Official Protocol Title:	A Phase III Multicenter, Double-Blind, Randomized, Active Comparator-Controlled Clinical Trial to Evaluate the Safety and Efficacy of MK-1439A Once-Daily Versus ATRIPLA™ Once-Daily in Treatment-Naïve HIV-1 Infected Subjects
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TITLE:

A Phase III Multicenter, Double-Blind, Randomized, Active Comparator-Controlled Clinical Trial to Evaluate the Safety and Efficacy of MK-1439A Once-Daily Versus ATRIPLA™ Once-Daily in Treatment-Naïve HIV-1 Infected Subjects

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SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
1.0 2.0 2.2 3.3 4.2.2 4.2.3.2 4.2.4 5.1.2 5.1.3 5.2 5.2.1.2 5.2.2.1 5.2.2.2 5.3	Trial Summary Trial Design Trial Diagram Exploratory Objectives Rationale for Dose Selection/Regimen Safety Endpoints Rationale for Study Extension Subject Inclusion Criteria Subject Exclusion Criteria Trial Treatment(s) Dose Modification\Interruption Base Study Study Extension Randomization or Treatment Allocation	Multiple changes in the sections noted to reflect the amended trial design, which now includes an open-label study extension in which subjects will receive active MK-1439A, after completion of the 96-week, double-blind period (base study). The updates include a description of the rationale for the study extension, the criteria for enrollment into this study extension, required procedures for the visits in this extension, and plans for summary of results.	The study is amended to allow an open-label study extension for 96 weeks (approximately 2 years) to collect long-term efficacy and safety data. Given that all subjects will be blinded at completion of the base study, they will be given the opportunity to enroll in the study extension as to not have an interruption in therapy.

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
5.4	Stratification		
5.5	Concomitant Medications/Vaccinations		
5.8	Subject Withdrawal/Discontinuation Criteria		
6.0	Trial Flow Chart		
7.1.1.2	Inclusion/Exclusion Criteria		
7.1.2.5	Adverse Events		
7.1.3.1	Serum /Urine Pregnancy Test		
7.1.3.2	Laboratory Safety Evaluations (Hematology, Chemistry and Others)		
7.1.3.4	Virology Test		
7.1.3.6	CD4 Cell Counts		
7.1.5.2	Treatment Visits Base Study		
7.1.5.3	Treatment Visits in Study Extension		

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
7.1.5.4	Virologic Failure Confirmation Visit – Base Study and Study Extension		
7.1.5.5	Early Discontinuation Visit - Base Study and Study Extension		
7.1.5.6	Post-Trial (Base Study and Study Extension)		
8.0	Statistical Analysis Plan		
8.2	Responsibility for Analyses/In-House Blinding		
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8.10	Subgroup Analyses and Effect of Baseline Factors (Base Study)		
8.11	Compliance (Medication Adherence)		
9.1	Investigational Product		

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
9.2 12.4.2	Packaging and Labeling Information Approximate Blood Volumes Drawn/Collected by Trial Visit and Sample Types - Week 100 Through Post-Study 14-Day Follow-up (Study Extension)		

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
2.0 6.0 7.1.3.5	Trial Design Trial Flow Chart Viral Resistance Testing	Text updated to note that plasma samples will be tested for resistance at the viral failure visit and confirmation visit for subjects, and at the discontinuation visit for all subjects who discontinue for any reason (if viral load is greater than 400 copies/mL).	Updated to ensure that comprehensive resistance testing is done for subjects with confirmed virologic failure and for all subjects who discontinue the study.
4.1.1	Pharmaceutical and Therapeutic Background	Updated preclinical information to include latest toxicity profile data	To ensure most recent data is captured in protocol amendment documentation
4.2.2	Rationale for Dose Selection/Regimen	Added reference details for MK-1439 safety and tolerability profile Included disoproxil fumarate with tenofovir for active comparator ATRIPLA™	To ensure most recent data is captured in protocol amendment documentation including updated reference information To ensure accurate description of drug is consistently captured throughout protocol
5.5	Concomitant Medication/Vaccination	Rosuvastatin removed as prohibited medication due to an interaction with MK-1439.	Deletion based on results of a recent drug-drug interaction study conducted with atorvastatin, which, similar to rosuvastatin, is a substrate for both OAT1B1 and BCRP transporter proteins.

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
5.5	Concomitant Medication/Vaccination	Specified that concomitant medications prohibited due to interactions with ATRIPLA™ in the base study are allowed in the study extension.	As subjects will receive open label MK-1439A in the extension these concomitant medications are allowed in the study extension.
6.0	Trial Flow Chart	Replaced the number 0 with the letter o for Post treatment footnote Updated all instances of Flow Chart reference with 'Trial' versus 'Study' wording throughout protocol Included timepoint and associated footnote 'r' for Chemistry sample (Creatinine Clearance only) at virologic failure confirmation visit. Added footnote 's' to indicate Patient Reported Outcomes timepoint of Early Discontinuation is not applicable for subjects who discontinue after Week 48	To ensure clarity of instruction for trial procedures To provide consistent terminology for trial procedures per standard template Section title Inadvertently omitted in protocol prior to amendment Clarification required to ensure correct trial procedures are followed for each study visit
7.1.2.5	Adverse Events	Updated instructions for documenting adverse events	To clarify evaluation for relationship/causality of IRIS
7.1.3.2	Laboratory Safety Evaluations (Hematology, Chemistry and Others)	Replaced Randomization Visit for Week 2 Visit of laboratory tests since correction aligns with protocol schedule Included footnote '9' of chemistry sample taken at virologic failure confirmation visits for creatinine visit only	To match study visits with trial procedures for all timepoints Inadvertently omitted in protocol prior to amendment

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
7.3.2	Executive Oversight Committee	Added external Data Monitoring Committee (eDMC) for source of EOC	To include complete description of EOC process
10.4	Compliance with Trial Registration and Results Posting Requirements	Text updated with language including reference to trial registration and results posting obligations to the European Medicines Agency (EMA)	Updated to comply with terms of the Food and Drug Administration Amendments Act (FDAAA) of 2007 and the EMA clinical trial Directive 2001/20/EC.
12.4.1	Approximate Blood Volumes Drawn/Collected by Trial Visit and Sample Types - Base Study	Included timepoint and footnote 'h' for chemistry sample (Creatinine Clearance only) at Virologic Failure Confirmation	Inadvertently omitted in protocol prior to amendment

1.0 TRIAL SUMMARY

Abbreviated Title	MK-1439A versus ATRIPLA™ in treatment-naïve HIV-infected subjects.
Trial Phase	Phase III
Clinical Indication	Treatment of HIV-1 infection
Trial Type	Interventional
Type of control	Active control
Route of administration	Oral
Trial Blinding	Double-blind for 96 weeks (base study), then open-label for additional 96 weeks (study extension)
Treatment Groups	Base Study (double-blind) Group 1: MK-1439A q.d. MK-1439A is a single-tablet, fixed-dose regimen (FDR) containing MK-1439 100 mg + lamivudine 300 mg + tenofovir disoproxil fumarate 300 mg. Group 2: ATRIPLA™ q.d. ATRIPLA™ is a single-tablet FDR containing efavirenz 600 mg + emtricitabine 200 mg + tenofovir disoproxil fumarate 300 mg (which is equivalent to 245 mg of tenofovir disoproxil). Study Extension (open-label) All subjects participating in the extension: MK-1439A q.d.
Number of trial subjects	Approximately 680 subjects will be enrolled.
Estimated duration of trial	The Sponsor estimates that the trial will require approximately 5 years from the time the first subject signs the informed consent until the last subject's last study-related phone call or visit.
Duration of Participation	For subjects who participate in the base study only, but do not continue into the study extension, each subject will participate in the trial for approximately 104 weeks from the time the subject signs the Informed Consent Form (ICF) through the final contact. For subjects who do continue into the study extension, each subject will participate for approximately 200 weeks from the time the subject signs the ICF through the final contact. After a screening phase of up to 45 days (or ~ 6.5 weeks), each subject will be receiving assigned treatment for approximately 96 weeks in the base study; for subjects who continue into the study extension, study treatment will continue for an additional 96 weeks, approximately, through a total of approximately 192 weeks of treatment. After the end of treatment each subject will be followed for 14 days in the study. Subjects who do not continue into the study extension will be followed through 14 days after the Week 96 treatment visit, while subjects who continue into the study extension will be followed through 14 days after the Week 192 visit.
Randomization Ratio	1:1 with ~ 340 on MK-1439A and ~ 340 on ATRIPLA™

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 the safety and efficacy of MK-1439A once-daily (q.d.) compared with ATRIPLA™ q.d. in antiretroviral treatment-naïve subjects with human immunodeficiency virus type 1 (HIV-1) infection. The study consists of a 96-week blinded base study of MK-1439A compared with ATRIPLA™, followed by a 96-week open-label study extension in which all subjects receive MK-1439A. Subjects who have completed the base study and are considered eligible for entering the study extension must provide consent in order to enroll in the study extension. The study is to be conducted in conformance with Good Clinical Practice.

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

Base Study

Approximately 680 subjects will be stratified by screening HIV-1 RNA (≤ or >100,000 copies/mL) and Hepatitis B and/or C co-infection status (yes/no) and randomized within strata in a 1:1 ratio to receive either MK-1439A or ATRIPLA™. The duration of treatment for a given subject is 96 weeks in the base study. The primary efficacy endpoint is the proportion of subjects achieving HIV-1 RNA < 50 copies/mL (by the Abbott RealTime HIV-1 Assay) at Week 48. The primary safety endpoint is the proportion of subjects with certain neuropsychiatric adverse events by Week 48.

The safety of the subjects in this trial will be monitored during the base study by an external Data Monitoring Committee (eDMC) which will provide ongoing review of the safety data with suggested periodic reviews to occur approximately every 6 months. The eDMC will recommend steps to ensure the safety of study participants and the integrity of the trial. To guarantee the unrestricted performance of its task, the eDMC will receive study data from the unblinded statistician. Details regarding the eDMC will be described in a charter document.

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

Subjects will complete a Work Productivity and Activity Impairment Questionnaire (WPAI) at Day 1, and Weeks 4, 8, and 48 (or the early discontinuation visit). This patient-reported outcome questionnaire is designed to assess the quantitative impact of health conditions on loss of time and impaired productivity for functional activities such as work-for-pay, school work, and work around the house.

Study Extension

At Study Week 96 (Visit 12 – Trial Flow Chart A) subjects who meet the following criteria will be eligible to enter the study extension: (1) completed the Week 96 (visit 12) study visit, (2) considered by the investigator to have derived benefit from participation in the base study, (3) treatment with study medication (MK-1439A) is considered clinically appropriate by the investigator, and (4) have provided informed consent to continue into the study extension, thus continuing study treatment for approximately 96 weeks beyond the base study. The total duration of treatment for a given subject in the base study will be 96 weeks (approximately 2 years); for subjects who continue into the study extension, the total duration of treatment will be 192 weeks (approximately 4 years).

All subjects entering the study extension will receive a q.d. regimen of open-label MK-1439A. Treatment group assigned during the base study will not be unblinded when a subject enters the study extension; unblinding will occur after all subjects have completed the base study and database lock has been achieved for the base study (96-week treatment).

During the study extension, subjects will continue to be monitored for safety, and maintenance of virologic suppression. Long-term safety and efficacy data will be collected during the extension phase of the study and summarized descriptively.

Viral Resistance Testing

Subjects who meet virologic failure criteria during the base study and the study extension (see Section 4.2.3.1) will return to the site for repeat viral RNA testing between one week 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 criteria for resistance testing (> 400 copies/mL), viral resistance testing will be performed. For subjects in the base study with confirmed virologic failures, the plasma sample collected for resistance testing from the virologic failure visit and the confirmation visit, will be sent for resistance testing provided the viral load meets the criteria for resistance testing.

For subjects in the study extension with confirmed virologic failure, the plasma sample from the virologic failure confirmation visit only will be sent for resistance testing provided the viral load meets the criteria for resistance testing.

Plasma samples for resistance testing collected at the early discontinuation visit from subjects who discontinue, from either the base study or the study extension, for reasons other than virologic failure will be sent for testing (if viral load > 400 copies/mL). (Note that if a sample from the early discontinuation visit is not available, a sample from the most recent previous visit will be sent for testing in the base study (if viral load > 400 copies/mL).

In addition, phenotypic testing will be conducted on screening samples for all subjects who discontinue for any reason or with confirmed virologic failure-See Section 7.1.3.5.

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

2.2 Trial Diagram

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

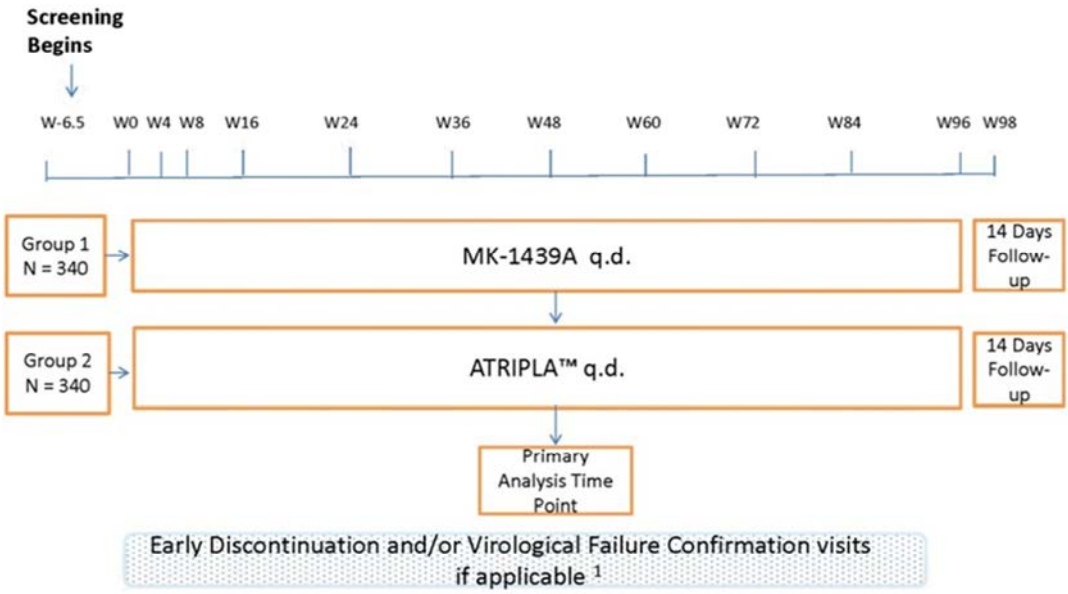


Figure 1 Trial Diagram Base Study

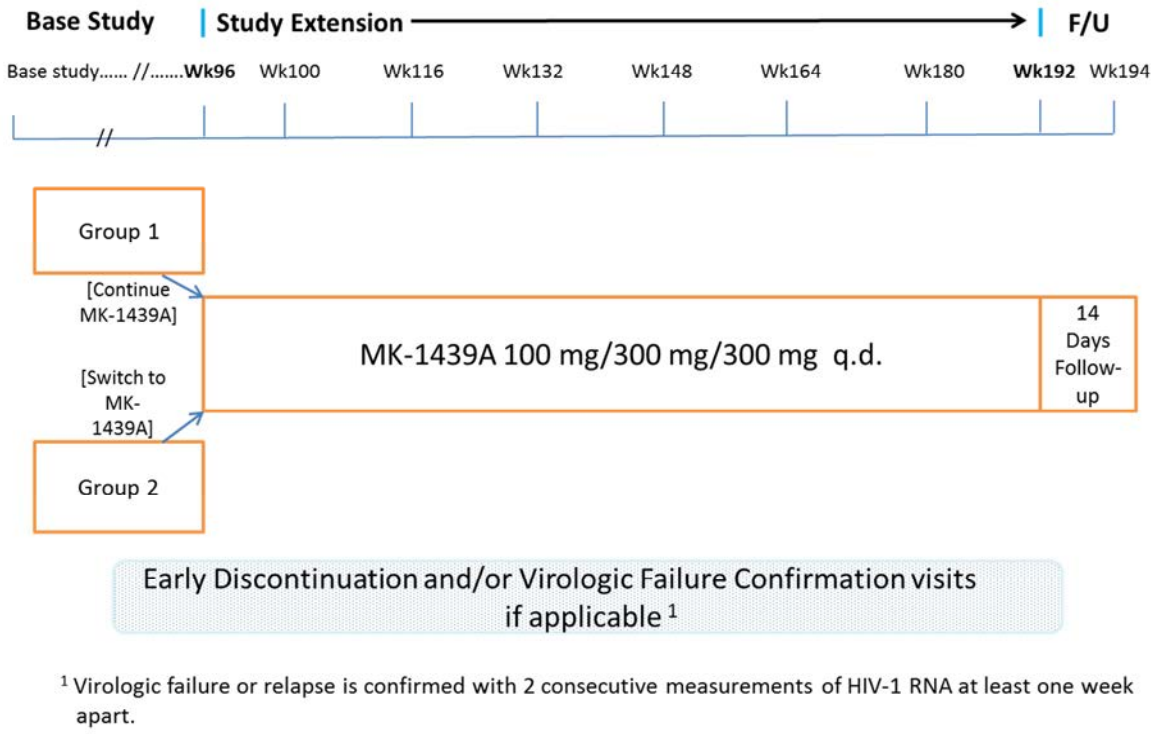


Figure 2 Trial Diagram Study Extension

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

3.1.1 Base Study

In HIV-1 positive, treatment-naive subjects with pre-treatment HIV RNA ≥ 1,000 copies/mL:

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

   Hypothesis: MK-1439A q.d. is non-inferior to ATRIPLA™ q.d. as assessed by the proportion of subjects with HIV-1 RNA <50 copies/mL (by the Abbott RealTime HIV-1 Assay) at Week 48. A margin of 10 percentage points is used to define non-inferiority.

2) **Objective:** To evaluate the safety and tolerability of MK-1439A q.d. compared with ATRIPLA™ q.d. as measured by the proportion of subjects with neuropsychiatric adverse events in the following categories:

   - Dizziness
   - Sleep disorders and disturbances
   - Altered Sensorium

   Hypothesis: MK-1439A q.d. is superior to ATRIPLA™ q.d. as measured by the proportion of subjects with neuropsychiatric adverse events in the following categories by Week 48 (superiority will be tested within category, sequentially, in the order indicated below):

   - Dizziness
   - Sleep disorders and disturbances
   - Altered Sensorium

3.2 Secondary Objective(s) & Hypothesis(es)

3.2.1 Base Study

In HIV-1 positive, treatment-naive subjects with pre-treatment HIV RNA ≥ 1,000 copies/mL:

1) **Objective**: To evaluate the safety and tolerability of MK-1439A q.d. compared to ATRIPLA™ q.d. as assessed by review of the accumulated safety data by Week 48 and Week 96.

2) **Objective**: To evaluate the effect of MK-1439A q.d. compared to ATRIPLA™ q.d. on fasting LDL-C as measured by the mean change from baseline at Week 48.

