proportion of Subjects Achieving HIV-1 RNA <50 copies/mL at 24 weeks post switch Proportion of Subjects Achieving HIV-1 RNA <40 copies/mL at 24 weeks post switch	Descriptive statistics	FAS	NC=F
Change from Baseline in CD4 cell count at 24 weeks post switch	Descriptive statistics	FAS	OF

The strategy to address multiplicity issues with regard to multiple treatment comparisons, multiple endpoints, multiple timepoints, and/or interim analyses is described in Section 8.7, Interim Analyses and in Section 8.8, Multiplicity.

8.6.3 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. Note that the data collected from the CNS toxicity questionnaire is not included as part of the safety analyses.

Safety data through Week 12 and through 24 weeks post-switch will be summarized separately. The treatment groups will be combined for the analysis of safety post-switch as both groups will receive the same treatment. All accumulated safety data through 14 days following the end of treatment will be included in the analyses of post-switch safety data. Key timepoints of interest are Week 12 (comparing treatment groups) and 24 weeks post-switch (combining treatment groups).

The analysis of safety results will follow a tiered approach as summarized in Table 13. The tiers differ with respect to the analyses that will be performed. Safety parameters or adverse experiences of special interest that are identified *a priori* constitute “Tier 1” safety endpoints that will be subject to inferential testing for statistical significance with p-values and 95% confidence intervals provided for between-group comparisons. Other safety parameters will be considered Tier 2 or Tier 3. Tier 2 parameters will be assessed via point estimates with 95% confidence intervals provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters.

Adverse experiences (specific terms as well as system organ class terms) and pre-defined limits of change in laboratory parameters that are not pre-specified as Tier-1 endpoints will be classified as belonging to "Tier 2" or "Tier 3", based on the number of events observed. Membership in Tier 2 requires that at least 4 subjects in any treatment group exhibit the event; all other adverse experiences and pre-defined limits of change will belong to Tier 3.

The threshold of at least 4 events was chosen because the 95% confidence interval for the between-group difference in percent incidence will always include zero when treatment

groups of equal size each have less than 4 events and thus would add little to the interpretation of potentially meaningful differences. Because many 95% confidence intervals may be provided without adjustment for multiplicity, the confidence intervals should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in adverse experiences and pre-defined limits of change.

Continuous measures such as changes from baseline in laboratory and vital signs parameters that are not pre-specified as Tier-1 endpoints will be considered Tier 3 safety parameters. Summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group in table format.

For this protocol, there are no Tier 1 events.

The change from baseline in fasting lipids will be analyzed using ANCOVA models adjusted by baseline lipid level and treatment group (pre-switch period only). The treatment differences and 95% confidence intervals will be provided for all lipid parameters. The missing lipid data will be handled by the following principle: For subjects who have missing lipid data, the last lipid observation after randomization will be carried forward. For subjects who modify (start, stop, increase or decrease dosage) lipid-lowering therapy use during the study, the last lipid observation before modifying the lipid-lowering therapy use will be carried forward for later time points.

The percentages of subjects who modify lipid-lowering therapy during the study will be summarized by treatment group in the pre-switch period and overall in the post-switch period. In the pre-switch period, the difference in percentages between treatment groups and the associated 95% confidence interval will be calculated using Miettinen and Nurminen's method.

In addition, the broad clinical and laboratory AE categories consisting of the percentage of subjects with any AE, with a drug-related AE, with a serious AE, with an AE which is both drug-related and serious, and who discontinued due to an AE will be considered Tier 2 endpoints. The 95% confidence intervals will be provided for between-treatment differences in the percentage of subjects with events; these analyses will be performed using the Miettinen and Nurminen's method and restricted to the comparative Week 12 safety analyses.

Table 13 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint†	p-Value	95% CI for Treatment Comparison‡‡	Descriptive Statistics
Tier 1	None			
Tier 2	Change from baseline in fasting lipids Starting lipid-lowering therapy Any AE Any Serious AE Any Drug-Related AE Any Serious and Drug-Related AE Discontinuation due to AE Specific AEs, SOCs, or PDLCs‡ (incidence ≥4 of subjects in one of the treatment groups‡‡)		X	X
Tier 3	Specific AEs, SOCs or PDLCs‡ (incidence <4 of subjects in all of the treatment groups‡‡) Change from Baseline Results (Labs, Vital Signs)			X

† Adverse Experience references refer to both Clinical and Laboratory AEs.
‡ Includes only those endpoints not pre-specified as Tier 1 and not already pre-specified as Tier-2 endpoints.
‡‡ Only for the Week 12 safety analysis.
Note: SOC=System Organ Class; PDLC=Pre-Defined Limit of Change; X = results will be provided.

8.6.4 Statistical Methods for Exploratory Endpoints

Other Subject-Report Outcomes and Neurocognitive Assessment

The analyses of the change from baseline (the day of the switch to MK-1439A) in sleep quality, neurocognitive function, anxiety and depression and health-related quality of life will be described in a separate statistical analysis plan.

8.6.5 Summaries of Baseline Characteristics, Demographics, and Other Analyses

8.6.5.1 Demographic and Baseline Characteristics

Baseline characteristics for all allocated and treated subjects will be summarized by treatment group and overall. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of subjects screened and allocated along with the primary reasons for screen failure and the primary reasons for discontinuation will be displayed. Demographic variables (e.g., age, gender and race), primary and secondary diagnoses, and prior and concomitant therapies will be summarized either by descriptive statistics or categorical tables. Summary statistics for baseline efficacy and CNS toxicity questionnaire measures will also be provided.

8.6.5.2 PK Analyses

Plasma concentrations of MK-1439 and efavirenz will be summarized.

8.7 Interim Analyses

There are no interim analyses planned for this study.

8.8 Multiplicity

No multiplicity adjustment is planned as there is a single comparison of 2 treatments using 1 endpoint in the primary hypothesis. Other analyses will be considered supportive and/or explanatory.

8.9 Sample Size and Power Calculations

8.9.1 Sample Size and Power for Primary Analysis to address the Primary Hypothesis

This study will randomize 42 subjects into the Immediate Switch Group and 42 into the Deferred Switch Group and has 80% power to demonstrate the superiority of an immediate switch to MK-1439A over continuation of ATRIPLA™ with respect to the proportion of subjects with a Grade 2 or worse CNS toxicity at Week 12 at an overall one-sided, 2.5% alpha-level, if the underlying treatment difference in the proportion of subjects with at least one Grade 2 or worse CNS toxicity at Week 12 is -24.5% (immediate switch – deferred switch) and the assumed proportion of subjects with at least one CNS toxicity of at least Grade 2 intensity at Week 12 is 67% in the Immediate Switch Group. These assumptions are based on a similarly designed study of a switch from ATRIPLA™ to an etravirine-based regimen that had the same primary endpoint [3]. The power calculation is based on an asymptotic method proposed by Farrington and Manning (1990) [19] and is carried out using SAS v9.3. The immediate switch group will be considered to have a statistically significantly smaller proportion of subjects with at least one CNS toxicity of at least Grade 2 intensity at Week 12 if the upper bound of the 95% confidence interval for the treatment difference (immediate – deferred) is less than 0. Given the assumed 67% event rate in the immediate switch group, this may occur when the observed difference between treatment groups is approximately -16.5% or smaller. Table 14 summarizes the power for the primary comparison under various assumptions for the deferred switch group proportion and underlying difference in proportions.

