Official Protocol Title:	A Phase 3 Multicenter, Double-Blind, Randomized, Active Comparator-Controlled Clinical Trial to Evaluate the Safety and Efficacy of Doravirine (MK-1439) 100 mg Once Daily Versus Darunavir 800 mg Once Daily plus Ritonavir 100 mg Once Daily, Each in Combination with TRUVADA™ or EPZICOM™/KIVEXA™, in Treatment-Naïve HIV-1 Infected Subjects
NCT number:	NCT02275780
Document Date:	23-Aug-2022

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This protocol amendment is applicable only to Australia, Russia and South Africa.

SPONSOR:

Merck Sharp & Dohme LLC
(hereafter referred to as the Sponsor or MSD)
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Protocol-specific Sponsor Contact information can be found in the Investigator Trial File Binder (or equivalent).

TITLE:

A Phase 3 Multicenter, Double-Blind, Randomized, Active Comparator-Controlled Clinical Trial to Evaluate the Safety and Efficacy of Doravirine (MK-1439) 100 mg Once Daily Versus Darunavir 800 mg Once Daily plus Ritonavir 100 mg Once Daily, Each in Combination with TRUVADA™ or EPZICOM™/KIVEXA™, in Treatment-Naïve HIV-1 Infected Subjects

IND NUMBER: 112,796

EudraCT NUMBER: [2014-001127-69]

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DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
12	23-Aug-2022	• Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.
11 (country-specific to Australia, Russia and South Africa)	06-Apr-2022	• Study extension 3 was added to (1) provide continued access to MK-1439 for participants who are deriving benefit from MK-1439 until the drug is available locally in countries participating in the trial or for an additional 2 years (whichever comes first), and (2) collect key safety information from participants who continue on MK-1439 in this study extension.
10 (country-specific to US)	05-Nov-2018	• Added an additional 32 weeks past the Week 192 visit so that a subject may continue to receive MK-1439 during this time or until commercial MK-1439 is locally available (whichever occurs first). • Added 2 treatment visits in the study extension and updated blood volumes.
09 (country-specific to Italy)	20-Apr-2018	• Added open-label study extension 2 to provide continued access to MK-1439 until the drug is available locally in countries participating in the trial or for an additional 2 years (whichever comes first).
08 (country-specific to Austria, Denmark, France, Germany, Romania, Russia, South Africa, Spain, UK)	19-Apr-2018	• Added open-label study extension 2 to provide continued access to MK-1439 until the drug is available locally in countries participating in the trial or for an additional 2 years (whichever comes first).
07 (country-specific to Argentina, Australia, Canada, Chile, US)	23-Apr-2018	• Added open-label study extension 2 to provide continued access to MK-1439 until the drug is available locally in countries participating in the trial or for an additional 2 years (whichever comes first).

Document	Date of Issue	Overall Rationale
06 (country-specific to Italy)	20-Sep-2016	• Added open-label study extension 1 for 2 years to collect long-term efficacy and safety data. • Requirements for use of oral contraceptives were modified to allow for use of hormonal contraceptives during the study extension.
05 (country-specific to Austria, Denmark, France, Germany, Romania, Russia, South Africa, Spain, UK)	20 Sep 2016	• Added open-label study extension 1 for 2 years to collect long-term efficacy and safety data. • Requirements for use of oral contraceptives were modified to allow for use of hormonal contraceptives during the study extension.
04 (country-specific to Argentina, Australia, Canada, Chile, US)	10-Aug-2016	• Added open-label study extension 1 for 2 years to collect long-term efficacy and safety data. • Requirements for use of oral contraceptives were modified to allow for use of hormonal contraceptives during the study extension.

Document	Date of Issue	Overall Rationale
03 (country-specific to Italy)	08-Apr-2015	• The HIV RNA cut-off used to define viral efficacy was changed from <40 copies/mL to <50 copies/mL. • Acceptable birth control methods (Inclusion Criterion 8) were modified to exclude oral contraceptives and the contraceptive rod; and to add a provision for more restrictive contraceptive methods to be used if locally required. • Clarified that (Child-Pugh Class C) hepatic impairment, as well as other significant conditions contraindicated in product labeling for the comparator products, are excluded (Exclusion Criterion 1). • Specified that all chronic hepatitis B-infected subjects for whom tenofovir was discontinued, be discontinued from the study to allow for appropriate hepatitis B treatment with medications not permitted by the protocol and to avoid hepatitis B treatment with lamivudine monotherapy. • Text was added to indicate that Kivexa may be packaged in either a bottle or blister pack. • Quetiapine, ergometrine, dronedarone, ranolazine, systemic lidocaine, sertindole, and ticagrelor were added as prohibited for darunavir; and clorazepate, diazepam, estazolam, flurazepam, pethidine, piroxicam propoxyphene, and alfuzosin were added as prohibited for ritonavir.

Document	Date of Issue	Overall Rationale
02 (country-specific to EU, Russia, South Africa)	10-Feb-2015	• The HIV RNA cut-off used to define viral efficacy was changed from <40 copies/mL to <50 copies/mL. • Acceptable birth control methods (Inclusion Criterion 8) were modified to exclude oral contraceptives and the contraceptive rod; and to add a provision for more restrictive contraceptive methods to be used if locally required. • Specified that all chronic hepatitis B-infected subjects for whom tenofovir was discontinued, be discontinued from the study to allow for appropriate hepatitis B treatment with medications not permitted by the protocol and to avoid hepatitis B treatment with lamivudine monotherapy. • Text was added to indicate that Kivexa may be packaged in either a bottle or blister pack.
01 (non-country specific)	04 Feb 2015	• The HIV RNA cut-off used to define viral efficacy was changed from <40 copies/mL to <50 copies/mL. • Acceptable birth control methods (Inclusion Criterion 8) were modified to exclude hormonal contraceptives containing ethinyl estradiol; and to add a provision for more restrictive contraceptive methods to be used if locally required. • Specified that all chronic hepatitis B-infected subjects for whom tenofovir was discontinued, be discontinued from the study to allow for appropriate hepatitis B treatment with medications not permitted by the protocol and to avoid hepatitis B treatment with lamivudine monotherapy. • Text was added to indicate that Kivexa may be packaged in either a bottle or blister pack.
Original protocol	01-Aug-2014	• Not applicable.

SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Sponsor underwent an entity name change and update to the address.

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
Title Page Section 12.1 Throughout	 Code of Conduct for Clinical Trials	Sponsor entity name and address change.	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

No additional changes.