   Hypotheses: MK-1439A q.d. is superior to ATRIPLA™ q.d. as assessed by the mean change from baseline in LDL-C at Week 48.

3) **Objective**: To evaluate the effect of MK-1439A q.d. compared to ATRIPLA™ q.d. on fasting non-HDL-C as measured by the mean change from baseline at Week 48.

   Hypotheses: MK-1439A q.d. is superior to ATRIPLA™ q.d. as assessed by the mean change from baseline in non-HDL-C at Week 48.

4) **Objective:** To evaluate the safety and tolerability of MK-1439A q.d. compared with ATRIPLA™ q.d. as measured by the proportion of subjects with neuropsychiatric adverse events in the following categories:

   - Depression and suicide/self-injury
   - Psychosis and psychotic disorders

5) **Objective:** To evaluate the safety and tolerability of MK-1439A q.d. compared with ATRIPLA™ q.d. as measured by the proportion of subjects with at least one neuropsychiatric adverse event across the 5 categories of: dizziness, sleep disorders and disturbances, altered sensorium, depression and suicide/self-injury, and psychosis and psychotic disorders.

6) **Objective:** To evaluate the safety and tolerability of MK-1439A q.d. compared to ATRIPLA™ q.d. as measured by the time to discontinuation from study due to an adverse experience.

7) **Objective**: To evaluate the immunologic effect of MK-1439A q.d. compared to ATRIPLA™ q.d., as measured by the change from baseline in CD4 cell count at Week 48 and Week 96.

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

   Hypothesis: MK-1439A q.d. is superior to ATRIPLA™ q.d. as assessed by the proportion of subjects with HIV-1 RNA <50 copies/mL (by the Abbott RealTime HIV-1 Assay) at Week 48.

9) **Objective**: To evaluate the non-inferior antiretroviral activity of MK-1439A q.d. compared to ATRIPLA™ q.d., as measured by the proportion of subjects achieving HIV-1 RNA < 50 copies/mL (by the Abbott RealTime HIV-1 Assay) at Week 96.

   Hypothesis: MK-1439A q.d. is non-inferior to ATRIPLA™ q.d. as assessed by the proportion of subjects with HIV-1 RNA <50 copies/mL (by the Abbott RealTime HIV-1 Assay) at Week 96. A margin of 10 percentage points is used to define non-inferiority.

10) **Objective**: To evaluate the superior antiretroviral activity of MK-1439A q.d. compared to ATRIPLA™ q.d., as measured by the proportion of subjects achieving HIV-1 RNA < 50 copies/mL (by the Abbott RealTime HIV-1 Assay) at Week 96.

    Hypothesis: MK-1439A q.d. is superior to ATRIPLA™ q.d. as assessed by the proportion of subjects with HIV-1 RNA <50 copies/mL (by the Abbott RealTime HIV-1 Assay) at Week 96.

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

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

3.3 Exploratory Objectives

3.3.1 Base Study

In HIV-1 positive, treatment-naive subjects with pre-treatment HIV RNA ≥ 1,000 copies/mL:

1) O**bjective:** To evaluate the antiretroviral activity of MK-1439A q.d. compared to ATRIPLA™ q.d. as measured by the proportion of subjects achieving HIV-1 RNA <200 copies/mL at Week 48 and Week 96.

2) **Objective:** To evaluate the antiretroviral activity of MK-1439A q.d. compared to ATRIPLA™ q.d., as measured by the Time to Loss of Virologic Response (TLOVR).

3) O**bjective:** To assess the development of resistance to MK-1439A in subjects who have virologic failure.

4) O**bjective:** To describe the outcomes for productivity and activity impairment related to general health during the study in MK-1439A relative to ATRIPLA™ q.d.

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

3.3.2 Study Extension

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

2) Objective: To assess efficacy and safety of switching to MK-1439A for up to 96 weeks in subjects initially randomized to ATRIPLA™ q.d. and enrolled in the extension phase of the study.

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

For initiation of combination antiretroviral therapy for HIV infection, currently-available NNRTIs constitute an important option for use as anchor agents, along with two NRTIs. Efavirenz and rilpivirine are both among the recommended therapies for treatment initiation according to multiple guidelines [1] [2]; however, each has limitations. For example, while efavirenz has shown excellent efficacy over many years of use, it is associated with substantial neuropsychiatric intolerance and skin rash, as well as lipid abnormalities. In addition it can be a perpetrator of drug-drug interactions as a mixed inducer or inhibitor of CYP3A and CYP2B6 enzymes. Rilpivirine has shown suboptimal efficacy in patients with high viral load or low baseline CD4 cells, and thus is not indicated in patients with baseline viral load above 100,000 copies/mL or CD4 count below 200 u/L. In addition, rilpivirine requires dosing with food, and while it is not a metabolic inducer or inhibitor, it is subject to metabolic induction/inhibition of CYP3A isoenzymes and should not be co-administered with proton pump inhibitors and several anticonvulsants. Importantly, high level resistance may occur in response to a single mutation for all currently available NNRTIs except etravirine, which must be dosed twice daily. Therefore, new agents of the NNRTI class that offer high potency, a distinct resistance profile, dosing convenience and a favorable safety and tolerability profile are needed.

MK-1439 is a novel NNRTI being studied for the treatment of HIV-1 infection in antiretroviral-naïve HIV-infected subjects. MK-1439 is a potent inhibitor of HIV-1

replication in vitro and 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 preclinical toxicity profile of MK-1439 is favorable in rats following dosing for up to 6 months at 3, 30, and 450 mg/kg/day, and in dogs following dosing for up to 9 months 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 of significant drug-drug interactions. Furthermore, the available long-term (beyond Week 48) data from a Phase 2 study in treatment-naive HIV-infected patients demonstrate that MK-1439 in combination with TDF/emtricitabine has a favorable safety and tolerability profile and potent efficacy, with ~76% of patients receiving MK-1439 achieving undetectable viral load (see Section 4.2.2.). These data provide key support for the initiation of the Phase 3 program, which includes evaluations of both MK-1439 as a single agent and MK-1439A as a fixed-dose regimen.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Factors that impact HIV treatment success include efficacy, safety and tolerability, barrier to resistance, simplicity/convenience of administration and drug-drug interactions. There is a clear medical need for new regimens that are highly effective, have a high barrier to resistance development, are very well tolerated, and are simple to administer (and thus facilitate increased adherence and prevent treatment fatigue). Therapies and regimens with these characteristics are particularly important for treatment-naïve patients for whom initial success is predictive of long term outcomes and in the setting of life-long treatment of HIV infection as many HIV patients become increasingly older with co-morbid diseases/conditions.

Currently, efavirenz is the preferred NNRTI for first-line therapy of treatment-naïve HIV-infected subjects. ATRIPLA™, an FDR consisting of efavirenz 600 mg + emtricitabine 200 mg + TDF 300 mg, is the leading agent in HIV treatment. Efavirenz has demonstrated potent viral suppression but is associated with an increased risk of neuropsychiatric adverse experiences (AEs) (especially dizziness and sleep disorders) and lipid abnormalities relative to other therapies [1]. Efavirenz is also a perpetrator of numerous drug-drug interactions and, thus, may have limitations for use in aging patients who have an increased likelihood of using concomitant mediations. MK-1439 has been observed to have a more favorable neuropsychiatric AEs and lipid profile relative to efavirenz in a Phase 2b study comparing the 2 agents, and, therefore, may result in improved patient tolerability and adherence [3] [4]. Additionally, based on in vitro data and drug-drug interactions studies conducted to date, MK-1439 is not expected to have many of the drug-drug interaction concerns currently

hampering the use of efavirenz. Therefore, both MK-1439 and MK-1439A will provide valuable new treatment options for patients.

4.2.2 **Rationale for Dose Selection/Regimen**

The investigational FDR, MK-1439A, contains 100 mg of MK-1439, a potent investigational 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 postdose) 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) [3] [4]. 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 [4].

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) [3].

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 the base study will be administered at the standard approved dose of one tablet once daily. Each tablet contains 600 mg of efavirenz, 300 mg of tenofovir disoproxil fumarate (which is equivalent to 245 mg of tenofovir disoproxil) and 200 mg of emtricitabine.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

The primary efficacy parameter in the study is viral load as measured by HIV-1 RNA, which is consistent with other clinical trials in HIV-infected patients and the current regulatory guidance. Suppressing HIV RNA to low levels preserves the immune system and prevents the development of opportunistic infections and progression of the disease. Clinical trials of antiretroviral agents in multiple classes have demonstrated that suppression of HIV RNA to levels below 50 copies/mL is a clinically meaningful endpoint. Therefore, the primary efficacy endpoint of this study is the proportion of subjects achieving HIV-1 RNA <50 copies/mL by the Abbott RealTime HIV-1 Assay. Week 48 was chosen as the primary efficacy time point and Week 96 as the secondary efficacy time point, as recommended by regulatory agencies for HIV treatment-naïve studies.

Secondary and exploratory measurements for efficacy include HIV RNA < 40 copies/mL (the lower limit of quantification of the Abbott RealTime HIV-1 Assay), HIV RNA <200 copies/mL, change from baseline in CD4 cell counts, time to loss of virologic response (TLOVR), and viral resistance for subjects who meet protocol defined virologic failure criteria and whose virus can be amplified.

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

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

OR

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

OR

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

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

4.2.3.2 Safety Endpoints

The primary safety endpoint in this study is assessed in the base study. The primary safety endpoint is the proportion of subjects with neuropsychiatric AEs by Week 48 in three categories; dizziness, sleep disorders, and altered sensorium (for example, depressed level of consciousness, lethargy, somnolence, syncope). The proportion of subjects with neuropsychiatric AEs by Week 48 in two additional categories, depression/suicide/self-injury

and psychosis/psychotic disorders, will be secondary endpoints. All Medical Dictionary for Regulatory Activities (MedDRA) preferred terms that fall under these categories will be grouped for the statistical tests on the difference in incidence rates between treatment groups within the categories. The full list of preferred terms defining these 5 categories is provided in Section 12.6.

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

Note that the first visit in the study extension is at Week 100, such that there is a 4-week interval following the last study treatment visit in the base study (Week 96). This interval was made shorter than the 12- to 16-week intervals beginning with Week 24 in the base study (and between subsequent visits in the study extension) in order to more closely monitor all subjects, including those who are switched from ATRIPLA™ to MK-1439A, since treatment in the base study remains blinded at the beginning of the study extension. Treatment group assigned during the base study will not be unblinded when a subject enters the study extension; unblinding will occur after all subjects have completed the base study and database lock has been achieved for the base study (96-week treatment).

Secondary and exploratory measurements for safety include clinical and laboratory adverse experiences, change from baseline in fasting serum lipids, time to discontinuation due to an adverse experience and predefined limits of change in laboratory parameters.

4.2.3.3 Pharmacokinetic Endpoints

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

4.2.3.4 Patient Reported Outcome Endpoints

Subjects will complete a Work Productivity and Activity Impairment Questionnaire (WPAI) at Day 1, Week 4, Week 8, Week 16, and Week 48 (or the discontinuation visit). This patient-reported outcome questionnaire is designed to assess the quantitative impact of health conditions on loss of time and impaired productivity for functional activities such as work-for-pay, school work, and work around the house.

4.2.3.5 Planned Exploratory Biomarker

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 DNA (blood) and plasma specimens collected during this clinical trial. This research may include genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma) and/or the measurement of other analytes.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented subjects. The objective of collecting specimens for Future Biomedical Research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. For instance, exploratory pharmacogenetic (PGt) studies may be performed if significant Pharmacokinetic/Pharmacodynamic (PK/PD) relationships are observed or adverse events are identified. Genomic markers of disease may also be investigated. Such retrospective pharmacogenetic studies will be conducted with appropriate biostatistical design and analysis and compared to PK/PD results or clinical outcomes. Any significant PGt relationships to outcome would require validation in future clinical trials. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that subjects receive the correct dose of the correct drug/vaccine at the correct time. The details of this Future Biomedical Research sub-trial are presented in Section 12.2 - Collection and Management of Specimens for Future Biomedical Research. Additional informational material for institutional review boards/ethics committees (IRBs/ERCs) and investigational site staff is provided in Section 12.3.

4.2.4 Rationale for Study Extension

This protocol is being amended to provide MK-1439A to patients who have completed the base study (96 weeks of treatment for PN021) for an additional 96 weeks, and to collect long-term efficacy and safety data with MK-1439A. MK-1439A is being evaluated as a potential treatment option for subjects infected with HIV-1. It is important to assess its long-term safety and efficacy since HIV-1 infection is chronic, with treatment generally lasting for years. Thus, after the 96-week period (base study) to evaluate the key primary and secondary objectives, there will be an extension for an additional 96-week period where all eligible subjects (from both treatment groups) can continue to receive MK-1439A without interruption to their therapy.

4.3 Benefit/Risk

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

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

Additional details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying Investigator 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 and naïve to antiretroviral therapy (ART) will be enrolled in this trial.

5.1.2 Subject Inclusion Criteria

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

1. be at least 18 years of age on the day of signing the informed consent

2. understand the study procedures and voluntarily agree to participate by giving written informed consent (or have a legal representative provide written informed consent, if considered acceptable by local regulatory agencies and/or ERCs/IRBs) for the trial. The subject or his/her legal representative (if considered acceptable by local regulatory agencies and/or ERCs/IRBs) may also provide consent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.

3. be HIV-1 positive as determined by a positive result on an enzyme-immunoassay, have screening plasma HIV-1 RNA (determined by the central laboratory) ≥1000 copies/mL within 45 days prior to the treatment phase of this study, and have HIV treatment indicated based on physician assessment. Local treatment guidelines should be considered in the decision to initiate therapy.

4. be naïve to antiretroviral therapy (ART) including investigational antiretroviral agents.

   Note: Naïve is defined as having received no (0 days of) ART therapy for the treatment of HIV infection.

5. have the following laboratory values at screening within 45 days prior to the treatment phase of this study:

   a. Alkaline phosphatase ≤3.0 x upper limit of normal

   b. AST (SGOT) and ALT (SGPT) ≤5.0 x upper limit of normal

   c. Hemoglobin ≥9.0 g/dL (if female) or ≥10.0 g/dL (if male).

   Note: A single repeat of a laboratory screening test will be allowed for test results that are unexpected based on documented prior laboratory results.

6. have a calculated creatinine clearance at the time of screening ≥ 50 mL/min, based on the Cockcroft-Gault equation which is as follows:

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

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

7. in the opinion of the investigator, be considered clinically stable with no signs or symptoms of active infection at the time of entry into the study (i.e., clinical status and all chronic medications should be unchanged for at least 2 weeks prior to the start of treatment in this study).

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

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

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

c. The subject is a female or a male who is of reproductive potential and agrees to avoid becoming pregnant or impregnating a partner while receiving study drug and for 12 weeks after the last dose of study drug in the base study and 14 days after the last dose of study drug in the study extension by complying with one of the following: (1) practice abstinence[†] from heterosexual activity OR (2) use (or have their partner use) acceptable contraception during heterosexual activity. Acceptable methods of contraception are[‡]:

Single method (one of the following is acceptable):

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

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

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

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

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

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

Investigators should provide appropriate guidance to the subjects regarding use of contraceptives after completion of the study treatment. It is recommended that all subjects should continue to use contraception for 12 weeks following their last dose of study treatment in the base study (continued contraceptive use for 12 weeks following the last dose of ATRIPLA™ is required as per ATRIPLA™ prescribing information, and patients' study drug assignments will likely still be blinded following study completion). However, continued contraceptive use for 14 days following the last dose of study treatment is recommended in the study extension since all subjects will be on MK-1439A.

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

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

5.1.3 Subject Exclusion Criteria

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

1. has a history or current evidence of any condition, therapy, laboratory abnormality or other circumstance that might confound the results of 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 been treated for a viral infection other than HIV-1, such as hepatitis B, with an agent that is active against HIV-1, including, but not limited to, adefovir, tenofovir, entecavir, emtricitabine, or lamivudine.

   <u>Note</u>: Subjects may be enrolled if treatment occurred prior to the diagnosis of HIV.

4. has documented or known resistance to study drugs including MK-1439, efavirenz, emtricitabine, lamivudine, and/or tenofovir, 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 emtricitabine, lamivudine and tenofovir includes the following mutations: K65R, M41L, T69S (insertion complex), Q151M, M184I, M184V, L210W, T215F, T215Y, K219E, K219Q, D67N, K70R and K70E.

5. has participated in a study with an investigational compound/device within 30 days prior to signing informed consent or anticipates participating in such a study involving an investigational compound/device during the course of this study.

6. 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.

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

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

9. 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).

10. has evidence of decompensated liver disease manifested by the presence of or a history of ascites, esophageal or gastric variceal bleeding, hepatic encephalopathy or other signs or symptoms of advanced liver diseases

    or

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

    Note: To calculate the CPT score and associated Child-Pugh Class, refer to the following website: http://www.mdcalc.com/child-pugh-score-for-cirrhosis-mortality.

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

12. 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 in the base study and 14 days after the last dose of study treatment in the study extension.

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

5.2 Trial Treatment(s)

Following completion of the Day 1 procedures and confirmation of eligibility, the site will contact the IVRS/IWRS for assignment of the study drug to be administered (MK-1439A or ATRIPLA). 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. The treatment groups to be used in this trial are outlined below in Table 1.

Table 1 Trial Treatment During the Base Study

Group 1	n = 340	MK-1439A one tablet PO q.d. † + placebo to match ATRIPLA™ one tablet PO q.d.#
Group 2	n = 340	ATRIPLA™ one tablet PO q.d. ‡ + placebo to match MK-1439A one tablet PO q.d. #

† MK-1439A is a single tablet FDR containing MK-1439 100 mg, lamivudine 300 mg, and tenofovir disoproxil fumarate (TDF) 300 mg.
‡ ATRIPLA™ is a single tablet FDR 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 Trial Treatment During the Study Extension

Group 1	Open Label MK-1439A q.d. †
Group 2	

† All subjects will receive MK-1439A (single-tablet, fixed-dose regimen (FDR) containing MK-1439 100 mg + lamivudine 300 mg + tenofovir disoproxil fumarate 300 mg) in the extension.

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

MK-1439A (during the base study and study extension) and the placebo to match MK-1439A are to be taken once daily without regard to food at approximately the same time each day.

ATRIPLA™ and the placebo to match ATRIPLA™ are to be taken once daily at bedtime on an empty stomach.

Study medications for the base study (MK-1439A/placebo or ALTRIPA™/placebo) and for the study extension (MK-1439A) 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 (Base Study or the Study Extension)

Dose Modification:

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

Dose Interruption:

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

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

5.2.2 **Timing of Dose Administration**

5.2.2.1 Base Study

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 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.

5.2.2.2 Study Extension

Bottle C (MK-1439A), open-label:

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 in the base trial. 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. During the trial extension, MK-1439A will be provided open-label.