Table 14 Power (%) Under Various Assumptions (With 42 Subjects Randomized in Each Treatment Group)

Percentage of subjects with a CNS toxicity (Grade 2 to higher) at Week 12 in the Deferred Switch Group	Underlying Difference in Percentage of Subjects with a CNS toxicity (Grade 2 or higher) at Week 12 (Immediate Switch – Deferred Switch)		
	-24.5	-20	-16.5
85%	72	56	43
91.5%	**80**	66	53
95%	86	74	61
Note: The power calculation assumes 42 subjects will be included in the analysis for each treatment group.			

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 57% chance of observing at least one adverse experience among the 84 subjects in this study (both treatment groups combined). If no adverse experience of that type is observed among the 84 subjects, this study will provide 95% confidence that the underlying percentage of subjects with that particular adverse experience is 4.3%.

The estimate of, and the upper bound of the 95% confidence interval for, the underlying percentage of subjects with an AE given various hypothetical observed numbers of subjects with the AE are provided in Table 15 . These calculations are based on the exact binomial method proposed by Clopper and Pearson (1934) [18].

Table 15 Estimate of Incidence of AEs and 95% Upper Confidence Bound Based on Hypothetical Numbers of Subjects With AEs Among 84 Subjects Randomized

Hypothetical Number of Subjects With An Adverse Event		Estimate of Incidence	95% Upper Confidence Bound†
0		0%	4.3%
1		1.2%	6.5%
2		2.4%	8.3%
3		3.6%	10.1%
4		4.8%	11.8%
5		6.0%	13.4%
6		7.1%	14.9%
7		8.3%	16.4%
8		9.5%	17.9%
9		10.7%	19.4%
10		11.9%	20.8%

8.10 Subgroup Analyses and Effect of Baseline Factors

To characterize the CNS toxicity profile across various subgroups, the primary endpoint will be summarized by treatment group and plotted within each category of the following classification variables:

- Age category (≤median vs. >median)
- Gender (female, male)
- Race (White, Black, Asian, Other)
- Baseline CD4 categories (<50, 50-200, and >200 cells/mm^3)

8.11 Compliance (Medication Adherence)

Study Medication Diary Cards will be used to document drug compliance in the base study and study extension 1.

Subjects are to take one tablet from Bottle A and one tablet from Bottle B once daily during the double-blind portion of the trial and one tablet from Bottle C once daily in the open-label phase. 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 one tablet from both Bottle A and Bottle B during the double-blind phase and a single MK-1439A tablet during the open-label phase of the trial.

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 the percent compliance in the FAS population. Compliance will be summarized for the double-blind phase through Week 12 by treatment group. In addition, compliance will be summarized using all data post-switch, pooling the 2 treatment groups.

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

Compliance data will not be collected and analyzed for study extension 2 or study extension 3.

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.

Extent of exposure will be summarized for the double-blind phase through Study Week 12 by treatment group. In addition, extent of exposure will be summarized using all data post switch, pooling the 2 treatment groups.

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 16.

Table 16 Product Descriptions

Product Name & Potency	Dosage Form
MK-1439A (MK-1439 100mg / Lamivudine 300mg / Tenofovir Disoproxil Fumarate 300mg) or placebo to match MK-1439A (MK-1439 100mg / Lamivudine 300mg / Tenofovir Disoproxil Fumarate 300mg) (Bottle A)	Tablets
Efavirenz 600mg / Emtricitabine 200mg / Tenofovir Disoproxil Fumarate 300mg (Tenofovir Disoproxil Fumarate, which is equivalent to 245 mg of Tenofovir Disoproxil) (ATRIPLA™) or placebo to match Efavirenz 600mg / Emtricitabine 200mg / Tenofovir Disoproxil Fumarate 300mg (Tenofovir Disoproxil Fumarate, which is equivalent to 245 mg of Tenofovir Disoproxil) (ATRIPLA™) (Bottle B)	Tablets
MK-1439A (MK-1439 100mg / Lamivudine 300mg / Tenofovir Disoproxil Fumarate 300mg) (Bottle C)	Tablets

All placebos were created by the Sponsor to match the active product.

9.2 Packaging and Labeling Information

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

Subjects will receive both blinded (Bottle A and B) and open label (Bottle C) bottles in accordance with the dispensing schedule. No kitting is required.

9.3 Clinical Supplies Disclosure

The emergency unblinding call center will use the treatment/randomization schedule for the trial to unblind subjects and to unmask treatment identity. The emergency unblinding call center should only be used in cases of emergency (see Section 7.1.4.2). In the event that the emergency unblinding call center is not available for a given site in this trial, the central electronic treatment allocation/randomization system (IVRS/IWRS) should be used in order

to unblind subjects and to unmask treatment/vaccine identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

After Week 12 / Visit 7 the trial is open-label; therefore, the subject, the trial site personnel, the Sponsor and/or designee are not blinded to the new treatment type from this point forward. Treatment (name, strength or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

Treatment identification information prior to study Week 16 is to be unmasked ONLY if necessary for the welfare of the subject. Every effort should be made not to unblind the subject unless necessary.

In the event that unblinding prior to study Week 16 has occurred, the circumstances around the unblinding (eg, date, reason and person performing the unblinding) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible. Once an emergency unblinding has taken place, the principal investigator, site personnel, and Sponsor personnel may be unblinded so that the appropriate follow-up medical care can be provided to the subject.

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.

At the close of the trial after unblinding, a letter is to be sent by the investigator to those subjects who received placebos in the image of the competitor's product to provide the following advice:

"You have participated in a trial conducted by the Sponsor. This is to advise you that you were among those who received a look-alike tablet created by the Sponsor to resemble the drug ATRIPLA™ (Efavirenz 600mg / Emtricitabine 200mg / Tenofovir Disoproxil Fumarate 300mg) as much as possible. You did not receive the active drug ATRIPLA™ (Efavirenz 600mg / Emtricitabine 200mg / Tenofovir Disoproxil Fumarate 300mg) as manufactured by Gilead Sciences."

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 or through a secure password-protected electronic portal 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 MSD, is provided in Section 12.1 - 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, MSD, 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. MSD, as Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. MSD 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. MSD 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.

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12.0 APPENDICES

12.1 Code of Conduct for Clinical Trials

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD)
Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, 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 participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (including all applicable data protection laws and regulations), and International Council for Harmonisation Good Clinical Practice (ICH-GCP), and also in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Highest ethical and scientific standards shall be endorsed for all clinical interventional investigations sponsored by MSD 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 that are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials, which are not under the full control of MSD.