1.0 TRIAL SUMMARY

Abbreviated Title	MK-1439 versus ritonavir-boosted darunavir, in combination with TRUVADA™ or EPZICOM™/KIVEXA™, in treatment-naïve HIV-1 infected subjects
Trial Phase	Phase 3
Clinical Indication	Treatment of HIV-1 infection
Trial Type	Interventional
Type of control	Active control
Route of administration	Oral
Trial Blinding	Double-blind for the base study then open-label for the study extensions.
Treatment Groups	Base Study (double-blind) Group 1: MK-1439 100 mg q.d. plus TRUVADA™ or EPZICOM™/KIVEXA™ Group 2: Ritonavir-boosted Darunavir (100 mg RTV with 800 mg Darunavir) plus TRUVADA™ or EPZICOM™/KIVEXA™ Study Extensions (open-label) (All subjects): MK-1439 100 mg q.d. plus either tenofovir (as tenofovir disoproxil fumarate [TDF] or tenofovir alafenamide fumarate [TAF]) or abacavir (ABC), each administered with either emtricitabine (FTC) or lamivudine (3TC).
Number of trial subjects	Approximately 680 subjects will be enrolled.
Estimated duration of trial	The sponsor estimates that the trial will require approximately 9 years from the time the first subject signs the informed consent until the last subject's last visit.
Duration of Participation	The study consists of a screening phase of up to 45 days (~6.5 weeks) followed by a 96-week double-blind base study, 3 open-label study extensions (study extensions 1, 2, and 3), and a 14-day follow-up period. The treatment duration of study extension 1 is 96 weeks; and the treatment duration of study extensions 2 and 3 is up to 96 weeks for each, depending on when MK-1439 becomes commercially available once approved in the local country (whichever comes first). The approximate cumulative durations of participation in the trial (from informed consent through follow-up) are 104 weeks for subjects who complete the base study; 200 weeks for subjects who complete the base study and study extension 1; up to 296 weeks for subjects who complete the base study and study extensions 1 and 2; and up to 392 weeks for subjects who complete the base study and study extensions 1, 2, and 3.
Randomization Ratio	1:1 with ~340 on MK-1439 + either TRUVADA™ or EPZICOM™/KIVEXA™ and ~340 on Ritonavir-boosted Darunavir + either TRUVADA™ or EPZICOM™/KIVEXA™

2.0 TRIAL DESIGN

2.1 Trial Design

This is a multicenter, double-blind (with in-house blinding), randomized, active-controlled, trial of MK-1439 100 mg once daily (q.d.) compared with ritonavir-boosted darunavir q.d. (given as separate tablets of 800 mg darunavir and 100 mg ritonavir, hereafter referred to as darunavir/ritonavir [800 mg/100 mg]), when each is given in combination with investigator-selected TRUVADA™ or EPZICOM™/KIVEXA™ q.d., in the treatment of antiretroviral treatment-naïve subjects with HIV-1 infection.

The study consists of a screening period of approximately 6.5 weeks, a 96-week blinded base study (MK-1439 100 mg q.d. compared with ritonavir-boosted darunavir q.d., each given in combination with investigator-selected TRUVADA™ or EPZICOM™/KIVEXA™ q.d.) followed by 3 consecutive open-label study extensions (MK-1439 100 mg q.d. in combination with investigator-selected NRTI backbone therapy), and a 14-day post-study follow-up visit after the last treatment visit. The treatment duration of the first open-label study extension (study extension 1) is 96 weeks; and the treatment duration of the second and third open-label study extensions (study extensions 2 and 3, respectively) is up to 96 weeks for each, depending on when MK-1439 becomes locally available (whichever comes first).

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

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

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

Base Study

Approximately six hundred and eighty (680) subjects will be stratified by: 1) screening HIV-1 RNA (≤ or >100,000 copies/mL) and 2) NRTI backbone therapy (TRUVADA™ or EPZICOM™/KIVEXA™, as selected by the investigator) and randomized within strata in a 1:1 ratio to receive either MK-1439 100 mg q.d. or darunavir/ritonavir (800 mg/100 mg q.d.), each in combination with the selected backbone therapy. The duration of treatment for a given subject in the base study is 96 weeks (approximately 2 years). The primary endpoint is the proportion of subjects achieving HIV-1 RNA <50 copies/mL at Week 48.

The safety of 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 every ~4-6 months. The eDMC will recommend any steps to ensure the safety of study participants and the integrity of the trial. The eDMC will also review interim efficacy data and make a recommendation on study conduct based on a pre-defined futility rule. To guarantee the unrestricted performance of its task, the eDMC will receive individual study data from a designated unblinded statistician. Details regarding the eDMC will be described in a charter document.

Subjects who meet the virologic failure criteria (see Section 4.2.3.1) in the base study or study extension 1 will return to the site between 1 and 4 weeks (≥1 and ≤4 weeks) later for repeat viral RNA testing (at a virologic failure confirmation visit). If virologic failure is confirmed and the viral load meets the criterion for resistance testing (greater than 400 copies/mL), in the base study or study extension 1, viral resistance testing will then be performed. In addition, viral resistance testing will be performed for subjects who discontinue for any reason from the study (if viral load is greater than 400 copies/mL).

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

All subjects entering the study extensions will receive open-label treatment with MK-1439 (100 mg q.d.) in combination with investigator-selected NRTI backbone therapy.

Treatment group assigned during the base study will not be unblinded when a subject enters study extension 1; unblinding will occur after all subjects have completed the base study and database lock has been achieved for the base study.

Study Extension 1

At Study Week 96, eligibility for enrollment into study extension 1 will be determined, thus continuing study treatment for approximately 2 years beyond the base study. The total duration of treatment for subjects who continue into study extension 1 is 192 weeks (approximately 4 years).

For all subjects who enter study extension 1, the backbone NRTI therapy will remain the same as that in the base study whenever possible. In order to address issues of either drug access or tolerability, single-drug or fixed-dose combinations of the 4 permitted NRTIs may be used, and both TAF and TDF formulations of tenofovir may be used. Decisions on potential changes in NRTI backbone therapy, between the base study and study extension 1, will be made on a case-by-case basis, as needed, by mutual agreement of the investigator and the Sponsor; in cases where lack of immediate access to allowed NRTIs presents a barrier to participation in study extension 1, provision of NRTI therapy between Week 96 and Week 100 for a given subject may be considered by the Sponsor. The same backbone therapy is to be maintained throughout study extension 1 for a given subject.

Subjects who meet virologic failure criteria during study extension 1 will follow the same procedures as those who do so during the base study. Subjects who discontinue from study extension 1 will have a serum sample collected for viral resistance testing, as in the base study.

Long-term safety and efficacy data will be collected during study extension 1 and summarized descriptively. Subjects will continue to be monitored for safety during study extension 1, including fasting lipids: long-term safety data will be collected and summarized.