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 or Treatment Allocation

Randomization will occur centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). There are two treatment arms. Subjects will be assigned randomly in a 1:1 ratio to MK-1439A q.d. or ATRIPLA™ q.d. in the base study.

5.4 Stratification

Randomization in the base study will be stratified according to the following factors:

1. Screening HIV-1 RNA (≤100,000 or >100,000 copies/mL), based on central laboratory result

2. Chronic Hepatitis B and/or C infection status (yes or no). Hepatitis status is defined by serologic evidence of chronic hepatitis B surface antigen and/or evidence of HCV RNA by a polymerase chain reaction (PCR) quantitative test for hepatitis C virus.

Thus, IVRS/IWRS will randomize subjects within 4 strata as outlined in Table 3.

Table 3 Stratification

Stratum	Screen HIV-1 RNA levels (copies/mL)	Chronic Hepatitis B and/or Chronic Hepatitis C
I	≤100,000	No
II	≤100,000	Yes
III	>100,000	No
IV	>100,000	Yes

5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

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

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

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

Permitted Concomitant Medications/Therapies

The concomitant use of other medications/therapies is allowed unless specifically prohibited in the Prohibited Concomitant Medications/Therapies section below. Before placing a subject on a specific medication/therapy, it is the responsibility of the investigator to check on potential drug-drug interactions between that medication/therapy 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 Merck Clinical Director or designee should be contacted if there are any questions about whether there is a potential drug-drug interaction with a specific treatment that the Investigator is planning to give the subject.

Prohibited Concomitant Medications/Therapies

In general, concomitant use of immune therapy agents or other immunosuppressive therapy, 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 those used in the study (MK-1439A, and ATRIPLA™) are also not permitted during the course of the study.

Investigational agents must be discontinued 30 days prior to treatment in this study and are not permitted during the course of the study.

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

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

The medications and/or substances below are prohibited in this study because they are moderate or potent inducers of CYP3A4 and their coadministration with MK-1439A could possibly result in reduced drug levels of MK-1439 or has the potential for additional drug-drug interactions.

Since this list is not comprehensive, the investigator should use his/her medical judgment when a subject presents with a medication not on the list or call the Sponsor Clinical Director or Designee for clarification.

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

Prohibited Concomitant Therapy Due to Potential Interactions with ATRIPLA

Specific medications are prohibited during the base study due to potential interactions with ATRIPLA™. 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.

Prohibited Medication/Therapy Due to ATRIPLA™ Interactions During the Base Study
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
† Several of these medications are also prohibited during the study extension because of interaction with MK-1439A: specifically, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin and St. John's Wort are prohibited throughout the base study and the study extension.

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 (or placebo) can be taken without regard to food and should generally be taken at approximately the same time each day.

ATRIPLA™ (or placebo) should be taken 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.

- 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 (base study)
    - severe depression, psychosis or suicidal ideation (base study).
- The subject has a confirmed positive serum/urine pregnancy test.

  Note: Subjects who become pregnant during the study will be asked to join a pregnancy registry which collects information about the outcome of the pregnancy.

- The subject fails to comply with the dosing, evaluations, or other requirements of the trial.
- A physician investigator feels it is in the best interest of the subject to discontinue.
- The subject has an adverse experience or tolerability issue related to study medication which requires discontinuation of the medication.
- Subject has a creatinine clearance of <50 mL/min (confirmed by repeat measurement) based on the Cockcroft-Gault equation:

  Male:

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

  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 should be discontinued, regardless of compliance with study therapy, if they meet the protocol defined virologic failure criteria in Section 4.2.3.1.

Subjects who require discontinuation of 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 a 14-day follow-up visit conducted.

Due to the potential for severe acute exacerbations of hepatitis B following discontinuation of 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 the study extension. A subject who completes the base study and does not elect to participate in the study extension is considered to have completed the study.

5.9 Subject Replacement Strategy

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

5.10 Beginning and End of the Trial

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

5.11 Clinical Criteria for Early Trial Termination

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

1. External Data Monitoring Committee (eDMC) recommends the trial be terminated and the Executive Oversight Committee (EOC) agrees.

Further recruitment in the trial or at a particular trial site(s) may be stopped due to insufficient compliance with the protocol, GCP, and/or other applicable regulatory requirements, procedure-related problems, or the number of discontinuations for administrative reasons is too high.

6.0 TRIAL FLOW CHART

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

Visit Number/Title:	1	2 Randomization	3	4	5	6	7	8	9	10	11	12	U (Virologic Failure Confirmation)	U (Early Discontinuation	99
Trial Period	Screening	Treatment[n]													Post treatment[o]
Trial Procedures	Screen	Fasting [a] Day 1[b]	WK 4	WK 8	WK 16	Fasting [a] WK 24	WK 36	Fasting [a] WK 48	WK 60	WK 72	WK 84	Fasting [a] WK 96	≥ 1 to ≤ 4 weeks after initial virologic failure	At time of Discon	Post study 14 day follow-up[o]
Administrative Procedures															
Informed Consent	X											X [q]			
Informed Consent for Future Biomedical Research[c]	X														
Inclusion/Exclusion Criteria	X	X										X [q]			
Provide Subject Identification Card	X														
Medical History[d]	X														
Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Treatment Allocation/Randomization		X													
Register Study Visit via Interactive Voice (Web) Response System (IVRS/IWRS)	X	X	X	X	X	X	X	X	X	X	X	X		X	
Dispense Study Therapy via IVRS/IWRS		X	X	X	X	X	X	X	X	X	X	X[p]			
Provide/Review Study Medication Diary		X	X	X	X	X	X	X	X	X	X	X		X	
Patient Reported Outcomes[e]		X	X	X	X			X						X[s]	
Clinical Procedures/Assessments															
Full Physical Examination	X														
Directed Physical Examination		X	X	X	X	X	X	X	X	X	X	X		X	X
Height	X														
Vital Signs (including pulse rate, blood pressure, respiratory rate, and body temperature) and Weight	X	X	X	X	X	X	X	X	X	X	X	X		X	X
12-Lead Electrocardiogram (ECG) (Local)[f]		X [f, h]													
Adverse Events Monitoring	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Birth Control Confirmation	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Laboratory Procedures/Assessments															
Serum Pregnancy Test [g]	X														
Urine Pregnancy Test [g]		X [h]	X	X	X	X	X	X	X	X	X	X		X	X

Visit Number/Title:	1	2 Randomization	3	4	5	6	7	8	9	10	11	12	U (Virologic Failure Confirmation)	U (Early Discontinuation	99
Trial Period	Screening	Treatment[n]													Post treatment[o]
Trial Procedures	Screen	Fasting[a] Day 1[b]	WK 4	WK 8	WK 16	Fasting[a] WK 24	WK 36	Fasting[a] WK 48	WK 60	WK 72	WK 84	Fasting[a] WK 96	≥ 1 to ≤ 4 weeks after initial virologic failure	At time of Discon	Post study 14 day follow-up[o]
Collect Blood for Safety Laboratory Tests (Hematology/Chemistry)[i]	X[h]	X	X	X	X	X	X	X	X	X	X	X	X[r]	X	X
Hemostatic Function Test[j]	X[h]														
HIV/Hepatitis Screen[k]	X[h]														
Virology Test Plasma HIV viral RNA quantification test (Abbott Real Time HIV-1)	X[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Collect Blood for CD4 Cell Count	X	X		X		X		X		X		X			
Collect Blood for MK-1439 PK[l]		X	X	X		X		X							
Collect Plasma for Viral Resistance Test	X		X	X	X	X	X	X	X	X	X	X	X	X[m]	
Collect Blood (DNA) for Genetic Analysis[c]		X													
Collect Plasma for Future Biomedical Research[c]		X						X				X			

a. Fasting for at least 8 hours. Fasting is required at these visits for lipids measurement
b. Within 45 days of screening visit and prior to the first dose on Day 1.
c. This sample should be drawn for planned genetic analysis of DNA and drug response unless there is either a documented law or regulation prohibiting collection, or unless the IRB/IEC does not approve of the collection of the sample for these purposes. If the sample is collected, any leftover extracted DNA will be stored for future biomedical research if the subject signs the FBR consent. Plasma samples for FBR should be collected at Day 1, and Weeks 48 and 96
d. Includes smoking history
e. Includes 1 questionnaire: Work Productivity and Activity Impairment Questionnaire (WPAI)
f. A local ECG should be performed prior to the subject's first dose of study medication (within 7 days prior to the Study Day 1 visit).
g. For women of childbearing potential.
h. Results of test must be available prior to randomization.
i. Refer to Table 4 for listing of specific blood safety tests.
j. Hemostatic Function Test includes: Prothrombin time (PT), Activated Partial Thromboplastin Time (APTT), and International Normalized Ratio (INR).
k. HIV/Hepatitis Screen tests includes: Enzyme immunoassay HIV antibody screen, Serum Hepatitis B surface antigen, Serum Hepatitis B surface antibody, Serum Hepatitis B e-antigen and Serum Hepatitis C antibody. A plasma hepatitis C virus PCR quantitative test will be performed if the Hepatitis C antibody test is positive.
l. One sample for assay of MK-1439 plasma concentrations will be collected at Day 1 (Pre-dose), Week 4 (pre-dose), and Week 8 (random). At Weeks 24 and 48, two samples will be collected, pre-dose and 30 mins to 2 hours postdose (the subject should be fasting for both samples).
m. If virologic failure is confirmed (with a confirmatory HIV-1 RNA at least one week later), and the decision is made to discontinue the subject, plasma for resistance need not be collected again at the early discontinuation visit. All other early discontinuation tests should be performed at the early discontinuation visit.

Visit Number/Title:	1	2 Randomization	3	4	5	6	7	8	9	10	11	12	U (Virologic Failure Confirmation)	U (Early Discontinuation	99
Trial Period	Screening	Treatment[n]													Post treatment[o]
Trial Procedures	Screen	Fasting [a] Day 1[b]	WK 4	WK 8	WK 16	Fasting [a] WK 24	WK 36	Fasting [a] WK 48	WK 60	WK 72	WK 84	Fasting [a] WK 96	≥ 1 to ≤ 4 weeks after initial virologic failure	At time of Discon	Post study 14 day follow-up[o]

n. Visit window periods are approximately +/- 3 days for the Week 4 to Week 24 visits and approximately +/- 7 days for the Week 36 to Week 96 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 follow-up visit 14 days after the Week 96 visit in the base study applies only to subjects who do not enter the study extension. The visit window period for the Post study 14-day follow-up visit is approximately - 2 to 0 days.

p. For Week 96, drug will be dispensed only to subjects who enter the study extension, after providing informed consent.

q. If the subject is eligible and elects to enter the study extension, he/she will be considered to have completed the base study and will, after providing informed consent for the study extension, immediately enter the study extension.

r. For creatinine clearance only.

s. Not applicable for subjects who discontinue after Week 48.

Flow Chart B (Study Extension): Week 100 Through Week 192 Plus 14 Days Follow-up

Visit Number/Title:	13 [a]	14	15	16	17	18	19	U (Virologic Failure Confirmation)	U (Early Discontinuation)	99
Trial Period	Treatment [b]									
TRIAL PROCEDURES	WK 100	WK 116	WK 132	Fasting WK 148	WK 164	WK 180	Fasting WK 192	≥1 to ≤ 4 wks after the time virologic failure is first identified	At time of Discontinuation	Post-study 14-day follow-up
Administrative Procedures										
Concomitant Medication Review	X	X	X	X	X	X	X		X	X
Register Study Visit via Interactive Voice Response System (IVRS/IWRS) [c]	X	X	X	X	X	X	X		X	
Dispense Study Therapy (Open Label MK-1439A)	X	X	X	X	X	X				
Provide/Review Study Medication Diary	X	X	X	X	X	X	X		X	
Clinical Procedures/Assessments										
Directed Physical Examination	X	X	X	X	X	X	X		X	X
Vital Signs (including pulse rate, blood pressure, respiratory rate, & 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
Laboratory Procedures/Assessments										
Urine Pregnancy test [d]	X	X	X	X	X	X	X		X	X
Collect Blood for Safety Laboratory Tests Hematology/Chemistry [f]	X	X	X	X [e]	X	X	X [e]	X [h]	X	X
Virology Test Plasma HIV viral RNA quantification test (Abbott RealTime HIV-1)	X	X	X	X	X	X	X	X	X	X
Collect Blood for CD4 Cell Count	X			X			X			
Collect Plasma for Viral Resistance Test								X	X [g]	

a. Subjects who enter the study extension are considered enrolled in the study extension upon providing written informed consent for the study extension at the Week 96 study visit of the base study.
b. The visit window for Week 100 is approximately +/- 7 days, for all visits from Week 116 through Week 192 the windows are approximately +/- 14 days and, for the post-study 14-day follow-up visit, the window is approximately –2 to 0 days. The timing of each visit is relative to the randomization (Day 1) visit. Every attempt must be made to keep subjects on schedule.
c. IVRS/IWRS will be used to allocate drug and to manage distribution of clinical supplies.
d. For women of childbearing potential
e. Fasting at least 8 hours prior to study visit is required for lipids measurement at Week 148 and Week 192.
f. Refer to Table 4 for listing of specific blood safety and chemistry tests.
g. If virologic failure is confirmed (with a confirmatory HIV-1 RNA at least one week later), and the decision is made to discontinue the subject, plasma for resistance need not be collected again at the early discontinuation visit. All other early discontinuation tests should be performed at the early discontinuation visit.
h. For creatinine clearance only.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

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

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

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

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

7.1.1.1.1 General Informed Consent

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

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

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

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

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

7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or qualified designee will explain the Future Biomedical Research consent to the subject, answer all of his/her questions, and obtain written informed consent before performing any procedure related to the Future Biomedical Research sub-trial. A copy of the informed consent will be given to the subject.

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial. A review of these criteria should occur at the Screening visit and on the Day 1 visit (prior to randomization). For subjects who wish to continue into the study extension, the additional inclusion criteria (9 to 12 Section 5.1.2) are to be reviewed at the Week 96 study visit.

7.1.1.3 Subject Identification Card

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

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

7.1.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee at the Screening visit. The medical history should include information pertaining to the diagnosis of HIV infection and the year diagnosed. If a subject has previously been diagnosed with any Acquired Immune Deficiency Syndrome (AIDS) defining condition, or CD4 <200, the condition as well as a corresponding medical history of Acquired Immune Deficiency Syndrome must be reported. In addition, the subject's history of smoking 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 study.

Investigational agents must be discontinued 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 allocation. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects.

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

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

7.1.1.7 Assignment of Randomization Number

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

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

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

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

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

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

7.1.1.9 Patient-Reported Outcomes

Subjects will complete the Work Productivity and Activity Impairment Questionnaire (WPAI) at Day 1, Weeks 4, 8, 16, and 48 or at the Early Discontinuation visit if the subject discontinues from the study early.

Work Productivity and Activity Impairment Questionnaire (WPAI)

This WPAI is a validated 6-item questionnaire that was created as a patient-reported quantitative assessment of the amount of absenteeism, presenteeism and daily activity impairment attributable to general health or a specific health problem. The questionnaire utilizes a one-week recall period. The measure assesses the quantitative impact of health conditions on loss of time and impaired productivity for functional activities such as work-for-pay, school work, and work around the house. The WPAI has been used in studies of HIV-infected patients.

Administration

Subjects are to complete the questionnaire on their own at the site using an electronic data capture tool at the beginning of the appropriate study visit (see trial flow chart). Every attempt should be made for the subjects to complete the questionnaire prior to receiving study treatment, discussing any medical conditions with the study personnel, or receiving any medical results. Subjects will be eligible to complete the questionnaire only if language translations are available in the subject's native language.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Physical Examination

All physical examinations should be performed as indicated in the Trial 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 [weight, pulse, respiratory rate, blood pressure, and body temperature]) must be obtained at the Screening visit. A complete physical examination generally includes the following assessments: general appearance, head, eyes, ears/nose/ throat, neck, lymph nodes, skin, lungs, heart, abdomen, musculoskeletal, and neurologic evaluations. Breast, rectal, and genitourinary/pelvic exams should be performed when clinically indicated.

Physical examinations after the Screening visit will be directed exams and will include vital signs. Any significant changes between the Screening and Day 1 visits should be noted in the Medical History eCRF at Day 1. Any significant changes in the physical examination

after receiving study therapy at Day 1 must be reported as adverse events and entered on the adverse event eCRF. If the subject is discontinued for any reason during the treatment phase, every attempt should be made to perform a final physical examination.

7.1.2.2 Height Assessment

The subject's height should be assessed as indicated in the Trial Flow Chart (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, and weight should be assessed as indicated in the Trial Flow Charts (Section 6.0). Subjects should be resting in a semi-recumbent position for at least 10 minutes prior to having vital sign measurements obtained.

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

After the Screening visit, the site should indicate whether or not the result is clinically significant and document 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)

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

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

7.1.2.5 Adverse Events

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

If a subject has been diagnosed with an AIDS defining condition following 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 in the base study and in the study extension.

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 (Section 12.8). 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 re-challenge must be approved in advance by the Merck Clinical Director or Designee and, if required, by the Independent Ethics Committee/Institutional Review Board and a re-challenge consent is needed prior to re-initiation of study therapy. If advance approval of re-challenge is not required by local regulations, the IEC/IRB will receive notification for information only.

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

7.1.2.7 Birth Control Confirmation

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

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

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. The total amount of blood/tissue to be drawn/collected over the course of the trial (from pre-trial to post-trial visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per subject can be found in Section 12.4.

7.1.3.1 Serum /Urine Pregnancy Test

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

7.1.3.2 Laboratory Safety Evaluations (Hematology, Chemistry and Others)

Laboratory tests (hematology, chemistry and other) which are to be performed during the trial are specified in Table 4.

Table 4 Laboratory Tests

Hematology	Chemistry[9]	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]
White Blood Cell Count (Total and Differential)	Direct Bilirubin	Hepatitis B e-Antigen[3]
CD4% and Absolute CD4/ Lymphocytes	Indirect Bilirubin	Hepatitis C Antibody[3]
CD8% and Absolute CD8/Lymphocytes	Amylase	Plasma hepatitis C virus PCR quantitative[4]
CD4/CD8 ratio	Lipase	Enzyme immunoassay HIV antibody (with confirmation WB)[3]
	Glucose, fasting[1]	HIV viral RNA Quantification
	Glucose, non-fasting[2]	Serum β-human chorionic gonadotropin (hCG) test[5]
	Blood Urea Nitrogen	Urine β-human chorionic gonadotropin (hCG) test[6]
	Creatinine[8]	HIV Viral resistance[7]
	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])	

Hematology	Chemistry[9]	Other
	Total Cholesterol (fasting[1])	

1. Perform at Randomization (Day 1), and the Weeks 24, 48, and 96 visits in base study; and at the Week 148 and 192 visits in study extension. Subjects should be fasting for 8 hours.
2. Perform at the Screening and Randomization visits, the Weeks 4, 8, 16, 36, 60, 72 and 84 visits in base study; in study extension at the Weeks 110, 116, 132, 164 and 180 visits; and the 14-day follow-up visit.
3. Perform at the screening visit only.
4. If the result of the Hepatitis C Antibody testing is positive, then a plasma hepatitis C virus PCR quantitative test will also be performed.
5. Serum β hCG test at the Screening visit to be performed by central laboratory.
6. Urine β hCG test to be performed at the investigator site at Day 1 and every study visit thereafter.
7. Collect plasma samples at the Screening visit, all scheduled study visits in the base study (except the Day 1 and Post-Study 14-day follow-up visit), the Virologic Failure confirmation visit, and the Early Discontinuation visit (if not collected at Virologic Failure confirmation visit). In the study extension, sample will be collected at the Virologic Failure Confirmation visit and at the Early Discontinuation Visit (if not already obtained at Virologic Failure Confirmation visit). The samples will be tested as specified in Section 7.1.3.5 Viral Resistance Testing.
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
9. Sample taken at virologic failure confirmation visits for creatinine clearance only.