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 MSD or comparator products. Alternatively, MSD may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine patient preferences, etc.

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial and shall respect the data protection rights of all participants, trial site staff and, where applicable, third parties. All trial protocols are and will be assessed for the need and capability to enroll underrepresented groups. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD's clinical trials are conducted globally in many different countries and in diverse populations, including people of varying age, race, ethnicity, gender, and accounting for other potential disease related factors. MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel (or individuals acting on behalf of MSD) to assess the ability to successfully conduct the trial.

Where appropriate, and in accordance with regulatory authority guidance, MSD will make concerted efforts to raise awareness of clinical trial opportunities in various communities. MSD will seek to engage underrepresented groups and those disproportionately impacted by the disease under study. MSD will support clinical trial investigators to enroll underrepresented groups and expand access to those who will ultimately use the products under investigation.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if potential fraud, scientific/research misconduct, privacy incidents/breaches or Clinical Trial-related Significant Quality Issues are reported, such matters are investigated. When necessary, appropriate corrective and/or preventative actions are defined and regulatory authorities and/or ethics review committees are notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish the primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the pre-specified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. 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 such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). 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. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

A. Regulatory Authority and Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

All protocols and protocol amendments will be submitted by MSD for regulatory authority acceptance/authorization prior to implementation of the trial or amendment, in compliance with local and/or national regulations.