Study Extension 2

At Study Week 192, eligibility for enrollment into study extension 2 will be determined. Subjects who meet eligibility criteria and continue into study extension 2 may continue to receive treatment with MK-1439 until it becomes locally available or for approximately 2 years beyond study extension 1 (whichever comes first). The maximum total duration of treatment with MK-1439 will be up to 288 weeks (i.e., up to approximately 2 years beyond study extension 1, depending on when MK-1439 is commercially available once approved in the local country) for subjects who continue into study extension 2.

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

Study Extension 3

At Study Week 288, eligibility for enrollment into study extension 3 will be determined. Subjects who meet eligibility criteria and continue into study extension 3 may continue to receive treatment with MK-1439 until it becomes locally available or for approximately 2 years beyond study extension 2 (whichever comes first). The maximum total duration of treatment with MK-1439 will be up to 384 weeks (i.e., up to approximately 2 years beyond study extension 2, depending on when MK-1439 is commercially available once approved in the local country) for subjects who continue into study extension 3.

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

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 for the base study and Figure 2 for study extensions 1, 2, and 3. (Note that subjects who continue into study extension 1 will have a single follow-up visit at the end of the extension only, not in the base study.)

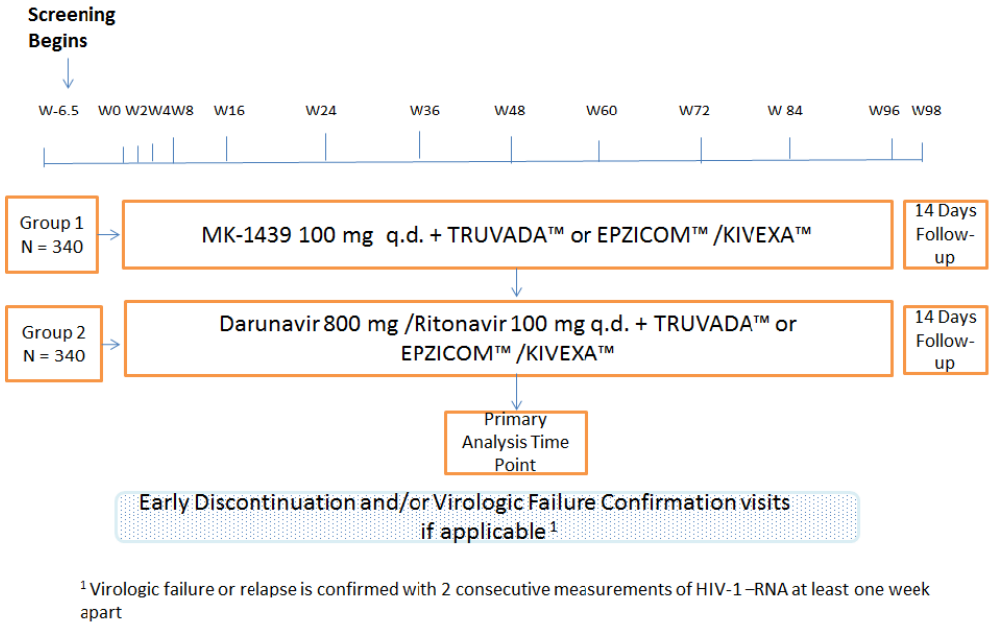


Figure 1 Trial Design for Protocol 018 Base Study

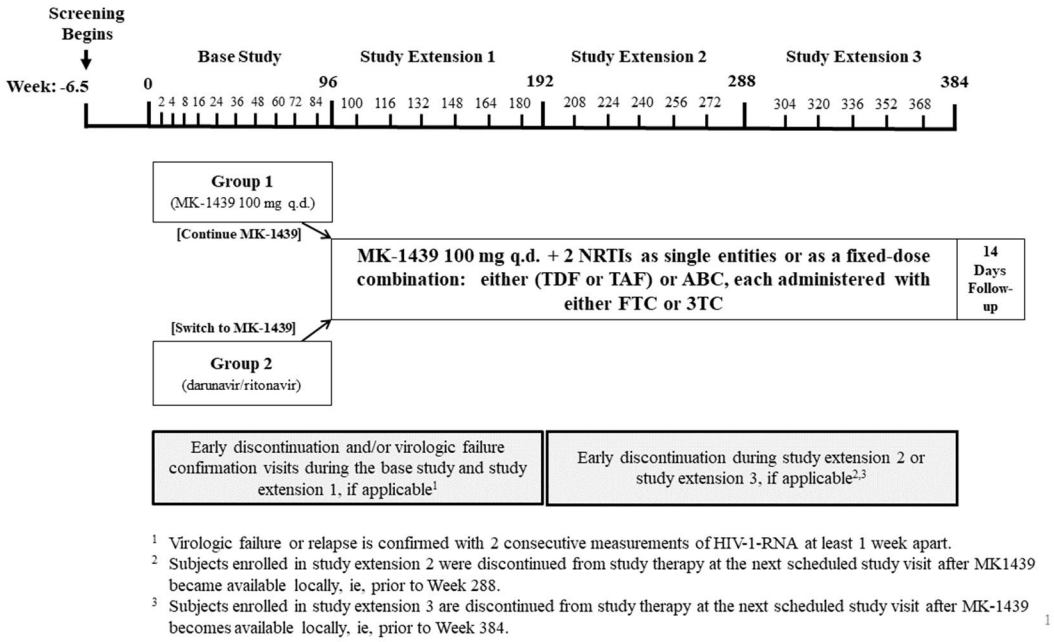


Figure 2 Trial Design for Protocol 018 Study Extensions 1, 2, and 3

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

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

Base Study:

(1) **Objective:** To evaluate the antiretroviral activity of MK-1439 100 mg q.d., compared to darunavir/ritonavir (800 mg/100 mg) q.d., each in combination with TRUVADA™ or EPZICOM™/KIVEXA™, as measured by the proportion of subjects achieving HIV-1 RNA <50 copies/mL at Week 48.

Hypothesis: MK-1439 100 mg q.d. is non-inferior to darunavir/ritonavir (800 mg/100 mg) q.d., each in combination with TRUVADA™ or EPZICOM™/KIVEXA™, as assessed by the proportion of subjects with HIV-1 RNA <50 copies/mL at Week 48. Superiority of MK-1439 100 mg q.d. to darunavir/ritonavir (800 mg/100 mg) q.d. will be assessed if non-inferiority is established.

3.2 Secondary Objective(s) & Hypothesis(es)

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

Base Study:

(1) **Objective:** To evaluate the safety and tolerability of MK-1439 100 mg q.d., compared to darunavir/ritonavir (800 mg/100 mg) q.d., each in combination with TRUVADA™ or EPZICOM™/KIVEXA™, as assessed by review of the accumulated safety data at Week 48 and Week 96.