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 both the base study and the study extension. The testing will be performed at the central laboratory using the Abbott RealTime HIV-1 assay.

7.1.3.5 Viral Resistance Testing

Blood samples will be collected for genotypic HIV viral resistance testing at the Screening visit to determine MK-1439, efavirenz, emtricitabine, tenofovir, and lamivudine resistance. Additional resistance testing on screening samples may be performed. In the base study, blood samples will also be collected for potential HIV viral resistance testing at all scheduled study visits (except the Day 1 and Post-Study 14-day follow-up visit), the Virologic Failure Confirmation visit and at the Early Discontinuation Visit (if not already obtained at Virologic Failure Confirmation visit). In the study extension, resistance sample will be collected at the Virologic Failure Confirmation Visit and at the Early Discontinuation Visit (if not already obtained at Virologic Failure Confirmation Visit). All resistance testing will be performed by the central laboratory.

7.1.3.6 CD4 Cell Counts

CD4 cell count (absolute and percentage) will be determined at Screening, Day 1, and at the Weeks 8, 24, 48, 72, and 96 visits in the base study; for subjects who continue into the study extension, CD4 cell count will also be determined at the Weeks 100, 148 and 192 visits. The testing will be performed at the central laboratory using a commercially available assay.

7.1.3.7 Pharmacokinetic/Pharmacodynamic Evaluations

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

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

Note: At Week 24 (Visit 6) and Week 48 (Visit 8), two PK samples will be collected, one pre-dose and one 0.5-2.0 hours post dose. Subjects should be fasting for the collection of both samples. Subjects will be given their dose of Bottle A in the office following the collection of the pre-dose sample and may stay in the office or return to the office for the collection of the post dose sample.

Table 5 Pharmacokinetic Sampling Timepoints

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

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

7.1.3.8 Future Biomedical Research

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

- Leftover DNA for future use
- Plasma for future biomedical research

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws from participation in the trial, all applicable activities scheduled for the Early Discontinuation Visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. In addition all investigative products must be retrieved from the subject.

7.1.4.1.1 Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox PPD 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 trial; treatment during the trial extension is open-label.

When the investigator or sub-investigator needs to identify the drug used by a subject and the dosage administered in case of emergency e.g., the occurrence of serious adverse experiences, 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 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.

In the event that unblinding has occurred, the circumstances around the unblinding (e.g., date and reason) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible. Only the principal investigator or delegate and the respective subject's code should be unblinded. Trial site personnel and Sponsor personnel directly associated with the conduct of the trial should not be unblinded.

7.1.4.3 Calibration of Critical Equipment

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

Critical Equipment for this trial includes:

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

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

7.1.5 Visit Requirements

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

7.1.5.1 Screening

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

- All procedures listed for the Screening visit (Visit 1) in the Trial Flow Chart (Section 6.0) must be completed and the subjects eligibility confirmed by the investigator prior to the subject's randomization and drug administration on Day 1.

- Blood will be collected for safety laboratory evaluations, Hemostatic function tests, HIV/Hepatitis Screen, HIV-1 RNA quantification, CD4 cell counts, and viral resistance testing. These samples will be sent to the appropriate central laboratory(ies) following the procedure(s) set forth in the manual(s).

- Female subjects of childbearing potential will have a serum pregnancy test (hCG) collected at the screening visit. Women who are found to be pregnant will be excluded from the study.

- Subjects will be instructed about the restrictions for concomitant medications, as noted in Section 5.5.

- Subjects will be given a study participation identification card. The card will contain contact information (including direct telephone numbers) to be utilized in the event of an emergency.

7.1.5.2 Treatment Visits in Base Study (Visit 2 – 12)

Randomization Day 1 (Visit 2)

- Procedures listed for Day 1 (Visit 2) on the Trial Flow Chart A (Section 6.0) should be performed prior to the subject's randomization and drug administration on Day 1, unless otherwise specified.

- For a female subject who is of childbearing potential, a urine pregnancy test will be performed at the site prior to study drug initiation. If the urine pregnancy test result is negative and the subject meets the other criteria, the subject will be eligible for randomization and the remainder of the pretreatment (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 safety laboratory evaluations, HIV-1 RNA quantification, CD4 cell counts, and PK measurements. These samples will be sent to the appropriate central laboratory(ies) following the procedure(s) set forth in the manual(s).

- Following completion of the Day 1 pretreatment procedures and confirmation of eligibility, the site pharmacist or study coordinator will contact the IVRS/IWRS for assignment of the drug to be administered. Sites should not call IVRS/IWRS for drug administration until the subject has met all criteria for the study and are ready to receive the first dose of study medication on Day 1.

- Randomized subjects will receive a 4-week supply of study medication (1 bottle each labeled A and B) on Day 1 (Visit 2). Subjects will be instructed to take their first dose of all study medication on the same day as the Day 1 study visit.

- The investigator/study coordinator will give the subject a study medication diary to be completed starting on Day 1 and continuing through the treatment period. The site must ensure that the subject is properly trained and comfortable with completing the medication diary prior to leaving the clinic.

Drug Administration

Subjects will be dispensed study drug as outlined in Table 6 for the base study.

Table 6 Study Drug Bottle (A and B) Components

Bottle Label	Component
Bottle A	MK-1439A or placebo
Bottle B	ATRIPLA™ or placebo

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 once a day (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 once a day (q.d.) orally, at bedtime, on an empty stomach.

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

Week 4 (Visit 3) to Week 96 (Visit 12)

- All procedures for treatment Week 4 (Visit 3) to Week 96 (Visit 12) listed on the Trial Flow Chart A (Section 6.0) should be performed.

- Blood will be collected for safety laboratory evaluations, HIV-1 RNA quantification, CD4 cell counts, HIV viral resistance and PK measurements at the time points specified on the Trial Flow Chart. These samples will be sent to the appropriate central laboratory(ies) following the procedure(s) set forth in the manual(s).

- For a female subject who is of childbearing potential, a urine pregnancy test will be performed at all study visits. If the urine pregnancy test result is positive, the subject must be discontinued.

- Subjects will be required to fast for at least 8 hours prior to study visits at Weeks 24, 48 and 96.

- All bottles of study drug will be returned to the study coordinator at each visit, at which time the drug supplies for the following time period will be dispensed. The number of tablets remaining in the bottle will be counted and recorded in the source documentation. The primary source of adherence data, however, will be the subjects study medication diary.

- Subjects will receive a 4-week supply of study drug (1 bottle each labeled A and B) at Week 4 (Visit 3); an 8-week supply (2 bottles each labeled A and B) at Week 8 (Visit 4) and Week 16 (Visit 5); and a 12-week supply (3 bottles each labeled A and B) at each visit from Week 24 (Visit 6) through Week 84 (Visit 11).

- At Week 96 (Visit 12), subjects who continue into the study extension will receive a 4-week supply of unblinded study drug: this will consist, for all subjects, of MK-1439A, packaged in a single bottle labeled 'Bottle C'.

- At each treatment visit, the study coordinator and subject will review the study medication diary information.

7.1.5.3 Treatment Visits in Study Extension (Visit 13 to Visit 19)

- All procedures listed in the Trial Flow Chart B (Section 6.0) should be performed, as applicable to each study visit, including collection of blood and urine (urine only for female subjects of childbearing potential) for laboratory evaluations.

- Subjects will be required to fast for at least 8 hours prior to the Week 148 and Week 192 visits.

- Subjects will receive a 16-week supply of unblinded study drug, i.e., MK-1439A at each visit through Week 180.

- 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 (except for Week 192). 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 visit, the study coordinator and subject will review the study medication diary information.

7.1.5.4 Virologic Failure Confirmation Visit - Base Study and Study Extension

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

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

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

OR

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

OR

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

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

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

7.1.5.5 Early Discontinuation Visit - Base Study and Study Extension

- When a subject discontinues/withdraws from participation in the trial, all procedures for the Early Discontinuation visit listed on the Trial Flow Charts should be performed.

  At a minimum, the following information should be collected when a subject discontinues:

  - The reason the subject discontinued
  - The data of the last dose of study medications from the trial
  - The date of the last assessment and/or contact
  - All Adverse events (including any Serious Adverse Events)
- 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 study are expected to return for a 14-day post therapy follow-up visit.

7.1.5.6 Post-Trial (Base Study and Study Extension)

- Following the completion of study therapy in the base study (at 96 weeks) or in the study extension (at 192 weeks) or in the event of early discontinuation, subjects will be required to return to the clinic approximately 14 days after the last dose of study drug for the post-study visit as outlined in the Trial Flow Charts (Section 6.0).

- If the post-study visit occurs less than 14 days after the last dose of study drug, a subsequent follow-up phone call should be made at 14 days post the last dose of study drug to determine if any adverse events have occurred since the post-study clinic visit.

7.2 Assessing and Recording Adverse Events

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

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

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

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

All adverse events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. From the time of treatment allocation/randomization through 14 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

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

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

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

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

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

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor either by electronic media or paper. Sponsor Contact information 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 7 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 7. The investigator's assessment of causality is required for each adverse event. Refer to Table 7 and Appendix 12.8 for additional instructions for evaluating adverse events.

Table 7 Evaluating Adverse Events

Maximum Intensity	**Mild**	awareness of sign or symptom, but easily tolerated (for pediatric trials, awareness of symptom, but easily tolerated)
	Moderate	discomfort enough to cause interference with usual activity (for pediatric trials, definitely acting like something is wrong)
	Severe	incapacitating with inability to work or do usual activity (for pediatric trials, extremely distressed or unable to do usual activities)
Seriousness	A serious adverse event (AE) is any adverse event occurring at any dose or during any use of Sponsor's product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred [Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.]; or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis); or	
	Is a cancer (although not serious per ICH definition, is reportable to the Sponsor within 24 hours to meet certain local requirements); **or**	
	Is associated with an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Sponsor's product to be discontinued?	
Relationship to Sponsor's Product	Did the Sponsor's product cause the adverse event? The determination of the likelihood that the Sponsor's product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information **The following components are to be used to assess the relationship between the Sponsor's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the adverse event:	
	Exposure	Is there evidence that the subject was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors
Relationship to Sponsor's Product (continued)	**The following components are to be used to assess the relationship between the Sponsor's product and the AE: (continued)**	
	Dechallenge	Was the Sponsor's product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)

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

7.3 TRIAL GOVERNANCE AND OVERSIGHT

7.3.1 Scientific Advisory Committee

This trial was developed in collaboration with a Scientific Advisory Committee (SAC). The SAC comprises both Sponsor and non-Sponsor scientific experts who provide input with respect to trial design, interpretation of trial results and subsequent peer-reviewed scientific publications.

7.3.2 Executive Oversight Committee

The Executive Oversight Committee (EOC) comprises members of Sponsor Senior Management. The EOC will receive and decide upon any recommendations made by the external Data Monitoring Committee (eDMC) regarding the trial.

7.3.3 Data Monitoring Committee

To supplement the routine trial monitoring outlined in this protocol, an external Data Monitoring Committee (DMC) will monitor the interim data from this trial. The voting members of the committee are external to the Sponsor. The members of the DMC must not be involved with the trial in any other way (e.g., they cannot be trial investigators) and must have no competing interests that could affect their roles with respect to the trial. The DMC will include at least 3 clinicians experienced in Infectious Disease and 1 external statistician; this is in addition to the unblinded trial statistician who will be a non-voting member of the committee. The eDMC will monitor the trial at an appropriate frequency, with suggested periodic reviews to occur approximately every 6 months during the base trial; there will be no involvement of the eDMC in the trial extension. Details regarding the eDMC will be described in a charter document.

The DMC will make recommendations to the EOC regarding steps to ensure both subject safety and the continued ethical integrity of the trial. Also, the DMC will review interim trial results, consider the overall risk and benefit to trial participants (see Section 8.7 - Interim Analyses) and recommend to the EOC if the trial should continue in accordance with the protocol.

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members and the Sponsor protocol team; meeting facilitation; the trial governance structure; and requirements for and proper documentation of DMC reports, minutes, and recommendations will be described in a separate charter that is reviewed and approved by the DMC. The DMC will monitor the trial at an appropriate

frequency, as described in the detailed DMC charter. The DMC will also make recommendations to the Sponsor protocol team regarding steps to ensure both subject safety and the continued ethical integrity of the trial.

8.0 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to any unblinding, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory 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 (i.e., separate documents from the sSAP) will be developed to detail other planned analyses (analysis of PK data, patient-reported outcomes, and future biomedical research). Post hoc exploratory analyses will be clearly identified in the CSR.

The key objectives and hypotheses are to be addressed by the base study (double-blind with active comparator for 96 weeks). Thus, between-treatment comparisons that address key efficacy and safety objectives will be limited to data from the base study. Demography, efficacy and safety data from the study extension for those subjects who continue into the extension will be summarized separately using descriptive statistics only.

8.1 STATISTICAL ANALYSIS PLAN SUMMARY

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 8.2-8.12.

Study Design Overview	A Phase III Multicenter, Double-Blind, Randomized, Active Comparator-Controlled Clinical Trial to Evaluate the Safety and Efficacy of MK-1439A Once-Daily Versus ATRIPLA™ Once-Daily in Treatment-Naïve HIV-1 Infected Subjects
Treatment Assignment	Approximately 680 subjects will be randomized in a 1:1 ratio with ~ 340 on MK-1439A and ~ 340 on ATRIPLA™ in a double-blind fashion with stratification for screening viral load (HIV RNA ≤100,000 vs. >100,000 copies /mL) and chronic hepatitis B and/or C status (yes, no).
Analysis Populations	Efficacy: Treatment Full Analysis Set (FAS) Safety: All Subjects as Treated (ASaT)
Primary Endpoints	1. Proportion of subjects with HIV-1 RNA <50 copies/mL (by the Abbott RealTime HIV-1 Assay) at Week 48 2. Proportion of subjects with neuropsychiatric AEs in the following categories by Week 48: o Dizziness o Sleep disorders and disturbances o Altered Sensorium

Key Secondary Endpoints	1. Safety and tolerability by Week 48 and Week 96 2. Fasting LDL-C as measured by the mean change from baseline at Week 48 3. Fasting non-HDL-C as measured by the mean change from baseline at Week 48 4. Proportion of subjects with neuropsychiatric AEs in the following categories by Week 48: o Depression and suicide/self-injury o Psychosis and psychotic disorders 5. Proportion of subjects with at least one neuropsychiatric AE in any of the 5 categories of: dizziness, sleep disorders and disturbances, altered sensorium, depression and suicide/self-injury, and psychosis and psychotic disorders. 6. Time to discontinuation from study due to an adverse experience 7. Change from baseline in CD4 cell count at Week 48 and Week 96 8. The proportion of subjects achieving HIV-1 RNA < 50 copies/mL (by the Abbott RealTime HIV-1 Assay) at Week 96 9. The proportion of subjects achieving HIV-1 RNA < 40 copies/mL (BLoQ) (by the Abbott RealTime HIV-1 Assay) at Week 48 and Week 96 10. PK of MK-1439 and the PK/PD association
Statistical Methods for Key Efficacy Analyses	The primary hypothesis will be assessed based upon the proportion of subjects maintaining HIV-1 RNA <50 copies/mL (by the Abbott RealTime HIV-1 Assay) at Week 48 post randomization. The Non-Completer=Failure approach (NC=F) as defined by the FDA "snapshot" approach will be used as the primary approach for handling missing data. All missing data will be treated as failures regardless of the reason. The difference in proportions of subjects with HIV-1 RNA <50 copies/mL between treatment groups and the associated 95% confidence interval will be calculated using the stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of the sample size per arm for each stratum (screening HIV RNA ≤100,000 or >100,000 copies/mL). Chronic hepatitis B or C co-infection is not considered to be associated with virologic response; therefore, stratification by hepatitis B or C status will not be included in the analyses of virologic response. For the primary hypothesis, MK-1439A will be considered non-inferior to ATRIPLA™ if the lower bound of the two-sided 95% confidence interval (CI) for the between-treatment difference in proportion of subjects with HIV-1 RNA <50 copies/mL at Week 48 (MK-1439A minus ATRIPLA™) is greater than -10 percentage points (non-inferiority margin). It can be further concluded that MK-1439A is superior to ATRIPLA™ if the lower bound of the two-sided 95% CI for the difference in the response rates (MK-1439A minus ATRIPLA™) is greater than zero contingent upon satisfying the multiplicity criteria. A similar approach will be used for the supportive secondary efficacy hypotheses for non-inferiority and superiority at Week 96.

Statistical Methods for Key Safety Analyses	Neither stratification factor is considered to be associated with the Tier I safety endpoints; therefore, stratification will not be included in the analyses of Tier I events. Tier I Neuropsychiatric AEs (primary safety hypothesis): The treatment differences and the associated 95% confidence intervals will be calculated using the Miettinen and Nurminen method [5]. The treatment differences (95% confidence intervals) will be provided for the proportion of subjects with at least one neuropsychiatric AE in any category as well as at least one AE in each category, and p-values will be provided for dizziness, sleep disorders and disturbances, and altered sensorium. MK-1439A will be considered superior to ATRIPLA™ if the upper bound of the two-sided 95% CI for the difference in proportion of subjects with neuropsychiatric AEs (each category separately) by Week 48 (MK-1439A minus ATRIPLA™) is less than zero. Lipids (secondary safety hypothesis): The change from baseline in fasting lipids (total cholesterol, LDL-C, non-HDL-C, and triglycerides) will be analyzed using ANCOVA models adjusted by baseline lipid level and treatment group. The treatment differences (95% confidence intervals) will be provided for all lipid parameters, and p-values for between treatment comparisons will be provided for LDL-C and non-HDL-C. Tier II The treatment differences and the associated 95% confidence intervals will be provided for the percentage of subjects with the following events based on specific AE categories (i.e., Tier-2 events): (1) at least one adverse experience; (2) at least one drug related adverse experience; (3) at least one serious adverse experience; (4) at least one serious and drug related adverse experience; (5) discontinued study therapy due to an adverse experience. Other Tier-2 events require a minimum of 4 subjects in at least one treatment group. These analyses will be performed using the Miettinen and Nurminen [5] method, an unconditional, asymptotic method.
Interim Analyses	No interim analyses for efficacy are planned. However, an external data monitoring committee will convene to review safety data approximately every 6 months during the study.