The protocol, protocol amendment(s), informed consent form, investigator's brochure, and other relevant trial documents must be reviewed and approved by an IRB/IEC before being implemented at each site, in compliance with local and/or national regulations. Changes to the protocol that are required urgently to eliminate an immediate hazard and to protect participant safety may be enacted in anticipation of ethics committee approval. MSD will inform regulatory authorities of such new measures to protect participant safety, in compliance with local and/or national regulations.

B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants 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.

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Participants may withdraw from an MSD 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

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible, as well as all applicable data protection rights. Unless required by law, only the investigator, Sponsor (or individuals acting on behalf of MSD), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

Genomic research will only be conducted in accordance with a protocol and informed consent authorized by an ethics committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is MSD's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of MSD trials. MSD does not pay incentives to enroll participants in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

MSD does not pay for participant referrals. However, MSD may compensate referring physicians for time spent on chart review and medical evaluation to identify potentially eligible participants.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by MSD, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local ethics committee may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, all publications resulting from MSD trials will indicate MSD 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.

V. Investigator Commitment

Investigators will be expected to review MSD's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

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 Future Biomedical Research.

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

d. Future Biomedical Research Specimen 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 MSD 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 future biomedical research protocol and consent. 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@MSD.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@MSD.com.

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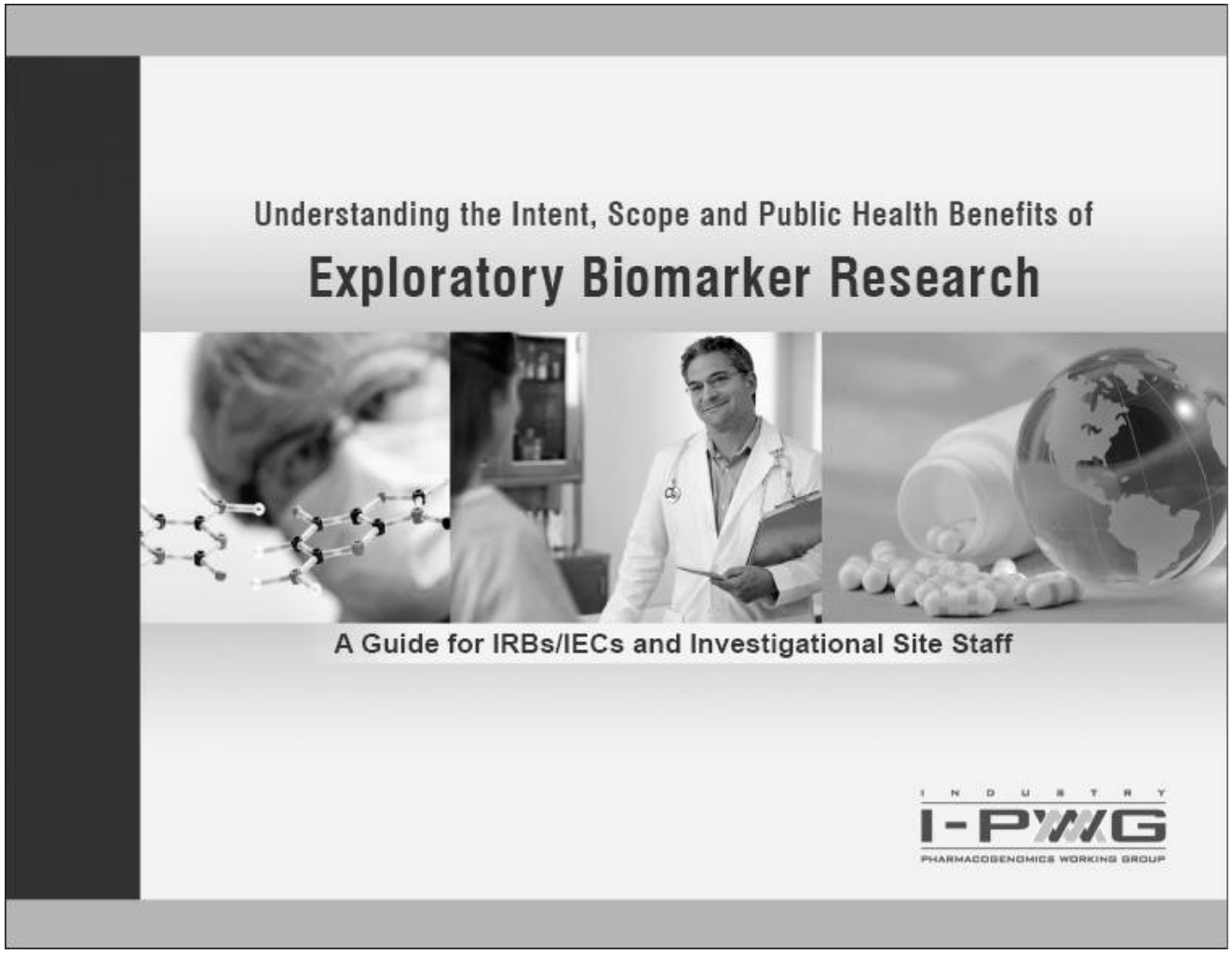
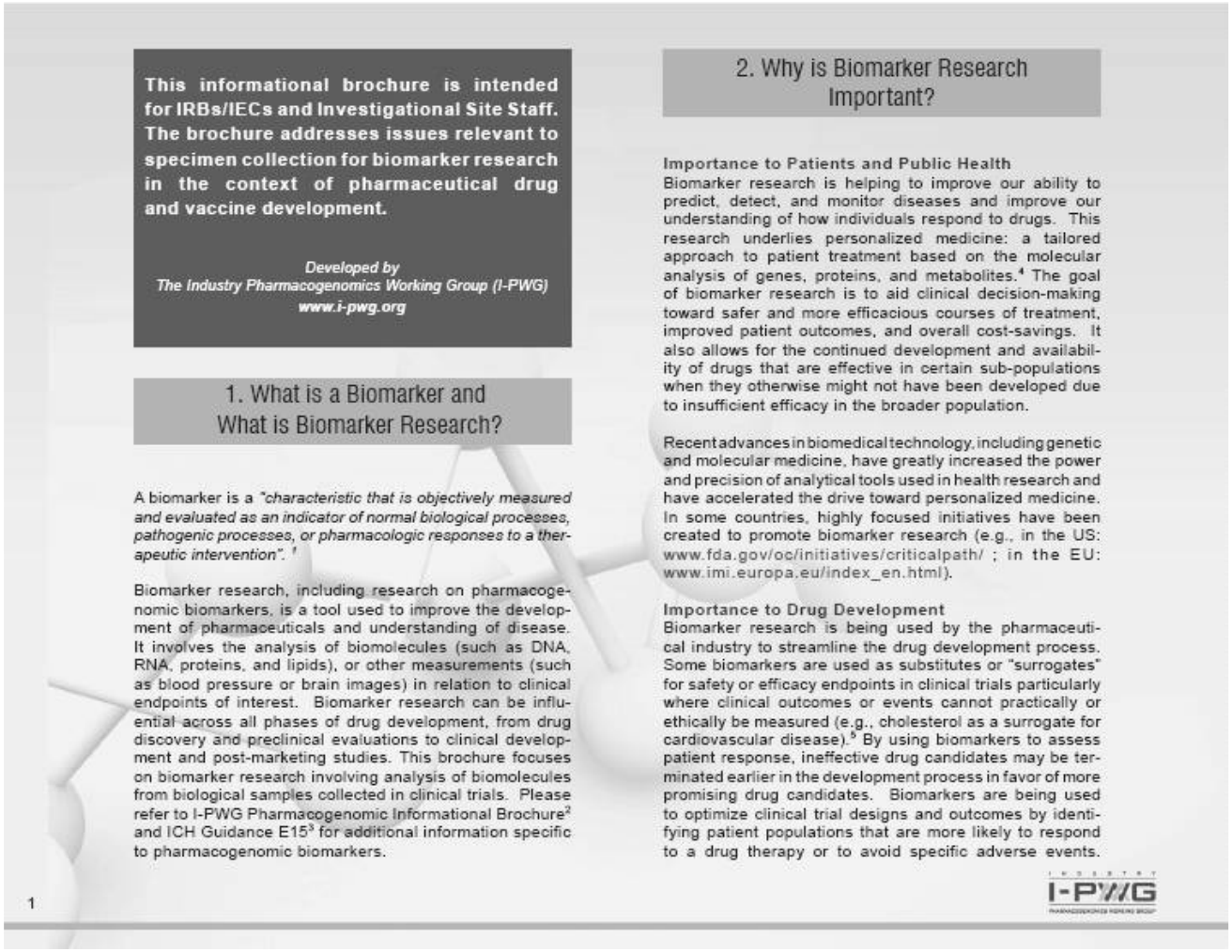
12.3 Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff





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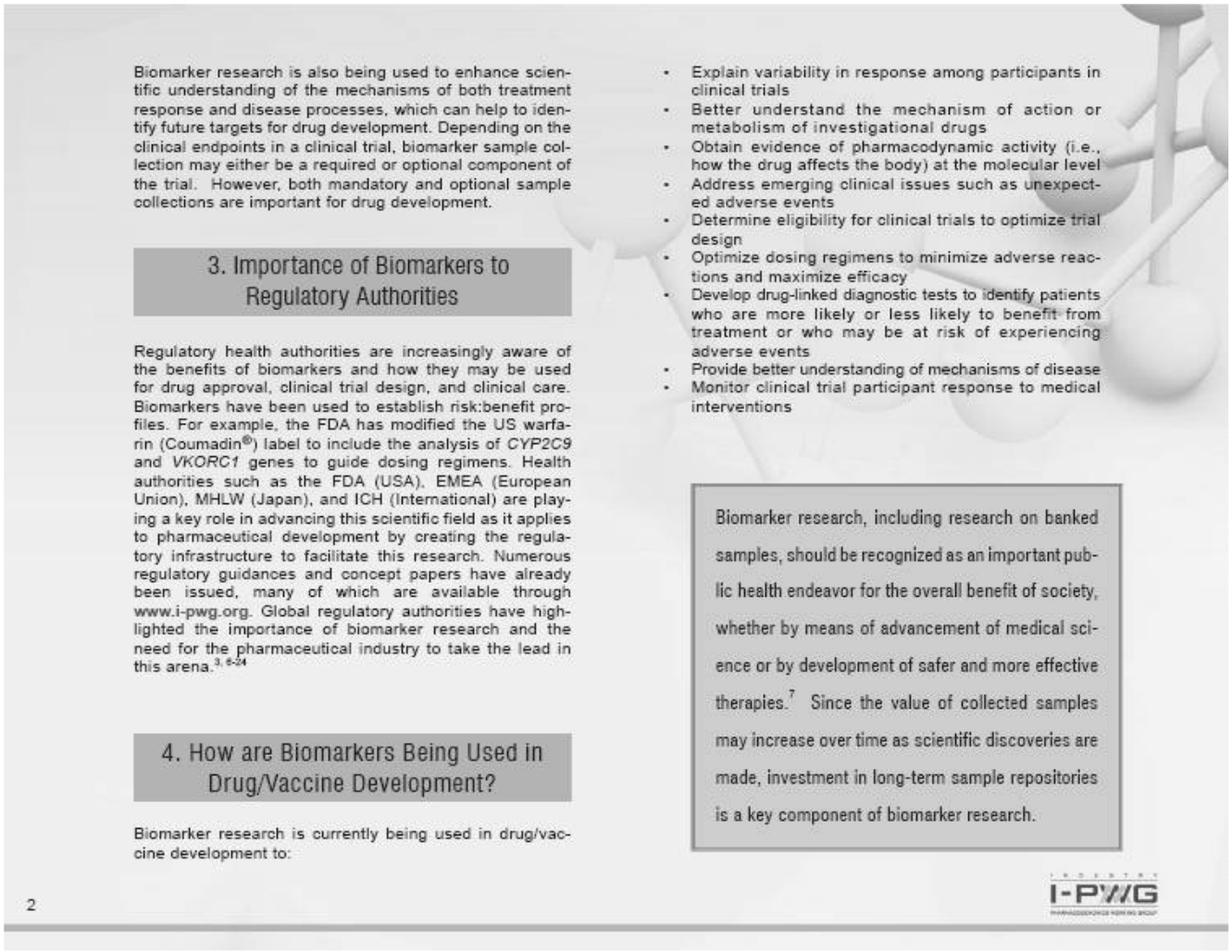
Biomarker research is also being used to enhance scientific understanding of the mechanisms of both treatment response and disease processes, which can help to identify future targets for drug development. Depending on the clinical endpoints in a clinical trial, biomarker sample collection may either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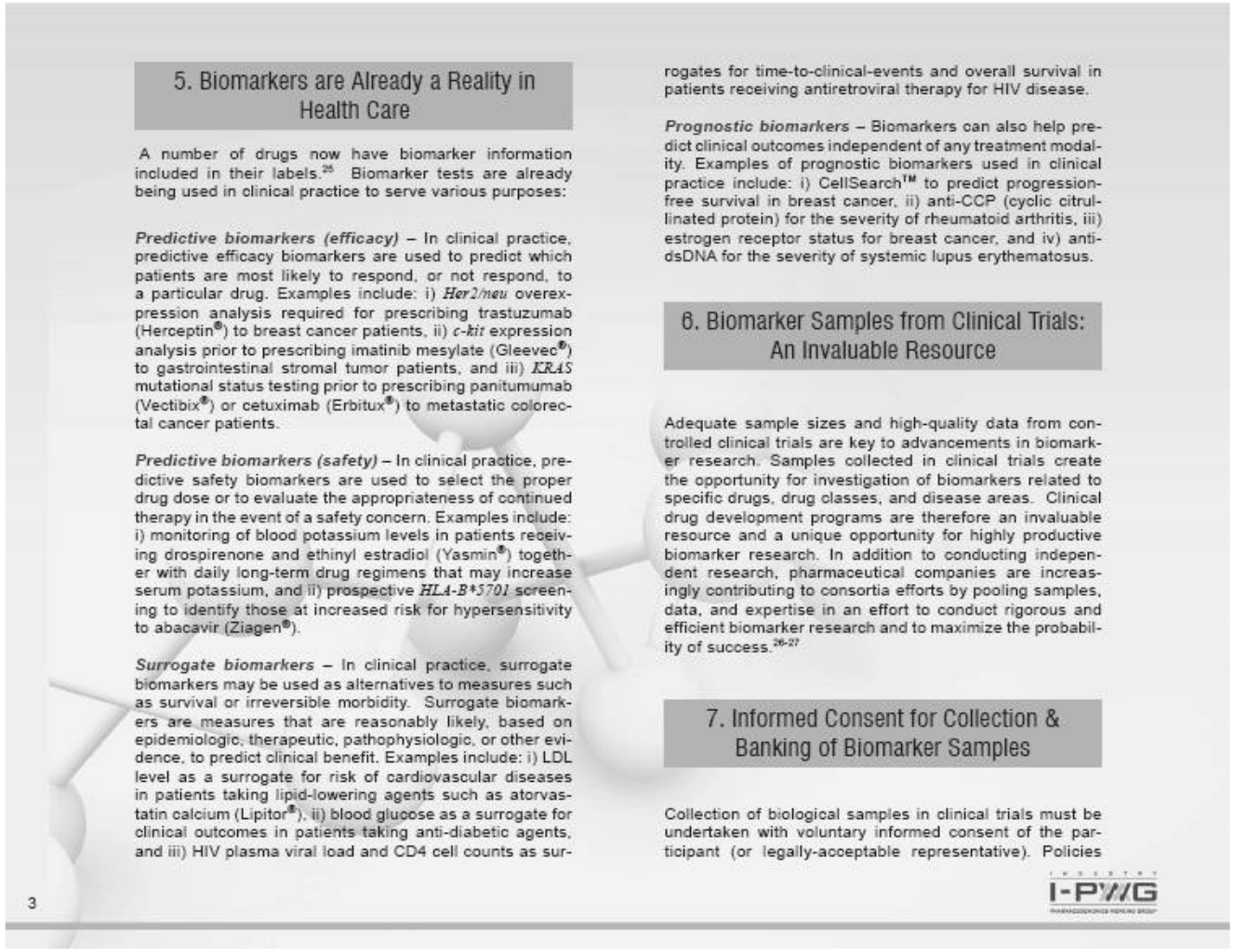