(2) **Objective:** To evaluate the effect on fasting serum lipids of MK-1439 100 mg q.d. compared to darunavir/ritonavir (800 mg/100 mg) q.d., each in combination with TRUVADA™ or EPZICOM™/KIVEXA™, as measured by mean change from baseline in fasting serum lipids at Week 48.

Hypothesis: MK-1439 100 mg q.d. is superior to darunavir/ritonavir (800 mg/100 mg) q.d., each in combination with TRUVADA™ or EPZICOM™/KIVEXA™, as assessed by the mean change from baseline in fasting LDL-C at Week 48. If superiority is established with respect to LDL-C, the following subsequent hypothesis will be tested: MK-1439 100 mg q.d. is superior to darunavir/ritonavir (800 mg/100 mg) q.d., each in combination with TRUVADA™ or EPZICOM™/KIVEXA™, as assessed by the mean change from baseline in fasting non-HDL-C at Week 48.

(3) **Objective**: To evaluate the safety and tolerability of MK-1439 100 mg q.d. compared to darunavir/ritonavir (800 mg/100 mg) q.d., each in combination with TRUVADA™ or EPZICOM™/KIVEXA™, as measured by the time to discontinuation from study due to an adverse experience.

(4) **Objective**: To evaluate the immunologic effect of MK-1439 100 mg q.d., compared to darunavir/ritonavir (800 mg/100 mg) q.d., each in combination with TRUVADA™ or EPZICOM™/KIVEXA™, as measured by the change from baseline in CD4 cell count at Week 48 and Week 96.

(5) **Objective**: To evaluate the antiretroviral activity of MK-1439 100 mg q.d. compared to darunavir/ritonavir (800 mg/100 mg) q.d., each in combination with TRUVADA™ or EPZICOM™/KIVEXA™, as measured by the proportion of subjects achieving HIV-1 RNA <50 copies/mL at Week 96.

Hypothesis: MK-1439 100 mg q.d. is non-inferior to darunavir/ritonavir (800 mg/100 mg) q.d., each in combination with TRUVADA™ or EPZICOM™/KIVEXA™, as assessed by the proportion of subjects with HIV-1 RNA <50 copies/mL at Week 96. Superiority of MK-1439 100 mg q.d. to darunavir/ritonavir (800 mg/100 mg) q.d. will be assessed if non-inferiority is established.

(6) **Objective**: To evaluate the antiretroviral activity of MK-1439 100 mg q.d., compared to darunavir/ritonavir (800 mg/100 mg) q.d., each in combination with TRUVADA™ or

EPZICOM™/KIVEXA™, as measured by the proportion of subjects achieving HIV-1 RNA <40 copies/mL at Week 48 and 96.

3.3 Exploratory Objectives

3.3.1 Base Study

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

(1) **Objective**: To evaluate the antiretroviral activity of MK-1439 100 mg q.d., compared to darunavir/ritonavir (800 mg/100 mg) q.d., each in combination with TRUVADA™ or EPZICOM™/KIVEXA™, as measured by the proportion of subjects achieving HIV-1 RNA <200 copies/mL at Week 48 and 96.

(2) **Objective:** To evaluate the antiretroviral activity of MK-1439 100 mg q.d., compared to darunavir/ritonavir (800 mg/100 mg) q.d., each in combination with TRUVADA™ or EPZICOM™/KIVEXA™, as measured by the Time to Loss of Virologic Response (TLOVR).

(3) **Objective:** To evaluate the pharmacokinetics of MK-1439 100 mg q.d. and pharmacokinetic-pharmacodynamic associations, if supported by the data.

(4) **Objective:** To assess the development of resistance to MK-1439 100 mg q.d. in subjects who are virologic failures.

3.3.2 Study Extension 1

(1) **Objective:** To assess data on long-term efficacy and safety of MK-1439 100 mg q.d. administered for up to 192 weeks (approximately 4 years) total in subjects enrolled in study extension 1.

4.0 BACKGROUND & RATIONALE

4.1 Background

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

4.1.1 Pharmaceutical and Therapeutic Background

HIV-infected patients have been successfully treated with combination antiretroviral therapy (cART) 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 5 distinct mechanistic classes known as reverse transcriptase inhibitors (nucleos(t)ide reverse transcriptase inhibitors [N(t)RTIs] and non-nucleoside reverse transcriptase inhibitors [NNRTIs]), PIs, fusion inhibitors, entry inhibitors (CCR5 co–receptor antagonists), and integrase strand transfer inhibitors (InSTIs). Successful combinations of antiretroviral medications generally utilize 3 agents from at least 2 different mechanistic classes. The goal of cART is to suppress HIV to undetectable levels so that

immune function is preserved or restored. Yet, while cART can favorably influence disease progression 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 medication non-compliance. In these circumstances, selection for resistant virus can and does occur. As a result, virus with reduced susceptibility to the licensed agents will remain a constant threat. Additionally, there is significant concern regarding long-term toxicities of some widely-used antiretroviral agents, including central nervous system toxicities associated with efavirenz (an NNRTI), gastrointestinal toxicities such as diarrhea associated with multiple protease inhibitors (PIs), and serum lipid abnormalities associated with multiple mechanistic classes.

Currently available NNRTIs constitute an important option for use as anchor agents, along with 2 NRTIs, for initiation of combination antiretroviral therapy for HIV infection. Efavirenz remains the preferred NNRTI for treatment initiation according to multiple guidelines, and rilpivirine, more recently approved, has been recommended by these guidelines as an alternative NNRTI agent for treatment initiation. However, each of the currently available NNRTI agents has disadvantages. For example, while efavirenz has shown excellent efficacy over many years of use, it is associated with substantial CNS 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 CD4 cells below 200/μL at baseline, and thus is not indicated in patients with baseline viral load above 100,000 copies/mL. 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. 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 potent non-nucleoside reverse transcriptase inhibitor (NNRTI) being studied for treatment of human immunodeficiency virus type 1 (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 most common NNRTI resistant variants at concentrations achieved with once daily dosing. MK-1439 displays excellent potency against wild type virus with 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 an IC_{50} of 21, 31, and 55 nM against mutants containing the most frequently transmitted NNRTI mutations K103N, Y181C and G190A respectively, under the same conditions. Its preclinical toxicity profile 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-naïve individuals

demonstrate that MK-1439, in combination with tenofovir/emtricitabine, is highly efficacious, even in patients with high baseline viral load, and is well tolerated.