Multiplicity	The following hypotheses will be tested sequentially at the one-sided Type 1 error rate of 2.5% (unadjusted for the efficacy hypotheses [#1,7] and after adjusting for interim DMC safety reviews for the safety hypotheses [#2-6]) in the following order: 1) Primary efficacy hypothesis testing non-inferiority at Week 48 2) Primary safety hypothesis for dizziness 3) Primary safety hypothesis for sleep disorders and disturbances 4) Primary safety hypothesis for altered sensorium 5) Secondary safety hypothesis for LDL-C 6) Secondary safety hypothesis for non-HDL-C 7) Secondary efficacy hypothesis testing superiority at Week 48 Testing will stop with the first of these tests failing to reach statistical significance and all subsequent tests would not be considered for statistical significance. In this way, the overall one-sided Type 1 error rate in testing these hypotheses is strongly controlled at a 2.5% level. Note the secondary efficacy hypotheses testing non-inferiority and superiority at Week 96 are supportive only to the primary and secondary efficacy hypotheses at Week 48 and are not considered in the strong control for the Type 1 error for this study. There are no other hypotheses that will be tested and analyses associated with objectives without hypotheses will be considered supportive and/or explanatory.
Sample Size and Power	The planned sample size is 340 subjects in each treatment group (680 total) to achieve 90% power to demonstrate the primary hypothesis that MK-1439A is non-inferior to ATRIPLA™ at an overall one-sided 2.5% alpha level, as measured by the proportion of subjects achieving HIV-1 RNA <50 copies/mL at Week 48 (by the Abbott RealTime HIV-1 Assay). The power calculation assumes a true response rate of 80% at Week 48 for both MK-1439A and ATRIPLA™ using the NC=F approach as defined by the FDA "snapshot" approach.

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 base study will be conducted as a double-blind study under in-house blinding procedures; the study extension, for eligible subjects who elect to continue into the extension, will be conducted as an open-label study. At Week 48 of the base study, when the primary efficacy hypothesis will be evaluated, a copy of the database will be frozen after medical/scientific review has been completed and data have been declared final and complete. This version of the database will be used for initial regulatory submissions. The study (after Week 48, when longer-term safety and efficacy data will be evaluated) will be unblinded to the Sponsor with the exception of a limited group of Sponsor personnel who will remain blinded at the subject level and continue to be responsible for the integrity of the database for ongoing study management. All Sponsor personnel who are unblinded at the subject level for the base period will be excluded from any future data review at the individual subject level. The Week 96 analysis for the base study will follow the same

approach as the Week 48 analysis. For the purpose of the final analysis (after all subjects complete their final visit in the study extension), the official clinical database will not be unblinded until medical/scientific review has been completed, and data have been declared final and complete. Results from the Week 96 (base study) and from the study extension will be presented in separate CSRs (separate from the CSR for the Week 48 analysis of the base study).

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

Treatment-level results of the periodic safety reviews will be provided by the unblinded statistician (external to the Sponsor) to the Data Monitoring Committee (DMC). Limited additional Sponsor personnel may be unblinded to the treatment level results of the safety analyses, if required, in order to act on the recommendations of the DMC. The extent to which individuals are unblinded with respect to results of safety reviews will be documented by the unblinded statistician.

The DMC will serve as the primary reviewer of the safety results from this study with respect to the periodic safety reviews and will make recommendations for discontinuation of or modifications to the study to an executive committee of the Sponsor. If the DMC recommends modifications to the design of the protocol or discontinuation of the study, this executive oversight committee (internal to the Sponsor) may be unblinded to results at the treatment level in order to act on these recommendations. Additional logistical details will be provided in the DMC Charter. Key aspects of the periodic safety reviews are described in Section 8.7.

Prior to final study unblinding, the unblinded statistician will not be involved in any discussions regarding modifications to the protocol, statistical methods, identification of protocol violators, or data validation efforts after the initial safety review.

Pharmacokinetic (PK) data may be unblinded early for the purpose of preparing a population PK model. A separate Modeling and Simulation Plan authored by the department of Quantitative Pharmacology and Pharmacometrics will describe the modeling work to be performed. If early unblinding occurs, a CRO, external to the Sponsor, will perform the modeling. Efficacy and safety data will not be unblinded. Interim data or results will be not shared with the study team prior to study unblinding. No alpha adjustment will be made for this early unblinding for modeling and simulation analysis.

8.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 2.1.

8.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated for within- and/or between-treatment differences are listed below, followed by the descriptions of the derivations of selected endpoints.

8.4.1 Efficacy /Pharmacokinetics Endpoints

8.4.1.1 Efficacy Endpoints

An initial description of efficacy measures is provided in Section 4.2.3.

Proportions of Subjects Achieving HIV-1 RNA < 50 copies/mL, <40 copies/mL and <200 copies/mL (by the Abbott RealTime HIV-1 Assay)

The proportions of subjects achieving HIV-1 RNA <50 copies/mL (and <40 and <200 copies/mL) will be estimated at each time point. The Abbott RealTime HIV-1 Assay, which has a lower limit of reliable quantification (LoQ) of 40 copies/mL, will be used to measure the HIV-1 RNA level in blood samples obtained at each visit.

The primary hypothesis will be assessed based upon the proportion of subjects achieving HIV-1 RNA <50 copies/mL at Week 48.

Change from Baseline in CD4 Cell Count

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

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

Protocol Defined Virologic Failure (PDVF)

Subjects with protocol defined virologic failure (PDVF) as defined in Section 4.2.3.1 will be identified and summarized for each treatment group.

8.4.2 Safety Endpoints

An initial description of safety measures is provided in Section 4.2.3.

Neuropsychiatric Adverse Events

The following categories of specific neuropsychiatric adverse events will be used to address the primary and secondary safety objectives:

- Dizziness
- Sleep disorders and disturbances
- Altered Sensorium
- Depression and suicide/self-injury
- Psychosis and psychotic disorders

A complete list of the preferred terms (based on MeDRA version 17.0) that will be used to define the neuropsychiatric categories can be found in Section 12.6.

Change From Baseline in Fasting Lipids

The change from baseline in fasting lipids (LDL-C, non-HDL-C, total cholesterol, HDL-C, and triglycerides) will be analyzed with primary interest in LDL-C and non-HDL-C.

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.

Time to Discontinuation from Study Due to Adverse Experience

In addition to the counts of subjects who discontinued study therapy due to an adverse experience, the time to discontinuation from study due to an adverse experience will also be estimated.

Predefined Limits of Change in Laboratory Parameters

For the summaries of laboratory tests, subjects must have both a baseline and post-randomization on-treatment measurement to be included. Subjects' laboratory values (based on their most abnormal laboratory test values, in the direction of interest, while on study therapy) will be classified as to whether or not they fall outside of the Pre-Defined Limit of Change (PDLC) and are worse in grade (i.e., more abnormal in the direction of interest) than at baseline. The criteria are adapted from DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS, PUBLISH DATE: AUGUST 2009 Version 1 (Section 12.8). A listing of the subjects who meet the criteria will be provided.

8.5 Analysis Populations

8.5.1 Efficacy Analysis Populations

The Full Analysis Set (FAS) population will serve as the primary population for the analysis of efficacy 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 data using the FAS population. Details on the approach to handling missing data are provided in Section 8.6 Statistical Methods.

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 group.

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 8.6.2. Efficacy results that will be deemed to be statistically significant after consideration of the Type I error control strategy are described in Section 8.8, Multiplicity. Nominal p-values may be computed for other efficacy analyses, but should be interpreted with caution due to potential issues of multiplicity, sample size, etc. Unless otherwise stated, all statistical tests will be conducted at the α=0.025 (1-sided) level.

The key objectives and hypotheses are to be addressed by the base study (double-blind with active comparator for 96 weeks). Thus, between-treatment comparisons that address key efficacy and safety objectives will be limited to data from the base study. Demography, efficacy and safety data from the study extension, for those subjects who continue into the extension, will be summarized separately using descriptive statistics only.

8.6.1 **Statistical Methods for Efficacy Analyses**

Time Window

Table 8 lists the definition of time windows and the target relative day for the scheduled visits in the study which will be used for all analyses by timepoint. The measurement closest to the target date within a window will be used for analyses at a specific timepoint.

Table 8 Definition of Study Timepoint

Treatment Phase	Treatment Period	Protocol Time	Day-Range Rules	Target Day[1]	CSR Time[2]
Pre-treatment	Baseline	Day 1 (Baseline)	≤1	1	Day 1
Treatment	Double-Blind (Base Study)	Week 4	>1 and ≤42	29	Week 4
		Week 8	≥43 and ≤84	57	Week 8
		Week 16	≥85 and ≤140	113	Week 16
		Week 24	≥141and ≤210	169	Week 24
		Week 36	≥211 and ≤294	253	Week 36
		Week 48	≥295 and ≤ 378	337	Week 48
		Week 60	≥379 and ≤ 462	421	Week 60
		Week 72	≥463 and ≤ 546	505	Week 72
		Week 84	≥547 and ≤ 630	589	Week 84
		Week 96	≥631 and ≤ 686	673	Week 96
Treatment	Open-label (Study Extension)	Week 100	≥687 and ≤ 756	701	Week 100
		Week 116	≥757 and ≤ 868	813	Week 116
		Week 132	≥869 and ≤ 980	925	Week 132
		Week 148	≥981 and ≤ 1092	1037	Week 148
		Week 164	≥1093 and ≤ 1204	1149	Week 164
		Week 180	≥1205 and ≤ 1302	1261	Week 180
		Week 192	≥1303	1345	Week 192

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

Missing Values

There are 3 types of missing values:

- intermittent missing values due to a missed or skipped visit or due to an inadequate sample;

- non-intermittent missing values due to premature discontinuations because of treatment-related reasons such as, “clinical adverse experience” (regardless of relationship to study drug), “laboratory adverse experience” (regardless of relationship to study drug), and “withdrew based on HIV-1 RNA results”;

- non-intermittent missing values due to premature discontinuations because of other reasons which are not related to treatment such as loss to follow-up, protocol violation, subject withdrew consent, etc.

Two approaches will be used to handle missing values (Table 9). The primary approach for the analysis of the proportion of subjects achieving HIV-1 RNA <50 copies/mL is the Non-Completer=Failure (NC=F) approach as defined by the FDA "snapshot" approach. Under this approach, only subjects meeting the following can be classified as virologic success at a given time point: 1) subject is on study-assigned double-blind-treatment, 2) subject has HIV-1 RNA measurement(s) within the time window specified in Table 8, and 3) subject has the measurement closest to the target date of the time point <50 copies/mL. The other subjects, either with an HIV-1 RNA measurement of ≥50 copies/mL or no virologic data within the time window due to intermittent missing or premature discontinuation regardless of reasons, will be considered as failures in the analyses of the proportion of subjects achieving HIV-1 RNA <50 copies/mL at that timepoint.

A second approach, the Observed Failure (OF) approach will be performed as a sensitivity analysis for the proportion of subjects achieving HIV-1 RNA<50 copies/mL at Week 48. Under this approach, non-intermittent missing data for subjects who prematurely discontinued assigned treatment due to lack of efficacy are considered as failures at timepoints thereafter. Subjects with other reasons for missing data will be excluded from the analyses.

The same approaches as described above will be used for the analysis of the proportion of subjects achieving HIV-1 RNA <40 and <200 copies/mL.

Table 9 Summary of the Two Approaches to Handle Missing Values

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

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

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

The proportion of subjects achieving HIV-1 RNA < 50 copies/mL will be summarized by treatment group at each time point, with primary interest at Week 48. For each time point of interest, the difference in proportions between treatment groups and the associated 95% confidence interval will be calculated using the stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of the sample size per arm for each stratum (screening HIV-1 RNA ≤100,000 copies/mL or HIV-1 RNA>100,000 copies/mL). The study has two stratification factors: screening HIV-1 RNA level and chronic hepatitis B or C status. Chronic hepatitis B or C co-infection may be associated with serious liver function abnormalities but is not considered to be associated with virologic response; therefore, stratification by hepatitis B or C status will not be included in the analyses of virologic response.

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 missing data will be treated as failures regardless of the reason.

To provide a full picture of virologic outcome at a timepoint, subjects who are not classified as virologic success will be further categorized as virologic failure (HIV-1 RNA ≥50 copies/mL) or as having no virologic data at the time window with reasons of 1) discontinued study due to an AE, 2) discontinued study for other reasons (includes withdraw consent, loss to follow-up, moved, etc.), or 3) on study but missing data in window. The full categorization of virologic outcome at Week 48 and Week 96 will be summarized by treatment group.

A sensitivity analysis will be performed using the Observed Failure (OF) approach under which non-intermittent missing data for subjects who prematurely discontinued assigned treatment due to lack of efficacy are considered as failures at timepoints thereafter. This sensitivity analysis will be limited to the primary efficacy analysis only (i.e., the proportion of subjects achieving HIV-1 RNA <50 copies/mL at Week 48).

A margin of 10 percentage points is used to define the non-inferiority of MK-1439A q.d. to ATRIPLA™ q.d.; this is consistent with regulatory recommendations. MK-1439A q.d. will be concluded non-inferior to ATRIPLA™ q.d. if the lower bound of the two-sided 95% CI for the difference in the proportion of subjects with HIV-1 RNA <50 copies/mL at Week 48 (MK-1439A minus ATRIPLA™ q.d) is greater than -10 percentage points. It can be further concluded that MK-1439A q.d. is superior to ATRIPLA™ q.d. if the lower bound of the two-sided 95% CI for the difference in response rates (MK-1439A minus ATRIPLA™ q.d) is greater than zero contingent upon satisfying the multiplicity criteria.

For the summary of virologic response over time, the difference in proportions between treatment groups at each time point will also be estimated and the associated two-sided 95% CI will be derived in a similar fashion to that described for the primary efficacy analysis.

Change from Baseline in CD4 cell counts

Change from baseline in CD4 cell counts will be summarized by treatment group at each time point at which CD4 cell count is collected, with a key interest at Week 48. The treatment difference in changes from baseline in CD4 cell count at each time point will be estimated between the two treatment groups. However, these estimates will not be subject to an absolute criterion for similarity. The clinical interpretation of the treatment difference is dependent upon the absolute value at baseline, and the magnitude and direction of the CD4 changes seen in each treatment arm.

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

Protocol Defined Virologic Failure (PDVF)

The number of subjects with protocol defined virologic failure will be summarized for each treatment group.

Table 10 summarizes the key efficacy analyses.

Table 10 Analysis Strategy for Key Efficacy Variables

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach[†]	Statistical Method	Analysis Population	Missing Data Approach
Primary Hypothesis				
Proportion of subjects achieving HIV-1 RNA <50 copies/mL at Week 48	P	Stratum-adjusted Mantel-Haenszel[‡]	FAS	NC=F approach
Proportion of subjects achieving HIV-1 RNA <50 copies/mL at Week 48	S	Stratum-adjusted Mantel-Haenszel[‡]	FAS	OF approach
Secondary Objectives				
Proportion of subjects achieving HIV-1 RNA <50 copies/mL at Week 96	P	Stratum-adjusted Mantel-Haenszel[‡]	FAS	NC=F approach
Change from baseline in CD4 cell counts at Week 48 and Week 96	P	Two sample t-test	FAS	OF approach assuming baseline-carried-forward

[†] P=Primary approach; S=Secondary approach.
[‡] Stratum-adjusted (screening HIV RNA-1 ≤100,000 vs. >100,000 copies /mL) Mantel-Haenszel method with the difference weighted by the harmonic mean of the sample size per arm for each stratum.

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.

8.6.2 **Statistical Methods for Safety Analyses**

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse experiences (AEs), laboratory tests and vital signs.

The analysis of safety results will follow a tiered approach Table 11. 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 predefined 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 predefined 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 predefined 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, the proportion of subjects with neuropsychiatric AEs by Week 48 in 3 prespecified categories (dizziness, sleep disorders and disturbances, and altered sensorium with each tested separately) and the change from baseline in fasting LDL-C and non-HDL-C at Week 48 are considered Tier 1 events.

The proportion of subjects with neuropsychiatric AEs by Week 48 in the depression and suicide/self-injury and psychosis and psychotic disorders categories as well as the proportion of subjects experiencing one or more AE in any of the 5 prespecified categories of neuropsychiatric adverse events will be considered Tier 2 events. For these as well as Tier 1 neuropsychiatric AEs, the treatment difference and the associated 95% confidence interval will be calculated using the Miettinen and Nurminen's method (1985) [5], an unconditional,

asymptotic method, and p-values based on this method will be provided for the Tier 1 categories of dizziness, sleep disorders and disturbances, and altered sensorium.

Note that there is no adjustment for safety stratification (Hepatitis B/C status) in the calculation of the confidence intervals or p-values, since the purpose of this stratification factor is to help balance the treatment groups for better interpretation of any potential imbalance in serious liver function abnormalities. This stratification factor has no expected impact on the primary safety endpoint of neuropsychiatric AEs.

The change from baseline in fasting lipids will be analyzed using ANCOVA models adjusted by baseline lipid level and treatment group. The treatment differences and 95% confidence intervals will be provided for all lipid parameters, and the p-value for the between treatment comparison will be provided for LDL-C and non-HDL-C. 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. 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 method.

Table 11 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint†	p-Value	95% CI for Treatment Comparison	Descriptive Statistics
Tier 1	Proportion of subjects with neuropsychiatric AEs in the following categories: • Dizziness • Sleep disorders and disturbances • Altered Sensorium	X	X	X
	Change from baseline in fasting LDL-C and non-HDL-C			
Tier 2	Proportion of subjects with neuropsychiatric AEs in the following categories: • Depression and suicide/self-injury		X	X
	• Psychosis and psychotic disorders		X	X
	Proportion of subjects with one or more neuropsychiatric AEs			
	Change from baseline in fasting lipids not classified as Tier 1			
	Starting lipid-lowering therapy		X	X
	Any AE		X	X
	Any Serious AE		X	X
	Any Drug-Related AE		X	X
	Any Serious and Drug-Related AE		X	X
	Discontinuation due to AE		X	X
	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)			X
	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-specifed as Tier-2 endpoints.
Note: SOC=System Organ Class; PDLC=Pre-Defined Limit of Change; X = results will be provided.

8.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

8.6.3.1 Demographic and Baseline Characteristics

The comparability of the treatment groups for each relevant characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of subjects screened, randomized, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables (e.g., age, gender, race, region, etc), baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

8.7 Interim Analyses

No interim analyses for efficacy are planned for this study. However, an external data monitoring committee will convene to review safety data approximately every 6 months during the study.