5. Biomarkers are Already a Reality in Health Care

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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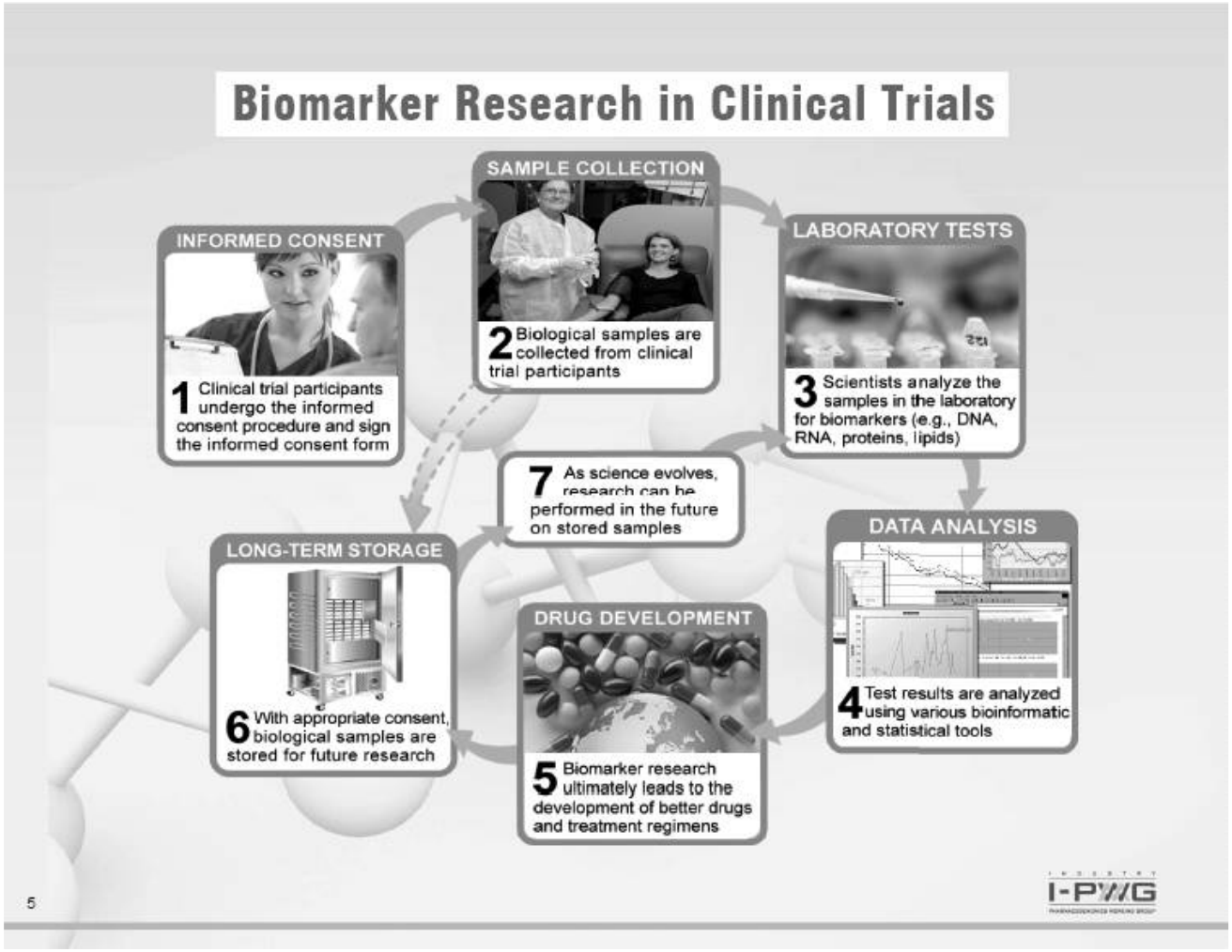
Biomarker Research in Clinical Trials
SAMPLE COLLECTION
2 Biological samples are collected from clinical trial participants
LABORATORY TESTS
3 Scientists analyze the samples in the laboratory for biomarkers (e.g., DNA, RNA, proteins, lipids)
INFORMED CONSENT
1 Clinical trial participants undergo the informed consent procedure and sign the informed consent form
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
5
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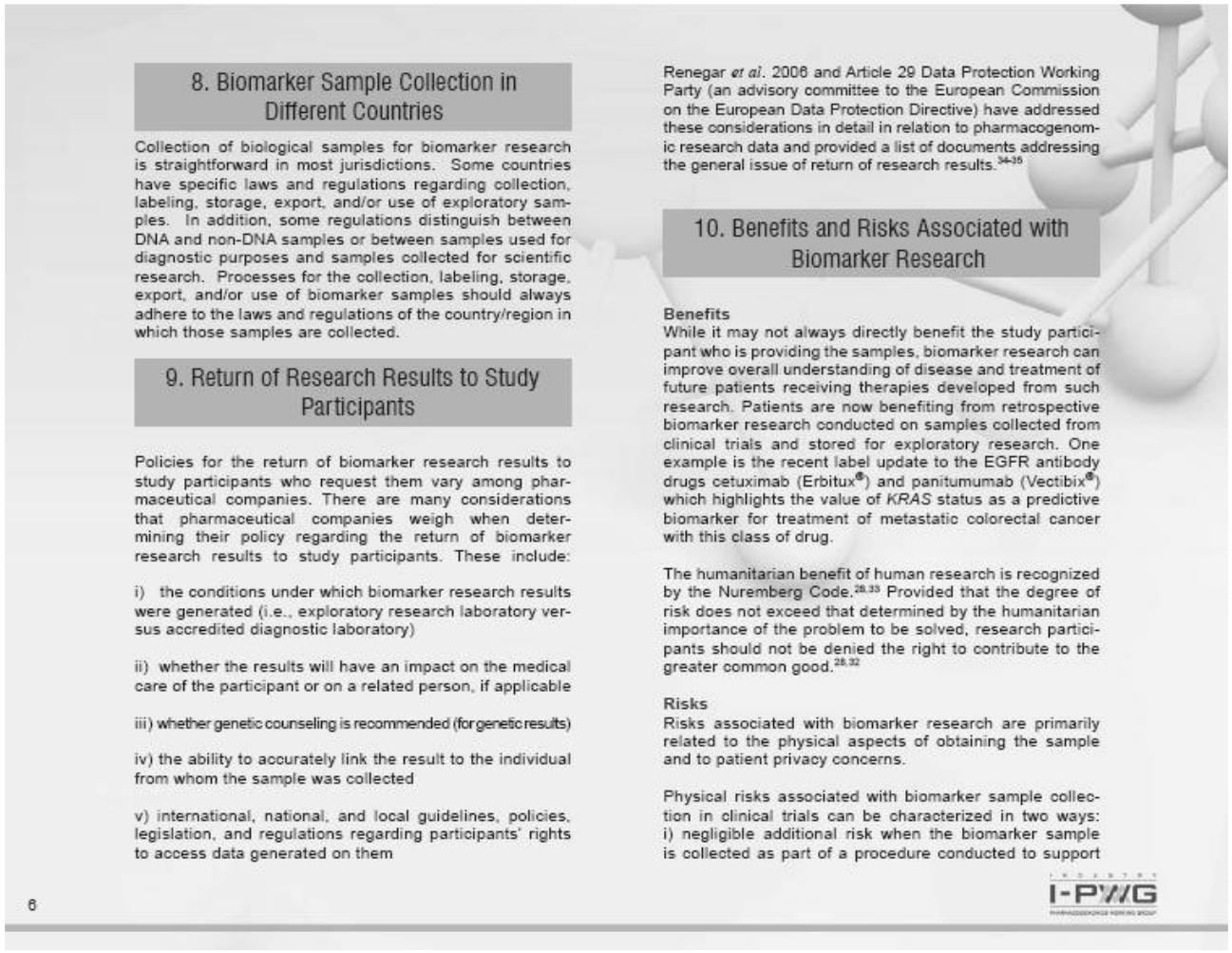