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 and strategies that are highly effective, have a high barrier to resistance development, are very well tolerated, are simple to administer, and thus will promote increased adherence and decrease treatment fatigue. Therapies and regimens with these characteristics are particularly important for treatment-naïve patients where initial success is predictive of long-term outcomes. This need is further driven by the necessity for lifelong treatment of HIV infection in patients who are increasingly older and have co-morbid diseases/conditions.

Currently available therapies for HIV infection include PIs, a diverse class of potent agents with a high genetic barrier to resistance, but which generally require boosting by ritonavir to achieve appropriate levels. As a class, PIs are highly efficacious, and several are recommended as preferred agents for first-line therapy of treatment-naïve HIV-infected subjects; however, they are also associated with a variety of toxicities including gastrointestinal issues (especially diarrhea), serum lipid abnormalities, and lipodystrophy, among others, which are of particular concern in view of the need for lifelong HIV therapy. Based on preclinical and clinical data to date, MK-1439 is not expected to have similar safety concerns. Therefore, establishing the efficacy and safety of MK-1439 relative to a PI will help establish it as a valuable new treatment option for treatment-naïve patients.

Darunavir/ritonavir has been extensively studied and was selected as the comparator agent in this study for a number of reasons including efficacy, tolerability, and ease of maintaining the study blind during the base study. As compared with the other recommended agents for treatment initiation in the Protease Inhibitor (PI) class such as atazanavir/ritonavir and lopinavir/ritonavir, it offers potent efficacy and generally good tolerability. With regard to safety, darunavir/ritonavir showed lower rates of diarrhea and discontinuation of treatment due to adverse events compared with lopinavir/ritonavir. Use of darunavir/ritonavir will also better maintain the blinding to randomized treatment assignment at a practical level, due to the high likelihood of obvious hyperbilirubinemia/icterus with atazanavir/ritonavir use, which would cue the patient and investigator to the actual treatment assignment. The choice of darunavir as the comparator anchor (or 3rd) agent is further supported by its recommended use in treatment-naïve patients according to multiple recent international guidelines (e.g., from EACS, BHIVA, and US-DHHS, IAS-USA).

Similarly, both tenofovir/emtricitabine and abacavir/lamivudine are also recommended backbones in these guidelines. Tenofovir and abacavir have relatively similar efficacy profiles but somewhat different safety profiles. Allowing investigator choice and optimization of NRTIs will provide data on the use of MK-1439 with both of the most

commonly used NRTI fixed-dose combinations. The potent efficacy for MK-1439 demonstrated in Phase 1 and 2 studies predict that MK-1439 in combination with either NRTI backbone should provide the expected efficacy.

Additional details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying Investigators Brochure (IB) and Informed Consent documents.

4.2.2 Rationale for Dose Selection/Regimen

MK-1439 is a potent NNRTI. In a Phase 1b study (Protocol 005), once daily oral administration of 25 mg and 200 mg MK-1439 as monotherapy for 7 days to treatment-naïve HIV-infected patients reduced plasma viral RNA 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 vs. 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 once daily versus efavirenz (600 mg once daily) both in combination with the fixed-dose combination of TDF/FTC 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) and < 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). The treatment differences (MK-1439 minus efavirenz) were not significant, and there was no dose response for efficacy observed. Overall 76.4% of patients receiving MK-1439 (at any dose) achieved < 40 copies/mL compared with 64.3% for efavirenz. In addition, approximately 30% of subjects in the study had baseline HIV RNA above 100,000 copies/mL, and, in this subgroup, MK-1439 at all dosing levels showed virologic responses comparable to efavirenz. It should be acknowledged that this high viral load subgroup was relatively small, with approximately 12 subjects per dosing group. However, the totality of these efficacy data strongly support that the dose range studied (25-200 mg daily) was on the plateau of the dose response curve.

Similarly, the data from in 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. In general, the incidence of CNS adverse

events was lower in the MK-1439 groups relative to the efavirenz group. Based upon the 24-week results of PN007, 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 CNS 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). Three of the 4 dose groups of MK-1439 had numerically lower proportion of patients with CNS adverse events by Week 8 and by Week 24 than efavirenz. The 50 mg group of MK-1439 had a similar proportion of patients with CNS adverse events compared to efavirenz.

The dose of MK-1439 that was selected for study in Phase 3 is 100 mg q.d. The MK-1439 100 mg daily dose was selected based on Week 24 safety and efficacy data from Protocol 007, as well as considerations for potential drug-drug interactions, forgiveness of the occasional missed dose, and coverage of a variety of NNRTI mutations against which MK-1439 is expected to be active with minimal (less than 3-fold) shift in the in vitro, 95% inhibitory concentration (IC95).

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 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, selection of a higher dose, such as 100 mg, may provide assurance of adequate MK-1439 exposures (similar to those achieved at 25 mg daily) even in the setting of moderate metabolic inducers. Secondly, the 100-mg dose may provide forgiveness in the setting of the occasional missed dose. Thirdly, the 100-mg dose is expected to provide adequate exposures and C_{trough} concentrations in the setting of certain common NNRTI resistance mutations against which MK-1439 is considered to be active in vitro, including the K103N, Y181C, and G190A mutations, as well as the dual K103N/Y181C mutation. Further details can be found in the Investigators' Brochure.

The doses of the active comparators (darunavir 800 mg and ritonavir 100 mg, each given as separate tablets q.d.) are the standard approved doses for these agents. In addition, the doses of the NRTI backbones, TRUVADA™ (tenofovir disoproxil fumarate 300 mg /emtricitabine 200 mg) and EPZICOM™/KIVEXA™ (abacavir sulfate 600 mg /lamivudine 300 mg) are the standard approved doses for these agents.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

The primary efficacy endpoint 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 (<50 copies/mL) has been demonstrated in many clinical trials to preserve the immune system and prevent the development of opportunistic infections and progression of the disease. The HIV RNA assay that will be used in the study (Abbott RealTime HIV-1 Assay) has a lower limit of quantification of

40 copies/mL. The primary efficacy endpoint, however, is the proportion of subjects achieving HIV-1 RNA <50 c/mL to reflect the clinically relevant standard used across antiretroviral medications. Week 48 was chosen as the primary efficacy time point and Week 96 was chosen as the secondary efficacy time point, as recommended by regulatory agencies for HIV treatment-naïve studies.

Secondary and exploratory measurements for efficacy include HIV-1 RNA <40 copies/mL, HIV-1 RNA <200 copies/mL, change from baseline 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 for this study is defined as one of the following:

1) Confirmed (2 consecutive measures at least one week apart) HIV-1 RNA ≥200 copies/mL at week 24 or week 36, or confirmed (2 consecutive measures at least one week apart) HIV-1 RNA ≥50 copies/mL at week 48;

OR

2) Confirmed (2 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**.