8.8 Multiplicity

There are no interim analyses for efficacy and no plans to stop for favorable safety in this study as part of the periodic (~every 6 months) DMC safety reviews. However, as it is customary to spend a small amount of alpha for interim analyses for safety performed by the DMC when there is a primary safety hypothesis, an alpha level of 0.00001 will be allocated for each DMC safety review through Week 48 before testing the primary safety hypothesis and subsequent safety hypotheses.

The primary efficacy hypothesis for non-inferiority will be tested at an unadjusted one-sided alpha level of 0.025 because no interim efficacy analysis will be performed. Furthermore, provided all safety hypotheses are satisfied after establishing the primary efficacy hypothesis, the superiority hypothesis for efficacy will be tested at the unadjusted alpha level of 0.025 as well.

The following hypotheses will be tested sequentially at the one-sided Type 1 error rate of 2.5% (unadjusted for the efficacy hypotheses [#1,7] and after adjusting for interim DMC safety reviews for the safety hypotheses [#2-6]) in the following order:

1) Primary efficacy hypothesis testing non-inferiority at Week 48
2) Primary safety hypothesis for dizziness
3) Primary safety hypothesis for sleep disorders and disturbances
4) Primary safety hypothesis for altered sensorium
5) Secondary safety hypothesis for LDL-C
6) Secondary safety hypothesis for non-HDL-C
7) Secondary efficacy hypothesis testing superiority at Week 48

Testing will stop with the first of these tests failing to reach statistical significance and all subsequent tests would not be considered for statistical significance. In this way, the overall one-sided Type 1 error rate in testing these hypotheses is strongly controlled at a 2.5% level.

Note the secondary efficacy hypotheses testing non-inferiority and superiority at Week 96 are only supportive to the primary and secondary efficacy hypotheses at Week 48 and are not considered in the strong control strategy for the Type 1 error for this study.

There are no other hypotheses that will be tested and analyses associated with objectives without hypotheses will be considered supportive and/or explanatory.

8.9 SAMPLE SIZE AND POWER CALCULATIONS

8.9.1 Sample Size and Power for Efficacy Analyses

The study will randomize 340 subjects into each treatment arm to achieve 90% power to demonstrate the primary hypothesis that MK-1439A q.d. is non-inferior to ATRIPLA™ q.d., at an overall one-sided 2.5% alpha level, as measured by the proportion of subjects achieving HIV-1 RNA <50 copies/mL (by the Abbott RealTime HIV-1 Assay) at Week 48. The power calculation assumes a true response rate of 80% at Week 48 for both the MK-1439A q.d. arm and the ATRIPLA™ q.d arm using the NC=F approach as defined by the FDA "snapshot" approach. A margin of 10 percentage points is used to define the non-inferiority of MK-1439A q.d. versus ATRIPLA™ q.d.; this is consistent with regulatory recommendations. Given the non-inferiority margin of 10%, the assumed response rates and the chosen sample size, non-inferiority may be established when the observed difference in response rates (MK-1439A q.d. minus ATRIPLA™ q.d.) is approximately -3.7% or larger; superiority may be concluded when the observed difference in response rates is approximately 5.7% or larger under the multiplicity testing strategy in Section 8.8. The power calculation is based on an asymptotic method proposed by Farrington and Manning (1990) [6] and is carried out using SAS v9.3. Table 12 summarizes the power for the primary comparison under various assumptions for the control response rate and underlying difference in response rates.

Table 12 Power (%) Under Various Assumptions (With 340 Subjects Randomized in Each Treatment Group)

Response Rate (%) in ATRIPLA™ q.d.	Underlying Difference in Response Rates (%) (MK-1439A q.d. – ATRIPLA™ q.d.)						
	-3	-2	-1	0	1	2	3
74	54	65	76	84	91	95	98
77	56	68	79	87	93	96	98
80	60	72	83	**90**	95	98	99
83	65	77	87	93	97	99	>99
86	70	82	91	96	98	>99	>99
Note: The power is calculated based on 340 subjects expected to be included in the analysis for each treatment group							

8.9.2 **Sample Size and Power for Safety Analyses**

Neuropsychiatric Adverse Experiences

MK-1439 Protocol 007 studied 4 doses of MK-1439 versus efavirenz, each in combination therapy with TRUVADA™, in HIV-1 infected treatment naïve subjects. Based on data from Protocol 007, the expected proportions of subjects with events in each of the categories of prespecified neuropsychiatric adverse events through Week 48 are as follows: dizziness (5% vs 24%), sleep disorders and disturbances (16% vs 29%), altered sensorium (3% vs 10%), depression and suicide/self-injury (4% vs 10%), and psychosis and psychotic disorders (2% vs 2%) in the MK-1439A group and the ATRIPLA™ group, respectively. Due to multiplicity and power considerations, only the first three neuropsychiatric adverse event categories (dizziness, sleep disorders and disturbances, and altered sensorium) were selected for statistical testing. If the proportions of subjects with neuropsychiatric AEs in this study are similar to those observed in Protocol 007, the power to detect a difference between MK-1439A and ATRIPLA™ in the respective Tier 1 categories (dizziness, sleep disorders and disturbances, and altered sensorium) with 340 subjects in each treatment arm is >99%, 97%, and 95%, respectively. Table 13 displays the observed percentage of subjects in each category by treatment group that would be necessary to demonstrate superiority of MK-1439A versus ATRIPLA™ assuming the efavirenz event percentages from Protocol 007 for ATRIPLA™:

Table 13 Observed Percentage in MK-01439A Necessary to Demonstrate Superiority versus ATRIPLA™

	MK-1439A q.d. Superiority will be achieved provided the observed % is less than or equal to	ATRIPLA™ q.d. (same as effaviranz in P007)
Dizziness	17%	24%
Sleep disorders and disturbances	22%	29%
Altered Sensorium	5%	10%

Lipids

The change from baseline in fasting LDL-C and non-HDL-C at Week 48 will be analyzed using ANCOVA models adjusted by baseline lipids level and treatment group. MK-1439A q.d. will be concluded to be superior to ATRIPLA™ q.d. if the mean change from baseline in LDL-C for the MK-1439 group is significantly lower than that for the ATRIPLA™ group. If superiority for LDL-C is established, sequential testing for non-HDL-C will be conducted.

If we assume that ATRIPLA™ q.d. has an effect on lipids at least as large as efavirenz, the treatment difference in mean change from baseline in lipids observed in Protocol 007 can be used as an estimate for the power calculation for this study.

The estimated between treatment differences in mean changes in fasting LDL-C and non-HDL-C, based on the interim data from MK-1439 Protocol 007, were 7.7 mg/dL (standard deviation of 20 mg/dL) and 20 mg/dL (standard deviation of 25 mg/dL), respectively. With 340 subjects in each treatment group, the study has >99% power to detect a between treatment difference of 7.7 mg/dL for mean change from baseline in LDL-C. The study also has >99% power to detect a between treatment difference of 20 mg/dL for mean change from baseline in non-HDL-C.

Adverse Experiences

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 96.7% chance of observing at least one adverse experience among 340 subjects in any treatment group. If no adverse experience of that type is observed among the 340 subjects in any treatment group, this study will provide 95% confidence that the underlying percentage of subjects with that particular adverse experience is <1.1% for the treatment group.

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 number of subjects with the AE within each treatment group are provided in Table 14. These calculations are based on the exact binomial method proposed by Clopper and Pearson (1934) [7].

Table 14 Estimate of Incidence of AEs and 95% Upper Confidence Bound Based on Hypothetical Numbers of Subjects with AEs Among 340 Subjects Randomized in Each Treatment Group

Hypothetical Number of Subjects With An Adverse Event	Estimate of Incidence	95% Upper Confidence Bound[†]
0	0%	1.1
5	1.5%	3.4
10	2.9%	5.3
15	4.4%	7.2
20	5.9%	8.9
25	7.4%	10.7
30	8.8%	12.4

[†] Based on the two-tailed exact confidence interval for a binomial proportion (Clopper and Pearson, 1934 [7]).

Table 15 gives the difference in the incidence of adverse experiences (MK-1439A q.d. – ATRIPLA™ q.d.) that can be ruled out with different power levels and 95% confidence when there are 340 subjects in each treatment group. The underlying incidence of adverse experiences is assumed to be the same for the two treatment groups. For a reasonably common adverse experience which occurs in 20% of subjects either in the MK-1439A q.d. arm or ATRIPLA™ q.d. arm, the study has 90% power to declare with 95% confidence that the true difference between the treatment groups is no more than 9.9 percentage points. The calculations are based on an asymptotic method proposed by Farrington and Manning (1990) [6].

Table 15 Differences in Incidences of AEs (MK-1439A q.d. minus ATRIPLA™q.d.) That Can Be Ruled Out With 340 Subjects in Each Treatment Group

	Difference† in Percentage Points That Can Be Ruled Out with Target Power Assuming the Underlying Incidence of the AE is				
Target Power	10%	20%	30%	40%	50%
80	6.4	8.6	9.8	10.5	10.7
85	6.9	9.2	10.5	11.3	11.5
90	7.5	**9.9**	11.4	12.2	12.4
95	8.3	11.1	12.7	13.5	13.8

†The upper bound of the two-sided 95% confidence interval (Farrington and Manning (1990) for the difference in AE incidences (MK-1439 100 mg q.d. minus darunavir/ritonavir [800 mg/100mg] q.d.) assuming the incidences are the same.

8.9.3 **Overall Power**

The following hypotheses will be tested sequentially at the one-sided Type 1 error rate of 2.5% (unadjusted for the efficacy hypotheses [#1,7] and after adjusting for interim DMC safety reviews for the safety hypotheses [#2-6]) in the following order:

1) Primary efficacy hypothesis testing non-inferiority at Week 48
2) Primary safety hypothesis for dizziness
3) Primary safety hypothesis for sleep disorders and disturbances
4) Primary safety hypothesis for altered sensorium
5) Secondary safety hypothesis for LDL-C
6) Secondary safety hypothesis for non-HDL-C
7) Secondary efficacy hypothesis testing superiority at Week 48

Testing will stop with the first of these tests failing to reach statistical significance and all subsequent tests would not be considered for statistical significance. In this way, the overall one-sided Type 1 error rate in testing these hypotheses is strongly controlled at a 2.5% level. The probability to reach steps 2 through 7 for statistical testing (could also be considered the power to establish the hypotheses in steps 1 through 6) is approximately 90%, 89%, 86%, 82%, 81%, and 80%, respectively.

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

To determine whether the treatment effect is consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI unadjusted for stratification factors) for the primary endpoint will be calculated and plotted within each category of the following classification variables:

- Age category (≤median vs. >median)
- Gender (female, male)
- Region (North America, South America, Europe, Asia, Africa, etc.)
- Race (White, Black, Asian, Other)
- Ethnicity (Hispanic/Latino, not Hispanic/Latino)
- Screening HIV-1 RNA categories (HIV-1 RNA ≤100,000 copies/mL, HIV-1 RNA >100,000 copies/mL)
- Baseline HIV-1 RNA categories (HIV-1 RNA ≤100,000 copies/mL, HIV-1 RNA >100,000 copies/mL)
- Chronic Hepatitis B or C status (HBV/HCV-infected or HBV/HCV-uninfected)
- Baseline CD4 categories (<50, 50-200, and >200 cells/mm^3)

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

8.11 Compliance (Medication Adherence)

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

Subjects are to take one pill once daily from each of the 2 bottles (A & B) of study medication during the base study. For the main analysis of compliance in the base study, a day within the study will be considered an "On-Therapy" day if the subject takes at least one tablet from any bottle provided for this study.

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 on percent compliance by treatment group for the FAS population.

A second analysis in the base study using a different definition of compliance will also be conducted. In this analysis, a day within the study will be considered an "On-Therapy" day only if the subject takes the required number of tablets from all bottles provided for this study (as noted in Section 7.1.5.2) will also be summarized.

During the study extension, MK-1439A will be provided as study medication by the sponsor. Compliance with MK-1439A administration will be summarized for the study extension. A day within the study will be considered an "On-Therapy" day if the subject takes 1 tablet of MK-1439A.

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

8.12 Extent of Exposure

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

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

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

Clinical Supplies will be provided by the Sponsor as summarized in Table 16.

Table 16 Product Descriptions: Base Study and Study Extension

Product Name & Potency	Dosage Form
Base Study	
MK-1439A 100 mg/ 300 mg/ 300 mg or Placebo to match MK-1439A 100 mg/ 300 mg/ 300 mg	Tablet
Efavirenz 600mg / emtricitabine 200mg / tenofovir disoproxil fumarate 300mg (which is equivalent to 245 mg of tenofovir disoproxil). (ATRIPLA™) or Placebo to match Efavirenz 600mg / emtricitabine 200mg / tenofovir disoproxil fumarate 300mg (which is equivalent to 245 mg of tenofovir disoproxil). (ATRIPLA™)	Tablet
Study Extension	
MK-1439A 100 mg/ 300 mg/ 300 mg	Tablet

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.

During the base study, subjects will receive blinded monthly bottles. No kitting is required. During the study extension, subjects will receive open-label MK-1439A.

9.3 Clinical Supplies Disclosure

The emergency unblinding call center will use the randomization schedule for the trial to unblind subjects and to unmask treatment identity. In the event that the emergency unblinding call center is not available for a given site in this trial, the central electronic randomization system (IVRS/IWRS) should be used in order to unblind subjects and to unmask treatment/vaccine identity. The Sponsor will provide random code/disclosure envelopes or lists to the emergency unblinding call center.

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 (e.g., date and reason) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible. Only the principal investigator or delegate and the respective subject's code should be unblinded. Trial site personnel and Sponsor personnel directly associated with the conduct of the trial should not be unblinded.

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 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, 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 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 (which is equivalent to 245 mg of tenofovir disoproxil).) 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 Merck, is provided in Section 12.1 - Merck Code of Conduct for Clinical Trials.

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

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

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

Trial documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the trial site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the trial documentation and worksheets/case report forms.

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

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

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

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

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

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

10.4 Compliance with Trial Registration and Results Posting Requirements

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

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

10.5 Quality Management System

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

10.6 Data Management

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

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

10.7 Publications

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

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

the efficacy and safety measures, the statistical analysis plan, and any amendments relating to those sections. The Sponsor reserves the right to redact proprietary information.

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

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

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

11.0 LIST OF REFERENCES

1. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. November 3, 2008; 1-139. Available at **http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.**

2. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection - recommendations for a public health approach. {03RT6N}

3. Anderson M, Gilmartin J, Cilissen C, etc., Safety, Tolerability, and Pharmacokinetics of Single and Multiple Doses of MK-1439, a Novel HIV Non-Nucleoside Reverse Transcriptase Inhibitor, in Healthy Subjects, Abstract presented at Conference on Retroviruses and Opportunistic Infections, March 3 – 6, 2014, Boston, MA

4. Gatell1 JM, Morales-Ramirez JO, Hagins DP, Thompson M, Arastéh K, Hoffmann C, Rugina S, Osiyemi O, Erscoiu S, Dretler R, Harvey C, Xu X, Teppler H. 48 week Efficacy and Safety and Early CNS tolerability of Doravirine, a novel NNRTI, with TDF/FTC in ART-Naïve HIV Infected patients. Presented at the Conference on HIV Drug Therapy, Glasgow, Nov. 2 – 6, 2014.

5. Miettinen OS, Nurminen M. Comparative analysis of two rates. Statistics in Medicine 1985; 4:213-226.

6. Farrington CP, Manning G. Test statistics and sample size formulae for comparative binomial trials with null hypothesis of non-zero risk difference or non-unity relative risk. Statistics in Medicine 1990; 9: 1447-54.

7. Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of binomial. Biometrika 1934; 26: 404-13.

12.0 APPENDICES

12.1 Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

Merck, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing and reporting these trials in compliance with the highest ethical and scientific standards. Protection of subject safety is the overriding concern in the design of clinical trials. In all cases, Merck clinical trials will be conducted in compliance with local and/or national regulations and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Such standards shall be endorsed for all clinical interventional investigations sponsored by Merck irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials which are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials which are not under the control of Merck.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of Merck or comparator products. Alternatively, Merck may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine subject preferences, etc.

The design (i.e., subject population, duration, statistical power) must be adequate to address the specific purpose of the trial. Research subjects must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

Merck selects investigative sites based on medical expertise, access to appropriate subjects, adequacy of facilities and staff, previous performance in Merck trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by Merck personnel to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice. Merck reviews clinical data for accuracy, completeness and consistency. Data are verified versus source documentation according to standard operating procedures. Per Merck policies and procedures, if fraud, misconduct or serious GCP-non-Compliance are suspected, the issues are promptly investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified and data disclosed accordingly.

B. Publication and Authorship

To the extent scientifically appropriate, Merck seeks to publish the results of trials it conducts. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing. In such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues of multiplicity.

Merck's policy on authorship is consistent with the requirements outlined in the ICH-Good Clinical Practice guidelines. In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. Merck funding of a trial will be acknowledged in publications.

III. Subject Protection

A. IRB/ERC review

All clinical trials will be reviewed and approved by an independent IRB/ERC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the IRB/ERC prior to implementation, except that changes required urgently to protect subject safety and well-being may be enacted in anticipation of IRB/ERC approval. For each site, the IRB/ERC and Merck will approve the subject informed consent form.

B. Safety

The guiding principle in decision-making in clinical trials is that subject welfare is of primary importance. Potential subjects will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care. Subjects are never denied access to appropriate medical care based on participation in a Merck clinical trial.

All participation in Merck clinical trials is voluntary. Subjects are enrolled only after providing informed consent for participation. Subjects may withdraw from a Merck trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

Merck is committed to safeguarding subject confidentiality, to the greatest extent possible. Unless required by law, only the investigator, sponsor (or representative) and/or regulatory authorities will have access to confidential medical records that might identify the research subject by name.

D. Genomic Research

Genomic Research will only be conducted in accordance with informed consent and/or as specifically authorized by an Ethics Committee.

IV. Financial Considerations

A. Payments to Investigators

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

Merck does not pay for subject referrals. However, Merck may compensate referring physicians for time spent on chart review to identify potentially eligible subjects.

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices including, in the U.S., those established by the American Medical Association (AMA).

V. Investigator Commitment

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

* In this document, "Merck" refers to Merck Sharp & Dohme Corp. and Schering Corporation, each of which is a subsidiary of Merck & Co., Inc. Merck is known as MSD outside of the United States and Canada. As warranted by context, Merck also includes affiliates and subsidiaries of Merck & Co., Inc."

12.2 Collection and Management of Specimens for Future Biomedical Research

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens collected in this trial as outlined in Section 7.1.3.8 – Future Biomedical Research 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 Merck 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 Merck or designees and research will be monitored and reviewed by a committee of our scientists and clinicians.

3. Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

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

b. Informed Consent

Informed consent for specimens (i.e., DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all subjects or legal guardians, at a trial visit by the investigator or his or her designate. Informed consent for Future Biomedical Research should be presented to the subjects on Visit 1. If delayed, present consent at next possible Subject Visit. Informed consent must be obtained prior to collection of all Future Biomedical Research specimens. Consent forms signed by the subject will be kept at the clinical trial site under secure storage for regulatory reasons. Information contained on the consent form alone cannot be traced to any specimens, test results, or medical information once the specimens have been rendered de-identified

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.

Each informed consent approved by an ethics committee is assigned a unique tracking number. The tracking number on this document will be used to assign specimen permissions for each specimen into the Entrusted Keyholder's Specimen Database.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of both consent and acquisition of Future Biomedical Research specimens will be captured in the electronic Case Report Forms (eCRFs). Reconciliation of both forms will be performed to assure that only appropriately-consented specimens are used for this sub-trial's research purposes. Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen Collections

Blood specimens for DNA or RNA isolation will usually be obtained at a time when the subject is having blood drawn for other trial purposes. Specimens like tissue and bone marrow will usually be obtained at a time when the subject is having such a procedure for clinical purposes.

Specimens will be collected and sent to the laboratory designated for the trial where they will be processed (e.g., DNA or RNA extraction, etc) following the Merck approved policies and procedures for specimen handling and preparation.

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, Merck has developed secure policies and procedures. All specimens will be de-identified 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.

This first code will be replaced with a second code at a Merck designated storage/lab facility. The second code is linked to the first code via a second key. The specimen is now double coded. Specimens with the second code are sometimes referred to as de-identified specimens. The use of the second code provides additional confidentiality and privacy protection for subjects over the use of a single code. Access to both keys would be needed to link any data or specimens back to the subject's identification.

The second code is stored separately from the first code and all associated personal specimen identifiers. A secure link, the second key, will be utilized to match the second code to the first code to allow clinical information collected during the course of the trial to be associated with the specimen. This second key will be transferred under secure procedures by the Merck designated facility to an Entrusted Keyholder at Merck. The second code will be logged into the primary biorepository database at Merck and, in this database, this identifier will not have identifying demographic data or identifying clinical information (i.e., race, sex, age, diagnosis, lab values) associated with it. The specimen will be stored in a designated biorepository site with secure policies and procedures for specimen storage and usage.

The second key can be utilized to reconstruct the link between the results of future biomedical research and the clinical information, at the time of analysis. This linkage would not be possible for the scientist conducting the analysis, but can only be done by the Merck Entrusted Keyholder under strict security policies and procedures. The Merck Entrusted Keyholder will link the information and then issue a de-identified data set for analysis. The only other circumstance by which future biomedical research data would be directly linked to the full clinical data set would be those situations mandated by regulatory authorities (e.g., EMEA, FDA), whereby this information would be directly transferred to the regulatory authority.

5. Biorepository Specimen Usage

Specimens obtained for the Merck Biorepository will be used for analyses using good scientific practices. However, exploratory analyses will not be conducted under the highly validated conditions usually associated with regulatory approval of diagnostics. The scope of research performed on these specimens is limited to the investigation of the variability in biomarkers that may correlate with a clinical phenotype in subjects.

Analyses utilizing the Future Biomedical Research specimens may be performed by Merck, or an additional third party (e.g., a university investigator) designated by Merck. The investigator conducting the analysis will be provided with double coded specimens. Re-association of analysis results with corresponding clinical data will only be conducted by the Merck Entrusted Keyholder. Any contracted third party analyses will conform to the specific scope of analysis outlined in this sub-trial. Future Biomedical Research specimens remaining with the third party after the specific analysis is performed will be returned to the sponsor or destroyed and documentation of destruction will be reported to Merck.

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 Merck using the designated mailbox PPD and a form will be provided by Merck 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 Merck 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 acquisition. 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 Merck 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 Merck policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

Separate databases for specimen information and for results from the Future Biomedical Research sub-trial will be maintained by Merck. This is done to separate the future exploratory test results (which include genetic data) from the clinical trial database thereby maintaining a separation of subject number and these results. The separate databases are accessible only to the authorized Sponsor 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 in international standards (e.g., ISO17799) to protect against unauthorized access. The Merck Entrusted Keyholder maintains control over access to all specimen data. These data are collected for future biomedical research purposes only as specified in this sub-trial will not be used for any other purpose.

9. Reporting of Future Biomedical Research Data to Subjects

There is no definitive requirement in either authoritative ethical guidelines or in relevant laws/regulations globally that research results have to be, in all circumstances, returned to the trial participant. Some guidelines advocate a proactive return of data in certain instances. No information obtained from exploratory laboratory studies will be reported to the subject or family, and this information will not be entered into the clinical database maintained by Merck on subjects. Principle reasons not to inform or return results to the subject include: lack of relevance to subject health, limitations of predictive capability, concerns of misinterpretation and absence of good clinical practice standards in exploratory research typically used for diagnostic testing.

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 as to how to offer clinical diagnostic testing (paid for by Merck) to subjects enrolled and will be advised that counseling should be made available for all who choose to participate in this diagnostic testing.

If any exploratory results are definitively associated with clinical significance after completion of a clinical trial, Merck will publish the results without revealing specific subject information, inform all trial sites who participated in the Merck clinical trial and post anonymized results on our website or other accredited website(s) that allow for public access (e.g., disease societies who have primary interest in the results) in order that physicians and patients may pursue clinical diagnostic testing if they wish to do so.

10. Gender, Ethnicity and Minorities

Although many diagnoses differ in terms of frequency by ethnic population and gender, every effort will be made to recruit all subjects diagnosed and treated on Merck clinical trials for future biomedical research. When trials with specimens are conducted and subjects identified to serve as controls, every effort will be made to group specimens from subjects and controls to represent the ethnic and gender population representative of the disease under current investigation.

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.

Merck 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.

It is necessary for subject-related data (i.e., ethnicity, diagnosis, drug therapy and dosage, age, toxicities, etc.) to be re-associated to double coded specimens at the time of data analysis. These subject data will be kept in a separate, secure Merck database, and all specimens will be stripped of subject identifiers. No information concerning results obtained from future biomedical research will be entered into clinical records, nor will it be released to outside persons or agencies, in any way that could be tied to an individual subject.

12. Self-Reported Ethnicity

Subjects who participate in future biomedical research will be asked to provide self-reported ethnicity. Subjects who do not wish to provide this data may still participate in future biomedical research.

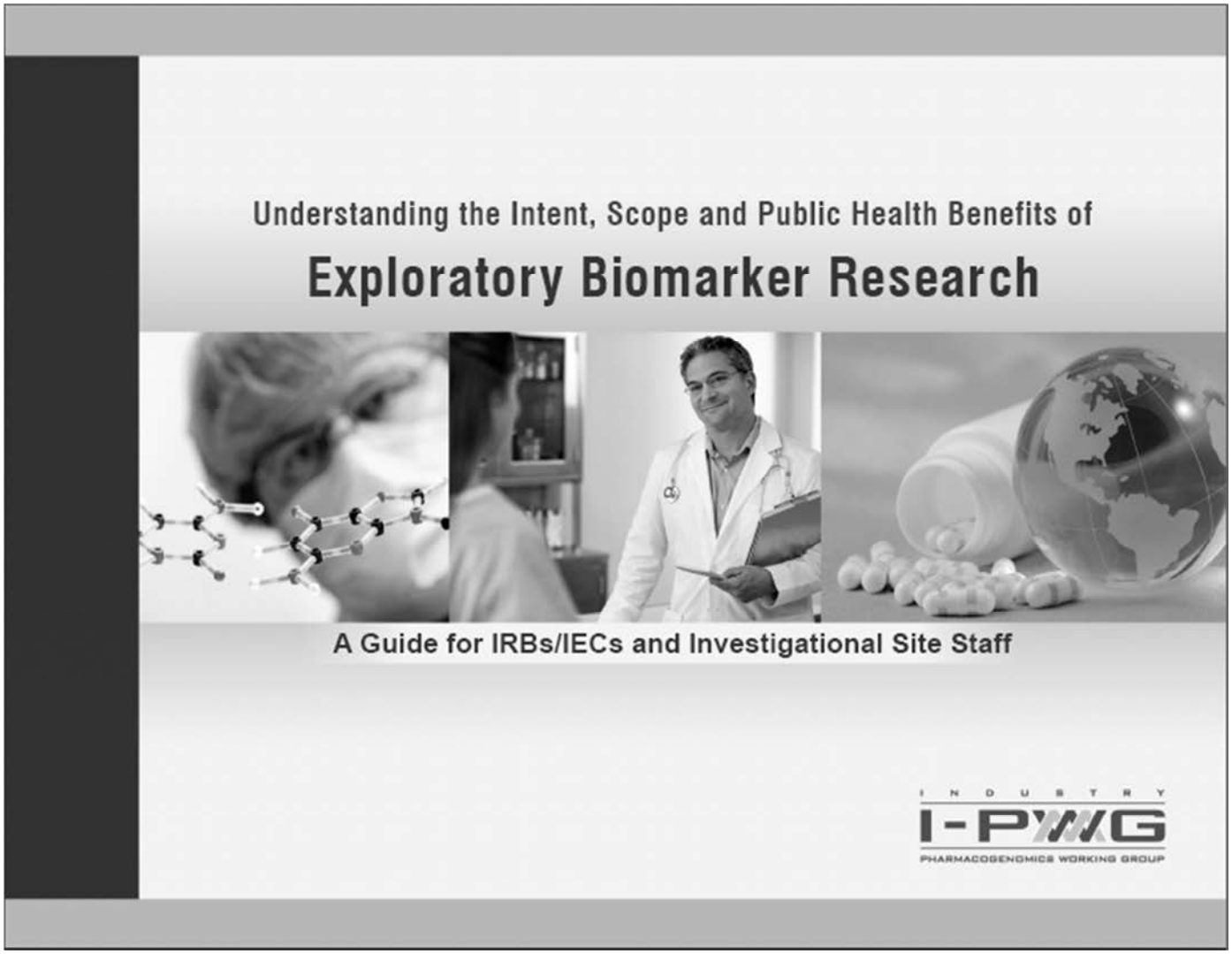
13. Questions

Any questions related to the future biomedical research should be e-mailed directly to PPD

14. References

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

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



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

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

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

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

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

2. Why is Biomarker Research Important?

Importance to Patients and Public Health

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

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

Importance to Drug Development

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

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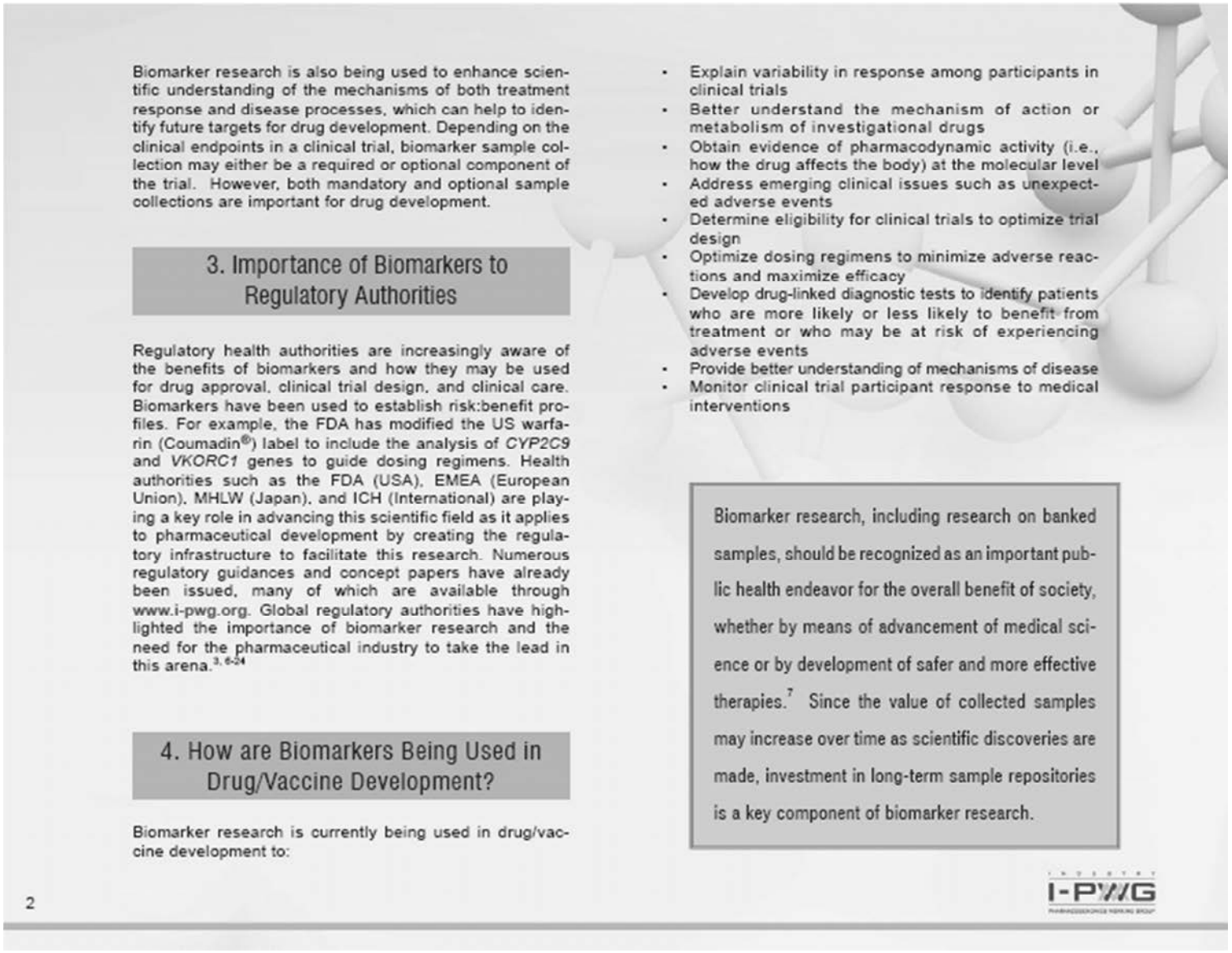
Biomarker research is also being used to enhance scientific understanding of the mechanisms of both treatment response and disease processes, which can help to identify future targets for drug development. Depending on the clinical endpoints in a clinical trial, biomarker sample collection may either be a required or optional component of the trial. However, both mandatory and optional sample collections are important for drug development.
3. Importance of Biomarkers to Regulatory Authorities
Regulatory health authorities are increasingly aware of the benefits of biomarkers and how they may be used for drug approval, clinical trial design, and clinical care. Biomarkers have been used to establish risk:benefit profiles. For example, the FDA has modified the US warfarin (Coumadin®) label to include the analysis of CYP2C9 and VKORC1 genes to guide dosing regimens. Health authorities such as the FDA (USA), EMEA (European Union), MHLW (Japan), and ICH (International) are playing a key role in advancing this scientific field as it applies to pharmaceutical development by creating the regulatory infrastructure to facilitate this research. Numerous regulatory guidances and concept papers have already been issued, many of which are available through www.i-pwg.org. Global regulatory authorities have highlighted the importance of biomarker research and the need for the pharmaceutical industry to take the lead in this arena.[3, 6-24]
4. How are Biomarkers Being Used in Drug/Vaccine Development?
Biomarker research is currently being used in drug/vaccine development to:
• Explain variability in response among participants in clinical trials
• Better understand the mechanism of action or metabolism of investigational drugs
• Obtain evidence of pharmacodynamic activity (i.e., how the drug affects the body) at the molecular level
• Address emerging clinical issues such as unexpected adverse events
• Determine eligibility for clinical trials to optimize trial design
• Optimize dosing regimens to minimize adverse reactions and maximize efficacy
• Develop drug-linked diagnostic tests to identify patients who are more likely or less likely to benefit from treatment or who may be at risk of experiencing adverse events
• Provide better understanding of mechanisms of disease
• Monitor clinical trial participant response to medical interventions
Biomarker research, including research on banked samples, should be recognized as an important public health endeavor for the overall benefit of society, whether by means of advancement of medical science or by development of safer and more effective therapies.[7] Since the value of collected samples may increase over time as scientific discoveries are made, investment in long-term sample repositories is a key component of biomarker research.
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5. Biomarkers are Already a Reality in Health Care

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

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

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

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

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

6. Biomarker Samples from Clinical Trials: An Invaluable Resource

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

7. Informed Consent for Collection & Banking of Biomarker Samples

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

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

Optional vs. Required Subject Participation

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

Consent for Future Research Use

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

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

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

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

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

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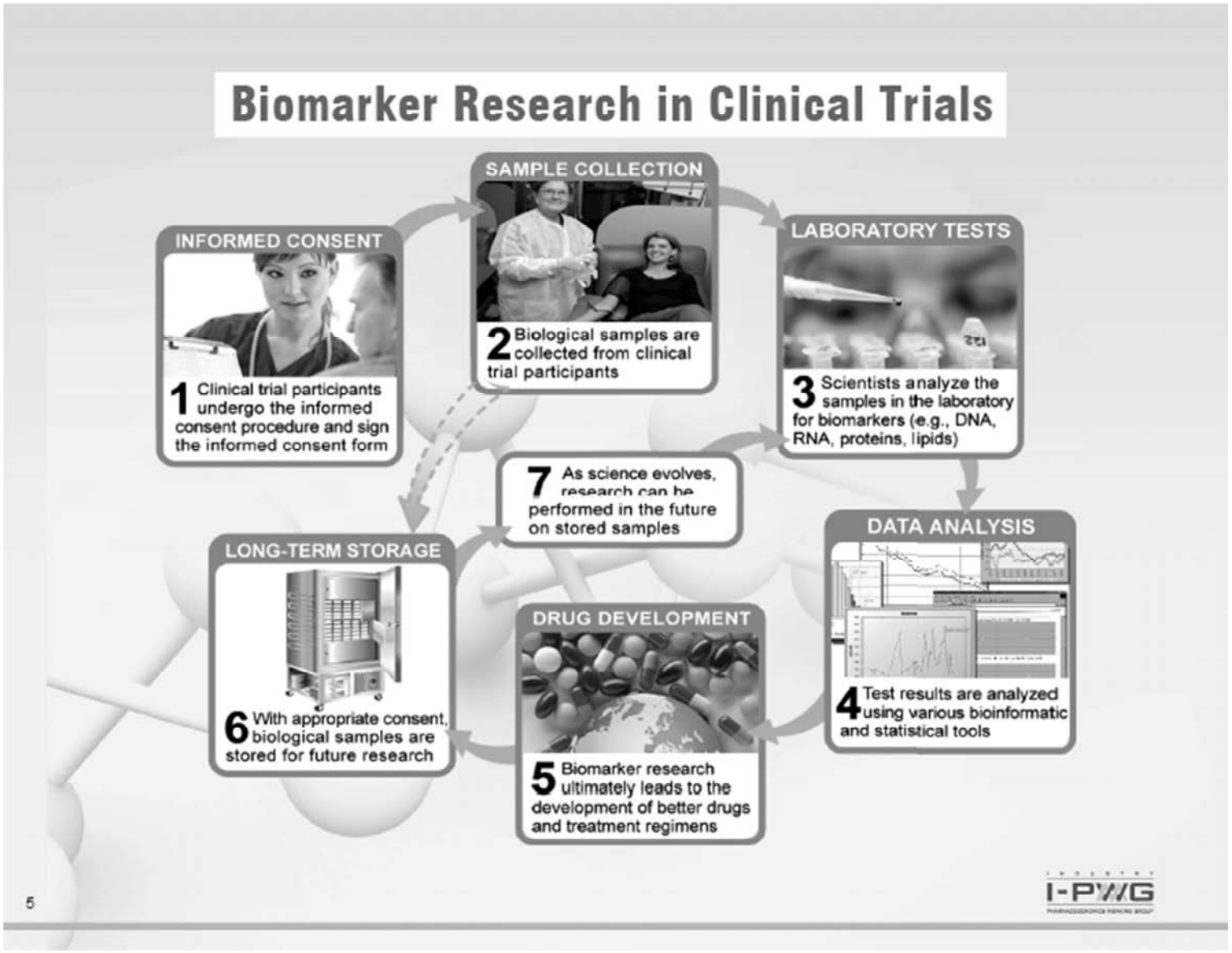
Biomarker Research in Clinical Trials
SAMPLE COLLECTION
2 Biological samples are collected from clinical trial participants
INFORMED CONSENT
1 Clinical trial participants undergo the informed consent procedure and sign the informed consent form
LABORATORY TESTS
3 Scientists analyze the samples in the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

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

9. Return of Research Results to Study Participants

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

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

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

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

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

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

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

10. Benefits and Risks Associated with Biomarker Research

Benefits

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

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

Risks

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

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

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

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

11. Privacy, Confidentiality, and Patient Rights

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

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

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

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

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

12.Where to Get More Information?