8. Biomarker Sample Collection in Different Countries

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*. 2006 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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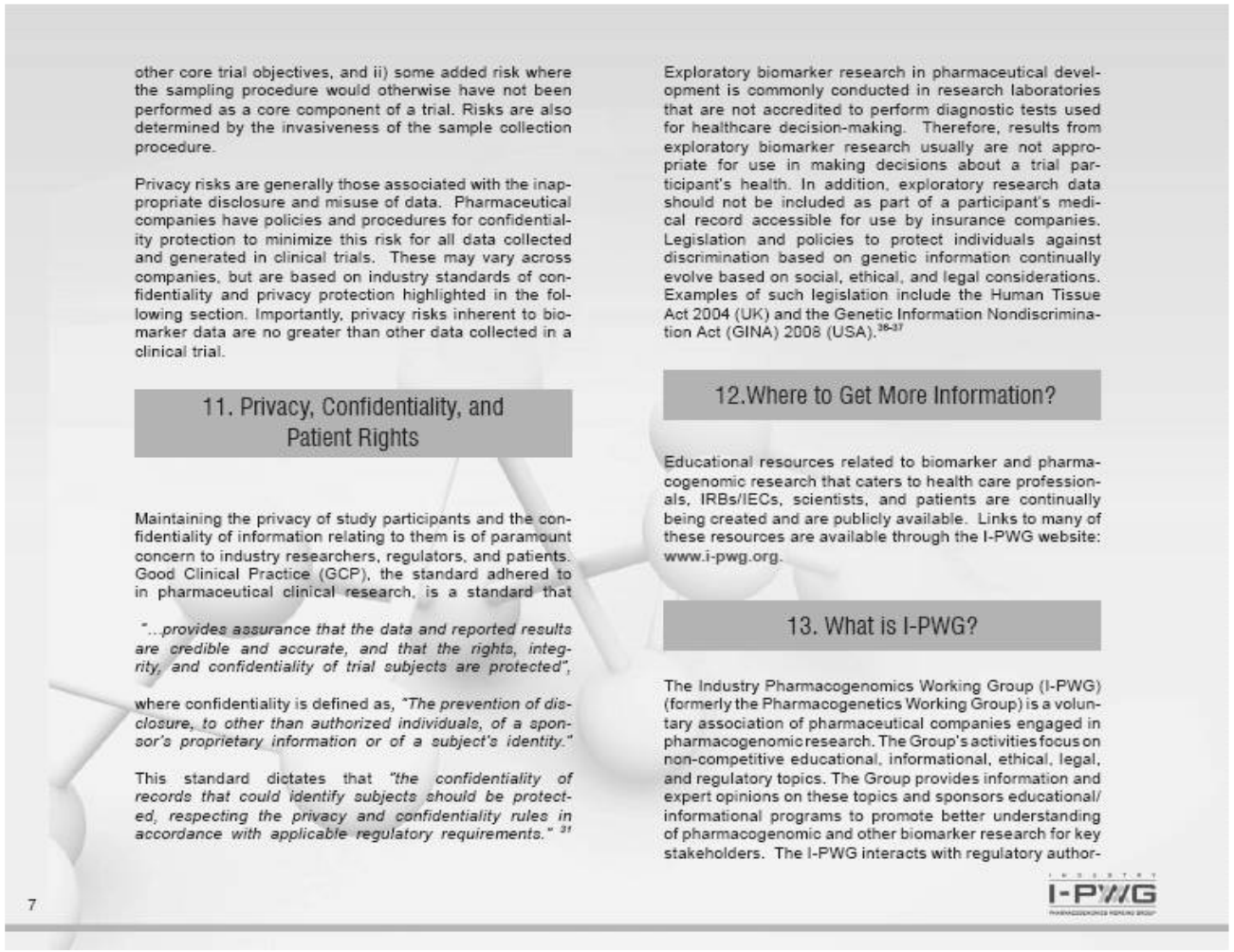

other core trial objectives, and ii) some added risk where the sampling procedure would otherwise have not been performed as a core component of a trial. Risks are also determined by the invasiveness of the sample collection procedure.

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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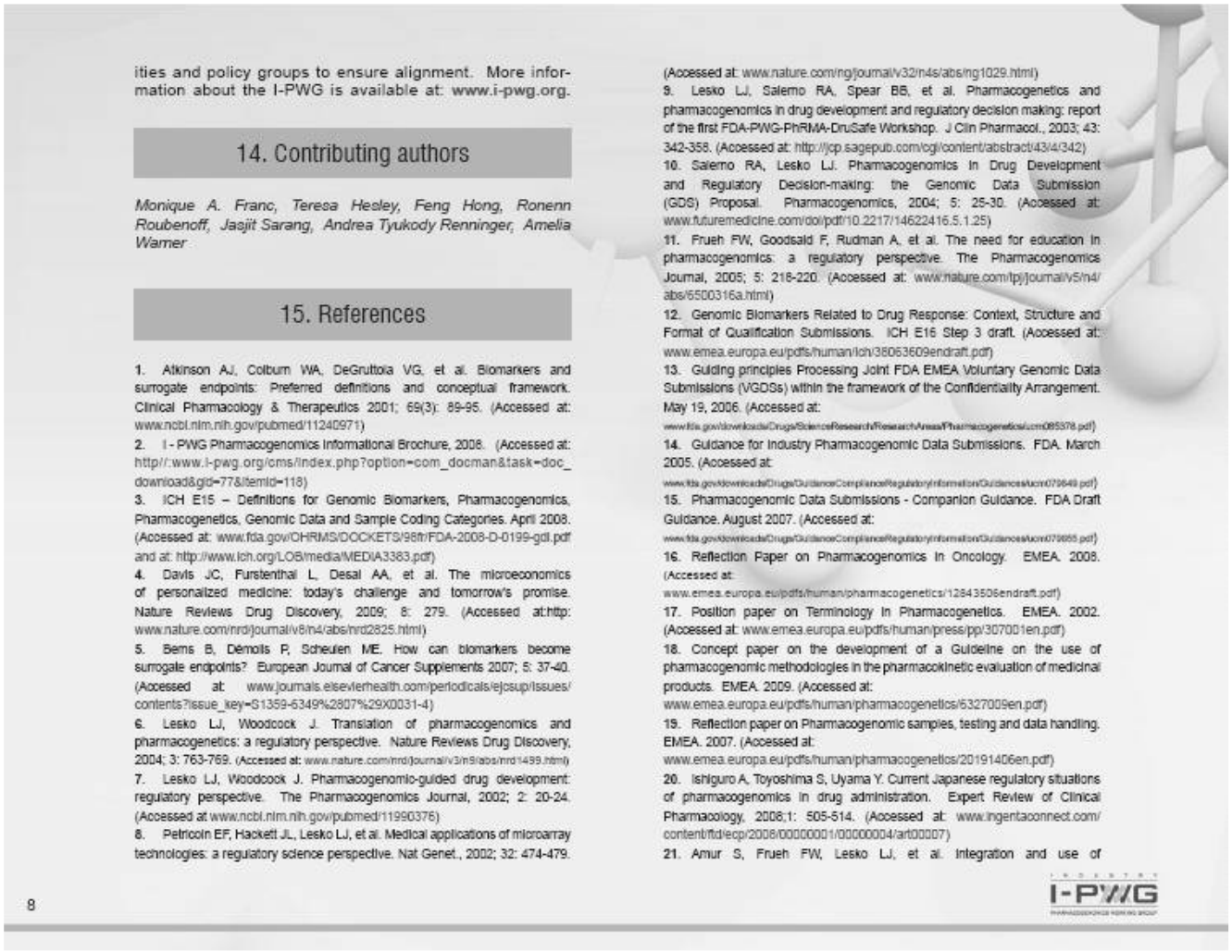

ities and policy groups to ensure alignment. More information about the I-PWG is available at: www.i-pwg.org.