Subjects should be discontinued, regardless of compliance to study therapy, if they meet the PDVF criteria.

The protocol allows a subject to switch from one of the study backbone NRTI regimens to the other (either from TRUVADA™ to EPZICOM™/KIVEXA™ or from EPZICOM™/KIVEXA™ to TRUVADA™) in the base study for management of toxic effects. If the switch occurs prior to the Week 2 visit, the subject will not be counted as a failure in the primary efficacy analysis; however if the switch occurs after Week 2 and the subject has HIV RNA ≥50 copies/mL at the time of the switch, the subject will be regarded as a failure for the primary efficacy analysis as specified by FDA's snapshot approach in the base study.

During the open-label extension, in order to address issues of drug access, tolerability, or subject convenience, single-drug or fixed-dose combinations of the 4 permitted NRTIs may be used, and both TAF and TDF formulations of tenofovir may be used. (Permitted combinations are tenofovir [as TDF or TAF] or ABC, each administered with either FTC or 3TC). A switch to another NRTI backbone regimen during study extension 1 for drug access, tolerability, or subject convenience reasons will not be counted as a failure in the efficacy analysis in the open-label study extension, regardless of viral load at the time of the switch.

4.2.3.2 Safety Endpoints

Primary and secondary safety endpoints include change from baseline in fasting serum lipids, summary of clinical and laboratory adverse experiences, the time to discontinuation from study due to an adverse experience, and predefined limits of change in laboratory parameters.

Safety evaluations in the base study will include physical examinations (including vital signs) and laboratory tests (blood) performed at the screening visit, Randomization (Day 1), Weeks 2, 4, 8, 16, 24, 36, 48, 60, 72, 84, and 96, a virologic failure confirmation visit, if applicable (no physical exam or vital signs), and, for subjects who do not enter study extension 1, an early discontinuation visit (for subjects who discontinue the study early) and the 14-day follow-up visit.

For subjects who enter study extension 1, safety evaluations will be performed at Weeks 100, 116, 132, 148, 164, 180, and 192, a virologic failure confirmation visit if applicable (no physical exam or vital signs), an early discontinuation visit (for subjects who discontinue the study early) and a 14-day follow-up visit. Adverse experiences will be evaluated at each visit and graded according to the guidelines which are 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 study extension 1 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 study extension 1) in order to more closely monitor all subjects, including those who were switched from ritonavir-boosted darunavir to MK-1439, since treatment in the base study remains blinded at the beginning of study extension 1. Treatment group assigned during the base study will not be unblinded when a subject enters study extension 1; unblinding will occur after all subjects have completed the base study and database lock has been achieved for the base study.

During study extension 2 and study extension 3, SAEs and pregnancy test results will be collected at each study visit (study extension 2: Week 208, Week 224, Week 240, Week 256, Week 272, and Week 288; study extension 3: Week 304, Week 320, Week 336, Week 352, Week 368, and Week 384) as applicable, depending on when MK-1439 is available locally, and, if applicable, at the early discontinuation and follow-up visits).

4.2.3.3 Pharmacokinetic Endpoints

C_{min} (defined as the minimum concentration for an individual subject collected predose) is the primary pharmacokinetic endpoint of this study. Individual patient data will also be assessed in regards to AUC, C_{max} and C_{24hr} for MK-1439. Population pharmacokinetic (PK) samples will be collected at the Day 1 Randomization visit as a pre-drug sample. Population PK samples will also be taken at Weeks 4, 8, 24 and 48. At Week 4 the sample must be collected predose. At weeks 24 and 48, the samples must be collected predose and within 0.5 to 2 hours postdose; at Week 8, the samples 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 Future Biomedical Research

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

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

4.2.4 Rationale for Study Extensions

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

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

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male/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) for the trial. The subject or their legal representative 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-immuno assay, 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:

   - Alkaline phosphatase ≤3.0 x upper limit of normal
   - AST (SGOT) and ALT (SGPT) ≤5.0 x upper limit of normal

   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 time of screening ≥50 mL/min, based on the Cockcroft-Gault equation which is as follows :

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

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

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 meets at least one of the following categories:

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

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

   c) The subject is a female or a male who is of reproductive potential and agrees to avoid becoming pregnant or impregnating a partner while receiving study drug and for 14 days after the last dose of study drug by complying with one of the following: (1) practice abstinence[†] from heterosexual activity OR (2) use (or have their partner use) acceptable contraception during heterosexual activity. Contraceptives containing ethinyl estradiol cannot be used as a method of birth control in the base study due to an interaction with ritonavir which may reduce their effectiveness. Therefore, it is recommended that a condom or other non-hormonal method of contraception should be used instead. Acceptable methods of contraception are[‡]:

   Single method (one of the following is acceptable):

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

   Combination method (requires use of 2 of the following):

   - diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
   - cervical cap with spermicide (nulliparous women only)
   - contraceptive sponge (nulliparous women only)
   - male condom or female condom (cannot be used together) [↑]

   During the study extensions, subjects may use hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

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

‡ If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region. In addition, more restrictive contraceptive methods must be used if required by local ethics or regulatory authorities.

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

In order to be eligible for participation in **study extension 1** 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 96 weeks (approximately 2 years) of treatment, following the end of the base study, with MK-1439 100 mg q.d. in combination with either tenofovir (as TDF or TAF) or ABC, each administered with either FTC or 3TC, as single entities or as a fixed-dose combination.

12. understand the procedures in study extension 1 and provide written informed consent to enter study extension 1, thus continuing for approximately 2 years beyond the base study.

In order to be eligible to continue receiving MK-1439 in **study extension 2** at the Week 192 visit the subject must:

13. have completed the Week 192 visit.

14. be considered, in the opinion of the investigator, to have derived benefit from MK-1439 by Week 192 of the study.

15. be considered, in the opinion of the investigator, a clinically appropriate candidate for an additional 2 years (additional 96 weeks) of treatment with MK-1439.

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

In order to be eligible to continue receiving MK-1439 in **study extension 3** at the Week 288 visit the subject must:

17. have completed the Week 288 visit.

18. be considered, in the opinion of the investigator, to have derived benefit from MK-1439 by Week 288 of the study.

19. be considered, in the opinion of the investigator, a clinically appropriate candidate for an additional 2 years (additional 96 weeks) of treatment with MK-1439.

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

5.1.3 Subject Exclusion Criteria

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

1. has a history or current evidence of any condition, therapy, laboratory abnormality or other circumstance that might confound the results of the study or interfere with the subject's participation for the full duration of the study, such that it is not in the best interest of the subject to participate.