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

13. What is I-PWG?

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

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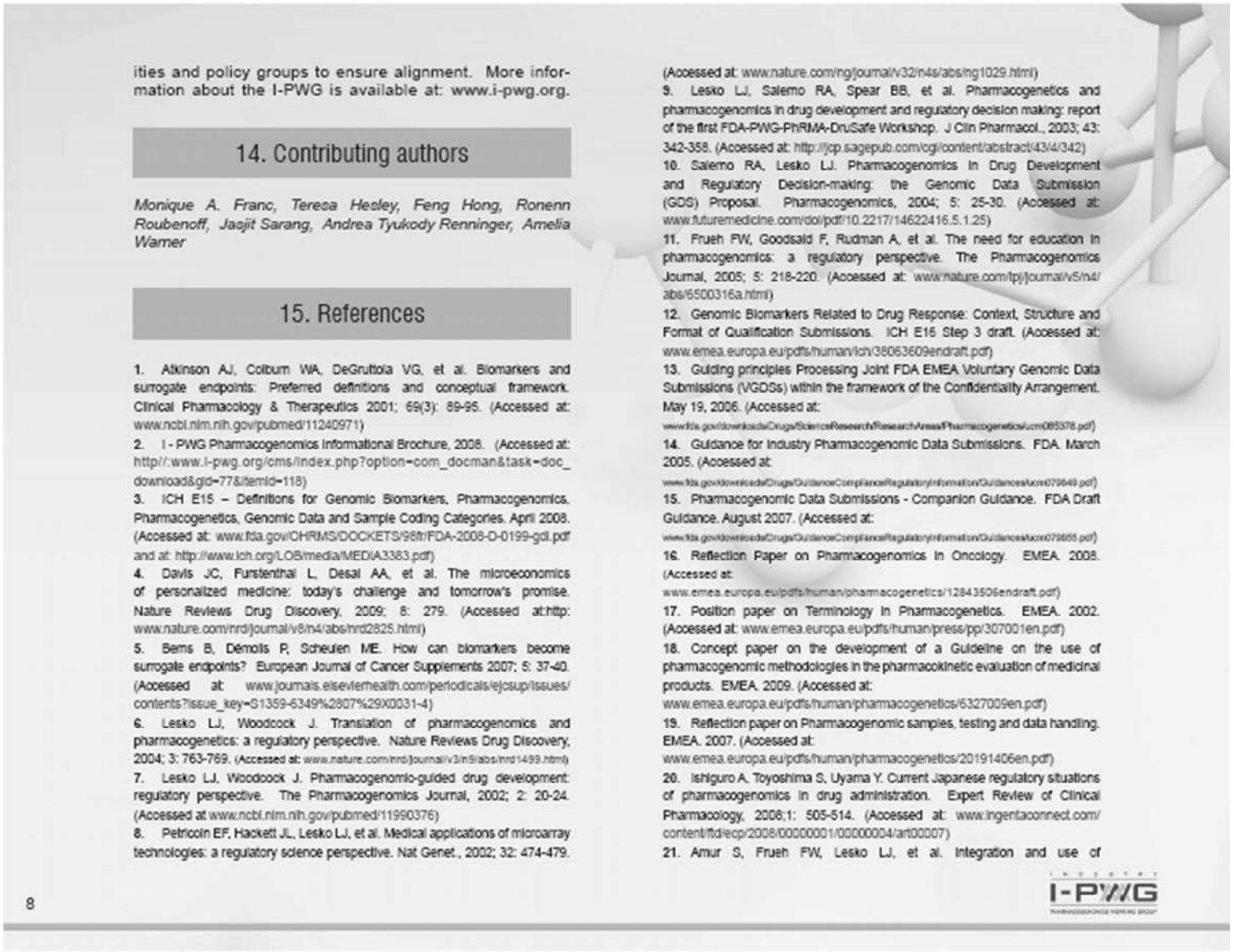

ities and policy groups to ensure alignment. More information about the I-PWG is available at: www.i-pwg.org.

14. Contributing authors

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

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

12.4.1 Base Study

Visit Number/Title:	1	2 Random-ization	3	4	5	6	7	8	9	10	11	12	U (Virologic Failure Confirmation)	U (Early Discon-tinuation	99	
Trial Period	Screen-ing	Treatment													Post treatment	
Trial Procedures	Screen	Fasting [a] Day 1[a]	WK 4	WK 8	WK 16	Fast-ing [a] WK 24	WK 36	Fast-ing [a] WK 48	WK 60	WK 72	WK 84	Fast-ing [a] WK 96	> 1week after initial virologic failure	At time of Discon	Post study 14-day follow-up	Total Volume
Laboratory Procedures/Assessments																
Hematology	2	2	2	2	2	2	2	2	2	2	2	2		2	2	28
Serum Pregnancy Test [c]	29															
Collect Blood for Safety Laboratory Tests (Chemistry)		7[a]	7	7	7	7[a]	7	7	7	7	7	7[a]	3.5[h]	7	7	123.5
HIV/Hepatitis Screen [b]																
Hemostatic Function Test [d]	4.5															4.5
Virology Test Plasma HIV viral RNA quantification test (Abbott Real Time HIV-1)	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	150
Collect Blood for CD4 Cell Count	2	2		2		2		2		2		2				14
Collect Blood for MK-1439 PK [e]		4	4	4		8		8								28
Collect Plasma for Viral Resistance Test	14		14	14	14	14	14	14	14	14	14	14	14	14[g]		182
Collect Blood (DNA) for Genetic Analysis[b]		8.5														8.5
Collect Plasma for Future Biomedical Research[b]		10						10				10				30
Total (mL)	61.5	43.5	37	39	33	43	33	53	33	35	33	45	27.5	33	19	568.5
Total (tablespoons)	4.1	2.9	2.5	2.6	2.2	2.9	2.2	3.5	2.2	2.3	2.2	3.0	1.8	2.2	1.3	~37.9

a. Fasting is required at these visits for lipids measurement.
b. Includes Enzyme Immunoassay HIV Antibody Screen, Serum Hepatitis B Surface Antigen, Serum Hepatitis B Surface Antibody, Serum Hepatitis B e-Antigen and Serum Hepatitis C Antibody. A plasma Hepatitis C virus PCR quantitative test (an additional ~6 ml= 0.4 tablespoon of blood) will be performed if the Hepatitis C antibody test is positive.
c. For women of childbearing potential.
d. Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT) and International Normalized Ratio (INR).

Visit Number/Title:	1	2 Random-ization	3	4	5	6	7	8	9	10	11	12	U (Virologic Failure Confirmation)	U (Early Discon-tinuation	99	
Trial Period	Screen-ing	Treatment													Post treatment	
Trial Procedures	Screen	Fasting [a] Day 1[a]	WK 4	WK 8	WK 16	Fast-ing [a] WK 24	WK 36	Fast-ing [a] WK 48	WK 60	WK 72	WK 84	Fast-ing [a] WK 96	> 1week after initial virologic failure	At time of Discon	Post study 14-day follow-up	

e. At Study Day 1 and Study Week 4, sample must be collected predose. At Study Week 12, the sample may be collected irrespective of time of dose. At Study Weeks 24 and 48, samples must be collected predose, and within 0.5 to 2 hours postdose (subjects should remain fasting until postdose PK sample is collected).
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 needs not be collected again at the discontinuation visit.
h. For creatinine clearance only.

12.4.2 **Week 100 Through Post-Study 14-Day Follow-up (Study Extension)**

Week (Visit)	**100 (V14)**	**116 (V15)**	**132 (V16)**	Fasting **148 (V17)** [d]	**164 (V18)**	**180 (V19)**	Fasting **192 (V20)** [d]	**Viral Failure Confirmation (U)**	**Early Discontinuation (U)**	**Post-Study 14-Day Follow-up (99)**	**Total Vol. in Study Extension** [a]
Hematology	2	2	2	2	2	2	2		2	2	18
Collect Blood for CD4 Cell Count	2			2			2				6
Collect Blood for Safety Laboratory Tests (Chemistry)	7	7	7	7	7	7	7	3.5[e]	7	7	66.5
Virology Test Plasma HIV viral RNA quantification test (Abbott Real Time HIV-1)	10	10	10	10	10	10	10	10	10	10	100
Collect Plasma for Viral Resistance								14	14 [c]		28
TOTAL for visit (mL)	**21**	**19**	**19**	**21**	**19**	**19**	**21**	**27.5**	**33**	**19**	**218.5**
Total (tablespoons) [b]	**1.4**	**1.3**	**1.3**	**1.4**	**1.3**	**1.3**	**1.4**	**1.8**	**2.2**	**1.2**	**~ 14.5**

[a] These samples are in addition to those collected during the base study. Because an early discontinuation visit could potentially happen during the base study or the study extension, but not both, and because there is no post-study follow-up visit after the base study for subjects who continue into the study extension, the total volume for both base study and study extension could be less than the sum.
[b] One tablespoon = 15 mL.
[c] Early Discontinuation Visit sample should be collected only if not done at Viral Failure Confirmation Visit.
[d] Fasting is required at these visits for lipids measurement.
[e] For creatinine clearance only.

12.5 **Plasma Assay—Sample Collection, Handling, Labeling, Storage, and Shipment**

See Laboratory Manual.

12.6 List of Preferred Neuropsychiatric Adverse Events

Category	Active PTs in MeDRA version 17.0
Dizziness	
	Dizziness
Sleep Disorders and Disturbances	
	Behavioural insomnia of childhood
	Hyposomnia
	Initial insomnia
	Insomnia
	Middle insomnia
	Terminal insomnia
	Breathing-related sleep disorder
	Dyssomnia
	Hypnagogic hallucination
	Hypnopompic hallucination
	Sleep attacks
	Abnormal dreams
	Abnormal sleep-related event
	Confusional arousal
	Loss of dreaming
	Nightmare
	Parasomnia
	Rapid eye movements sleep abnormal
	Sleep inertia
	Sleep sex
	Sleep talking
	Sleep terror
	Sleep-related eating disorder
	Somnambulism
	Sleep disorder due to a general medical condition
	Sleep disorder due to general medical condition, hypersomnia type
	Sleep disorder due to general medical condition, insomnia type
	Sleep disorder due to general medical condition, mixed type
	Sleep disorder due to general medical condition, parasomnia type
	Hypersomnia-bulimia syndrome
	Sleep disorder
	Sopor
	Hypersomnia related to another mental condition
	Insomnia related to another mental condition
Altered Sensorium	
	Altered state of consciousness
	Apallic syndrome
	Consciousness fluctuating
	Depressed level of consciousness
	Hyperglycaemic unconsciousness
	Lethargy

Category	Active PTs in MeDRA version 17.0
	Loss of consciousness
	Neonatal oversedation
	Post-injection delirium sedation syndrome
	Postictal state
	Preictal state
	Sedation
	Somnolence
	Somnolence neonatal
	Stupor
	Syncope
Depression and suicide/self-injury	
	Activation syndrome
	Adjustment disorder with depressed mood
	Adjustment disorder with mixed anxiety and depressed mood
	Agitated depression
	Anhedonia
	Antidepressant therapy
	Childhood depression
	Decreased interest
	Depressed mood
	Depression
	Depression postoperative
	Depressive symptom
	Dysphoria
	Dysthymic disorder
	Electroconvulsive therapy
	Feeling guilty
	Feeling of despair
	Feelings of worthlessness
	Major depression
	Menopausal depression
	Post stroke depression
	Postictal depression
	Postpartum depression
	Completed suicide
	Depression suicidal
	Intentional overdose
	Intentional self-injury
	Poisoning deliberate
	Self injurious behaviour
	Self-injurious ideation
	Suicidal behaviour
	Suicidal ideation
	Suicide attempt
Psychosis and psychotic disorders	Acute psychosis
	Alcoholic psychosis
	Alice in wonderland syndrome
	Brief psychotic disorder with marked stressors

Category	Active PTs in MeDRA version 17.0
	Brief psychotic disorder without marked stressors
	Brief psychotic disorder, with postpartum onset
	Charles Bonnet syndrome
	Childhood psychosis
	Clang associations
	Cotard's syndrome
	Delusion
	Delusion of grandeur
	Delusion of reference
	Delusion of replacement
	Delusional disorder, erotomanic type
	Delusional disorder, grandiose type
	Delusional disorder, jealous type
	Delusional disorder, mixed type
	Delusional disorder, persecutory type
	Delusional disorder, somatic type
	Delusional disorder, unspecified type
	Delusional perception
	Delusions, mixed
	Dementia of the Alzheimer's type, with delusions
	Depressive delusion
	Derailment
	Epileptic psychosis
	Erotomanic delusion
	Flight of ideas
	Hallucination
	Hallucination, auditory
	Hallucination, gustatory
	Hallucination, olfactory
	Hallucination, synaesthetic
	Hallucination, tactile
	Hallucination, visual
	Hallucinations, mixed
	Hypnagogic hallucination
	Hypnopompic hallucination
	Hysterical psychosis
	Ideas of reference
	Illusion
	Jealous delusion
	Loose associations
	Neologism
	Paranoia
	Paranoid personality disorder
	Parkinson's disease psychosis
	Paroxysmal perceptual alteration
	Persecutory delusion
	Postictal psychosis
	Post-injection delirium sedation syndrome
	Posturing
	Psychosis postoperative
	Psychotic behaviour

Category	Active PTs in MeDRA version 17.0
	Psychotic disorder
	Psychotic disorder due to a general medical condition
	Reactive psychosis
	Rebound psychosis
	Schizoaffective disorder
	Schizoaffective disorder bipolar type
	Schizoaffective disorder depressive type
	Schizophrenia
	Schizophrenia simple
	Schizophrenia, catatonic type
	Schizophrenia, disorganised type
	Schizophrenia, paranoid type
	Schizophrenia, residual type
	Schizophrenia, undifferentiated type
	Schizophreniform disorder
	Schizotypal personality disorder
	Senile psychosis
	Shared psychotic disorder
	Somatic delusion
	Somatic hallucination
	Substance-induced psychotic disorder
	Tangentiality
	Thought blocking
	Thought broadcasting
	Thought insertion
	Thought withdrawal
	Transient psychosis
	Waxy flexibility

12.7 List of Abbreviations and Acronyms

Abbreviation	Definition
3TC	Lamivudine
AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
ALT	Serum alanine aminotransferase
ART	Antiretroviral therapy
ASaT	All Subjects as Treated
AST	Serum aspartate aminotransferase
BLoQ	Below the limit of quantification
CCR5	Chemokine Receptor Type 5
CL	Confidence Interval or (as in section 10.3 only) Coordinating Investigator
Cl_{cr}	Creatinine Clearance
CNS	Central Nervous System
CSR	Clinical Study Report
CYP	Cytochrome
DAIDS	Division of Acquired Immunodeficiency Syndrome
DILI	Drug induced liver injury
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
eDMC	External Data Monitoring Committee
ECI	Event of Clinical Interest
EFV	Efavirenz
EOC	Executive Oversight Committee
ERC	Ethical Review Committee
FAS	Full Analysis Set
FBR	Future Biomedical Research
FDA	Food and Drug Administration
FDR	Fixed Dose Regimen
FTC	Emtricitabine
GCP	Good Clinical Practice
HAART	Highly Active Antiretroviral Therapy
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HDL-C	High Density Lipoprotein Cholesterol
HIV-1	Human Immunodeficiency Virus Type I
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
INR	International Normalized Ratio
InSTI	Integrase Strand Inhibitors
IRB	Institutional Review Board
IRIS	Immune Reconstitution Syndrome
IUD	Intrauterine Device
IVRS/IWRS	Interactive voice response system/Integrated web response system
LDL-C	Low Density Lipoprotein Cholesterol
LOQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
NC=F	Non-Completer = Failure

Abbreviation	Definition
NHS	Normal Human Serum
NNRTI	Non-Nucleoside Reverse transcriptase inhibitor
NRTI	Nucleoside Reverse transcriptase inhibitor
N(t)RTI	Nucleotide Reverse transcriptase inhibitor
OF	Observed Failure
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 oral
PT	Prothrombin Time
QD	Once Daily
SAC	Scientific Advisory Committee
(s)SAP	(supplemental) Statistical Analysis Plan
SOC	System Organ Class
TDF	Tenofovir disoproxil fumarate
TDF/FTC	Tenofovir disoproxil fumarate/ Emtricitabine (TRUVADA™)
TLOVR	Time to Loss of Virologic Response
(V)RNA	(viral) Ribonucleic Acid
ULN	Upper Limit of Normal
WPAI	Work Productivity and Activity Impairment Questionnaire

12.8 DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS VERSION 1.0, DECEMBER, 2004; CLARIFICATION AUGUST 2009

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 10^9 – 0.650 x 10^9/L*	500 – 599/mm3 *0.500 x 10^9 – 0.599 x 10^9/L*	350 – 499/mm3 *0.350 x 10^9 – 0.499 x 10^9/L*	< 350/mm3 < *0.350 x 10^9/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 10^9 – 1.300 x 10^9/L*	750 – 999/mm3 *0.750 x 10^9 – 0.999 x 10^9/L*	500 – 749/mm3 *0.500 x 10^9 – 0.749 x 10^9/L*	< 500/mm3 < *0.500 x 10^9/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).				

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

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	