14. Contributing authors

Monique A. Franc, Teresa Hesley, Feng Hong, Ronenn Roubenoff, Jasjit Sarang, Andrea Tyukody Renninger, Amelia Warner

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

Table A: Approximate Blood Volumes Drawn in Base Study: Screening Through Week 24 (ISG) or Week 36 (DSG) Plus 14 days Follow Up

Visit number/Title	1	2 Randomi-zation	3	4	5	6	7	8	9	10	U	U	99	Total Volume
TRIAL PROCEDURES	Screen-ing	Day 1 [a]	WK 1	WK 2	WK 3	WK 4	WK 12[a]	WK 16	WK 24[a]	WK 36 (DSG ONLY) [a]	Virologic Failure Confirm-ation	Early Discont-inuation	14-Day Follow-Up	
Immediate Switch Group (ISG) **Weeks Post Switch**		Day 1	WK 1	WK 2	WK 3	WK 4	WK 12	WK16	WK 24					
Deferred Switch Group (DSG) **Weeks Post Switch**		(-12 WKs)	(-11 WKs)	(-10 WKs)	(-9 WKs)	(-8 WKs)	Day 1	WK 4	WK 12	WK 24				
Laboratory Procedures/Assessments														
Hematology	2	2				2	2	2	2	2	2	2	2	20
Chemistry	29	7				7	7	7	7	7	7	7	7	92
Serum Pregnancy Test [b]														
HIV/Hepatitis Screen [c]														
Hemostatic Function Test [d]	4.5													4.5
HIV Viral RNA (Plasma)	10	10				10	10	10	10	10	10	10	10	100
CD4 Cell Count		2					2		2	2				8
Viral Resistance Test (Plasma)		14				14	14	14	14	14	14	14 [g]	14	112
Blood for Genetic Analysis		8.5												8.5
Plasma for Future Biomedical Research		10												10
MK1439 and EFV PK [e]		8	8	8	8	8								40
Expected Total (mL)	45.5	61.5	8	8	8	41	35	33	35	35	33	33	9	385
Total (tablespoons) [f]	~3.0	~4.1	~0.5	~0.5	~0.5	~2.7	~2.3	~2.2	~2.3	~2.3	~2.2	~2.2	~0.6	~25.7

a. Fasting required at these visits for lipid measurements.
b. For women of childbearing potential.
c. 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.
d. Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT) and International Normalized Ratio (INR).
e. Sample must be collected predose.

Visit number/Title	1	2 Randomi-zation	3	4	5	6	7	8	9	10	U	U	99	Total Volume
TRIAL PROCEDURES	Screen-ing	Day 1 [a]	WK 1	WK 2	WK 3	WK 4	WK 12[a]	WK 16	WK 24[a]	WK 36 (DSG ONLY) [a]	Virologic Failure Confirm-ation	Early Discont-inuation	14-Day Follow-Up	
Immediate Switch Group (ISG) **Weeks Post Switch**		Day 1	WK 1	WK 2	WK 3	WK 4	WK 12	WK16	WK 24					
Deferred Switch Group (DSG) **Weeks Post Switch**		(-12 WKs)	(-11 WKs)	(-10 WKs)	(-9 WKs)	(-8 WKs)	Day 1	WK 4	WK 12	WK 24				

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 does not need to be collected again at the discontinuation visit

Table B: Approximate Blood Volumes Drawn in Study Extension 1: Week 40 (ISG) or 52 (DCG) Through Week 120 (ISG) or 132 (DSG) Plus 14 Days Follow Up

							U	U	99	Total Volume
TRIAL PROCEDURES							Virologic Failure Confirm-ation	Early Discont-inuation	14-Day Follow-Up	
Immediate Switch Group (ISG): Study Week	WK 40	WK 56	WK 72	WK 88	WK 104	WK 120				
Deferred Switch Group (DSG): Study Week	WK 52	WK 68	WK 84	WK 100	WK 116	WK 132				
Laboratory Procedures/Assessments										
Hematology	2	2	2	2	2	2	2	2	2	18
Chemistry	7	7	7 [a]	7	7	7 [a]	7	7	7	63
HIV Viral RNA (Plasma)	10	10	10	10	10	10	10	10	10	90
CD4 Cell Count			2			2				4
Viral Resistance Test (Plasma)							14	14 [b]		28
Expected 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 discontinuation visit.
c. One tablespoon = 15 mL.

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12.6 DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS, PUBLISH DATE: AUGUST 2009 Version 1

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

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
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 – 1.13 mmol/L*	2.5 – 2.9 mg/dL *0.81 – 0.96 mmol/L*	1.5 – 2.4 mg/dL *0.48 – 0.80 mmol/L*	< 1.50 mg/dL < *0.48 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).				

12.7 List of Abbreviations and Acronyms

3TC	Lamivudine
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ALT	Serum Alanine Aminotransferase
ANCOVA	Analysis of covariance
APTT	Activated Partial Thromboplastin Time
ART	Antiretroviral Therapy
ASaT	All Subjects as Treated
AST	Serum Aspartate Aminotransferase
BLoQ	Below the Limit of Quantification
cART	Combination Antiretroviral Therapy
CBB	Cogstate Brief Battery
CCR5	Chemokine Receptor Type 5
CI	Confidence Interval; or (as in Section 10.3 only) Coordinating Investigator
Cl_{cr}	Creatinine Clearance
CNS	Central Nervous System
CSR	Clinical Study Report
CTCAE	Common Terminology for Adverse Events
CYP	Cytochrome
DAIDS	Division of Acquired Immunodeficiency Syndrome
DILI	Drug-induced Liver Injury
DNA	Deoxyribonucleic Acid
DSG	Deferred Switch Group
ECG	Electrocardiogram
ECI	Event of Clinical Interest
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture System
EFV	Efavirenz
EOC	Executive Oversight Committee
EQ-5D-5L	EuroQol Five Dimensional Descriptive System, Five Level Version
ERC	Ethical Review Committee
FAS	Full Analysis Set
FBR	Future Biomedical Research
FDA	Food and Drug Administration
FDC	Fixed-Dose Combination
FDR	Fixed-dose Regimen
FTC	Emtricitabine
GCP	Good Clinical Practice
HAART	Highly Active Antiretroviral Therapy

HADS	Hospital Anxiety and Depression Scale Questionnaire
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HDL-C	High-Density Lipoprotein Cholesterol
HIV-1	Human Immunodeficiency Virus Type 1
HIV-SI	Human Immunodeficiency Virus - Symptom Index
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
INR	International Normalized Ratio
InSTI	Integrase Strand Inhibitors
IRB	Institutional Review Board
ISG	Immediate Switch Group
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
MedDRA	Medical Dictionary for Regulatory Activities
N(t)RTI	Nucleotide Reverse Transcriptase Inhibitor
NC=F	Non-Completer = Failure
NHS	Normal Human Serum
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
OF	Observed Failure
OTC	Over the counter
PCR	Polymerase Chain Reaction
PDLC	Pre-Defined Limit of Change
PDVF	Protocol-Defined Virologic Failure
PGt	Pharmacogenetic
PI	Protease Inhibitors
PK	Pharmacokinetics
PK/PD	Pharmacokinetic/Pharmacodynamic
PO	Per os
PSQ1	Pittsburgh Sleep Quality Index Questionnaire
PT	Prothrombin Time
q.d.	Once Daily
RAL	Raltegravir
RBC	Red blood cell
(v)RNA	(viral) Ribonucleic Acid
SAE	Serious Adverse Event

SOC	System Organ Class
(s)SAP	(supplemental) Statistical Analysis Plan
TDF	Tenofovir Disoproxil Fumarate
TDF/FTC	Tenofovir Disoproxil Fumarate/ Emtricitabine (TRUVADA™)
TLOVR	Time to Loss of Virologic Response
ULN	Upper Limit of Normal
US	United States

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	