2. is, at the time of signing informed consent, a user of recreational or illicit drugs or has had a recent history of drug or alcohol abuse or dependence. The nature and potential clinical context of the subject's illicit drug use, in relation to their exclusion from this trial, will be at the discretion of the Investigator.

3. has been treated for a viral infection other than HIV-1, such as hepatitis B, with an agent that is active against HIV-1, including but not limited to adefovir, tenofovir, entecavir, emtricitabine, or lamivudine.

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

4. has documented or known resistance to study drugs including MK-1439, darunavir, ritonavir, emtricitabine, tenofovir, abacavir and/or lamivudine, as defined below:

   a. Resistance to MK-1439, for the purpose of this study, includes mutants containing the following 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 darunavir/ritonavir includes any of the following PI mutations: V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, or L89V.

c. Resistance to emtricitabine, tenofovir, abacavir and lamivudine includes the following mutations: M184V/I, K65R, M41L, D67N, K70R/E, T69S, L210W, T215Y/F, K219Q/E, L74V, and Y115F.

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.

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

11. 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.

12. is or has an immediate family member (spouse or children) 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 for assignment of the drug (MK-1439 or darunavir/ritonavir) to be administered. Trial treatment should begin on Day 1. Sites should not call IVRS 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 2 treatment regimens/groups to be used in this trial are outlined below in Table 1 and Table 2.

Table 1 Treatment Regimens During Base Study

Group 1	n = ~ 340	MK-1439 100 mg q.d. + TRUVADA™ or EPZICOM™/KIVEXA™, q.d.†, ‡
Group 2	n = ~ 340	Darunavir 800 mg / Ritonavir 100 mg PO q.d. + TRUVADA™ or EPZICOM™/KIVEXA™ q.d. †, ‡

† TRUVADA™ is a fixed-dose combination (FDC) tablet containing 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate. EPZICOM™/KIVEXA™ is an FDC tablet containing 600 mg of abacavir sulfate and 300 mg of lamivudine.

‡ A dosing interval adjustment of TRUVADA™ to 1 tablet every 48 hours is recommended in all subjects with creatinine clearance of 30-49 mL/min (see TRUVADA™ package insert for further details).

Table 2 Treatment Regimen During Study Extensions

Group 1	MK-1439 100 mg q.d. + investigator-selected NRTI backbone therapy†, consisting of either tenofovir (as TDF or TAF) or ABC, each administered with either FTC or 3TC, q.d.
Group 2	

† The NRTI backbone therapy may be administered as single entities or as a fixed-dose combination.

ABC = abacavir; FTC = emtricitabine; TAF = tenofovir alafenamide fumarate; TDF = tenofovir disoproxil fumarate; 3TC = lamivudine.

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

MK-1439 (or placebo) will be taken without regard to food. In the base study, darunavir and ritonavir (or their respective placebos) will be taken with food. If TRUVADA™ is selected as background therapy it will be taken with food. If EPZICOM™/KIVEXA™ is selected as background therapy, it can be taken without regard to food.

MK-1439 for the base study and for the study extensions (provided that development of MK-1439 is continuing) will be provided centrally by the Sponsor, as will TRUVADA™ and EPZICOM™/KIVEXA™ during the base study only. In the study extensions, NRTIs will be provided by the trial site as part of standard of care; these medications will be administered according to the labeling in use in each country.

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\Discontinuation

Dose Modification:

No dose modification of MK-1439, darunavir, ritonavir or EPZICOM™/KIVEXA™ is allowed during the base study or the study extensions.

A dosing interval adjustment of TRUVADA™ to 1 tablet every 48 hours is recommended in all subjects with creatinine clearance of 30-49 mL/min (see TRUVADA™ package insert for further details).

Dose Interruption:

Consideration should be given to interrupting study therapy for toxicity management (see 7.1.2.6). If study therapy is interrupted, all ARTs should be interrupted to minimize risk of resistance, and, if appropriate, should be restarted concurrently at full dose.

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.

Dose Discontinuation

A discontinuation of TRUVADA™ is recommended in all subjects with a creatinine clearance of < 30 mL/min (see TRUVADA™ package circular for further details).

Subjects who require discontinuation of any component of study therapy (MK-1439, darunavir, ritonavir, TRUVADA™, or EPZICOM™/KIVEXA™) must be discontinued from the trial with the following exception: if an Investigator determines that a subject needs to discontinue from one of the open label therapies (TRUVADA™ or EPZICOM™/KIVEXA™), the Subject will be allowed to stay in the protocol as long as they transition to the other open label therapy that is available as part of the protocol.

5.2.2 Timing of Dose Administration

5.2.2.1 Base Study

EPZICOM™/KIVEXA™ is packaged as either blister packs or bottles. Therefore packaging for this product is referred to hereafter as 'container.'

All subjects will take one tablet daily from each of 4 bottles/containers as follows:

Bottle A (MK-1439 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.

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 (darunavir or placebo) and Bottle C (ritonavir or placebo):

Subjects will be instructed to take one tablet from Bottle B and one tablet from Bottle C, once a day (q.d.) orally, together, with food at approximately the same time each day.

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

All subjects will take one tablet once daily from EITHER Bottle D or Container E as follows:

Bottle D (TRUVADA™)

Subjects will be instructed to take one tablet from Bottle D once a day (q.d.) orally, with food at approximately the same time each day.

OR

Container E (EPZICOM™/KIVEXA™)

Subjects will be instructed to take one tablet from Container E once a day (q.d.) orally, with or without food at approximately the same time each day.

If a subject misses a dose of drug from Bottle D or Container E, then the subject should take it as soon as he/she remembers within a 24 hour day. The subject should not take more than 1 dose of Bottle D or Container E in a day. The subject should not double the next dose in order to compensate for what has been missed.

5.2.2.2 Study Extensions

Subjects will be instructed to take 1 tablet of MK-1439 once a day (q.d.) orally along with 2 NRTIs, as either 2 single-drug entities or as an FDC, as determined appropriate by each investigator. The NRTIs will be supplied by each site, and instructions on dose regimen will be based on the recommendations according to the labeling in use in each country.

MK-1439 will be supplied open-label in a bottle labeled ‘F’ (oral compressed tablets) or, if subsequently available, ‘G’ (film-coated tablets). The instructions are the same as those in the base study for Bottle A (MK-1439 or placebo).

5.2.3 Trial Blinding/Masking

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

TRUVADA™ and EPZICOM™/KIVEXA™ will be supplied open-label during the base study. During the study extensions, MK-1439 will be provided open-label, and the NRTI backbone medications of choice will be provided open-label by each site.

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 (Base Study)

Randomization will occur centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). There are 2 treatment arms. Subjects will be assigned randomly in a 1:1 ratio to MK-1439 100 mg q.d., or darunavir/ritonavir (800 mg/100 mg) q.d.

5.4 Stratification

Randomization 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. NRTI backbone therapy, TRUVADA™ or EPZICOM™/KIVEXA™

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

Table 3 Stratification

Stratum	Screening HIV-1 RNA levels (copies/mL)	NRTI backbone therapy
I	≤100,000	TRUVADA™
II	≤100,000	EPZICOM™/KIVEXA™
III	>100,000	TRUVADA™
IV	>100,000	EPZICOM™/KIVEXA™

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 darunavir, ritonavir, TRUVADA™ (tenofovir, or emtricitabine), and EPZICOM™/KIVEXA™ (lamivudine and abacavir).

1. Short courses of corticosteroids (e.g., as for asthma exacerbation) are allowed.

2. During the study extensions only, use of oral or other hormonal birth control is permitted.

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

Prohibited Medications

With the exception of short courses of corticosteroids (e.g., as for asthma exacerbation), concomitant use of immune therapy agents or other immunosuppressive therapy is not allowed during the course of the study. Several important exceptions should be noted with regard to immune therapy or other immunosuppressive therapy:

- 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 potential benefits outweigh the risks. Depending on the type of chemotherapy, study medication may need to be interrupted until completion of the chemotherapy.

- If a subject requires interferon-based treatment for hepatitis C after randomization, the subject may receive treatment and remain in the study if, in the opinion of the investigator, the potential benefits outweigh the risks. If it is possible, interferon-based therapy should be deferred until the completion of the study.

Other antiretroviral therapies beyond those described in the study (MK-1439, darunavir, ritonavir, TRUVADA™, EPZICOM™/KIVEXA™) are also not permitted during the course of the study.

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

*Prohibited Medications Acting as **moderate or strong** Inducers of **CYP3A4** Drug Metabolism*

MK-1439 is expected to be eliminated mainly via CYP3A (cytochrome)-mediated oxidation.

The medications and/or substances below are prohibited in this study because they are moderate or potent broad inducers of CYP3A4 and their coadministration with MK-1439 could possibly result in reduced drug levels of MK-1439, or they have 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 Interaction During Base Study and Study Extension
Carbamazepine
Oxcarbazepine
Rifapentine
Phenobarbital
Phenytoin
Rifabutin
Rifampin
St. John's Wort
Modafinil
Bosentan
Nafcillin
Mitotane
Enzalutamide

Prohibited Concomitant Therapy Due to Potential Interaction with Darunavir or Ritonavir

The following medications are prohibited during the base study because competition for CYP3A4 by darunavir (or ritonavir) could result in inhibition of metabolism of these drugs and create the potential for serious and/or life-threatening adverse events. Several of these medications are also prohibited during the study extensions because of interaction with MK-1439; see footnotes in table below. For complete information, refer to the most recent darunavir (or ritonavir) package circulars.

Prohibited Medication/Therapy During Base Study Due to Darunavir Interaction
Alfuzosin
Dihydroergotamine
Ergonovine
Ergotamine
Methylergonovine
Cisapride
Pimozide
Oral midazolam
Triazolam
St. John's Wort†
Lovastatin
Simvastatin
Sildenafil (for treatment of pulmonary arterial hypertension)
Rifampin†
Amiodarone
Dronedarone
Lidocaine, systemic
Quinidine
Astemizole
Terfenadine
Bepridil
Colchicine when used in patients with renal and/or hepatic impairment
Quetiapine
Sertindole
Ranolazine
Ticagrelor
† Several of these medications are also prohibited during the study extensions because of interaction with MK-1439: specifically, rifampin, and St. John's Wort are prohibited throughout the base study and the extensions.

Prohibited Medication/Therapy During Base Study Due to Ritonavir Interaction
Alfuzosin HCL
Amiodarone
Bepridil
Flecainide
Propafenone
Quinidine
Voriconazole
Astemizole
Terfenadine
Dihydroergotamine
Ergonovine
Ergotamine
Methylergonovine
Midazolam
Triazolam
Pimozide
Cisapride
Eletriptan
Avanafil
Vardenafil
Clorazepate
Flurazepam
Diazepam
Estazolam
Clozapine
Quetiapine
Encainide
Fusidic acid
Rifabutin†
Pethidine
Piroxicam
Propoxyphene
† Rifabutin is also prohibited during the study extensions because of interaction with MK-1439.

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

Concomitant Therapy to be used With Caution

For complete information, please refer to the darunavir, ritonavir, TRUVADA™, EPZICOM™/KIVEXA™, TDF/TAF, ABC, FTC and 3TC package circulars, as appropriate, for drugs that are permitted in the protocol but that should be used with caution, since they have established drug interactions with these agents.

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-1439 (or placebo) can be taken without regard to food.

Darunavir, and ritonavir (or their respective placebos) will be taken with food.

TRUVADA™, if selected as the backbone NRTI regimen, will be taken with food.

EPZICOM™/KIVEXA™, if selected as the backbone NRTI regimen, can be taken without regard to food.

These drugs should generally be taken at approximately the same time each day.

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.

NRTI backbone therapy and recommended treatment guidelines.

The Investigator should consider local treatment guidelines when determining the backbone therapy for subjects in this protocol.

- Subjects with hepatitis B co-infection should be treated with TRUVADA™.

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.

- All chronic hepatitis B-infected subjects who require discontinuation of tenofovir should be discontinued from the study to allow for appropriate hepatitis B treatment with medications not permitted per protocol and to avoid lamivudine monotherapy.

- 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.

- The subject has an adverse experience or tolerability issue related to study medication which requires discontinuation of the medication.

- A physician investigator feels it is in the best interest of the subject to discontinue.

- The subject experiences a severe skin or hypersensitivity reaction.

- The subject has a creatinine clearance of <30 mL/min based on the following Cockcroft-Gault equation:

  Male:

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

Female:

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

- Subjects should be discontinued regardless of compliance with study therapy if they meet the PDVF criteria in Section 4.2.3.1.

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

Subjects who discontinue study therapy prior to the last scheduled treatment visit must be discontinued from the trial and should have an Early Discontinuation visit conducted. All applicable procedures will be done at this time. Subjects will be required to return to the clinic approximately 14 days after the last dose of study drug for a post-study visit as outlined in the Study Flow Chart (Sec 6.0).

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

Once discontinued from the base study, a subject is not eligible to enter study extension 1. Note that a subject who completes the base study and does not elect to participate in study extension 1 is considered to have completed the study. Once discontinued from study extension 1, a subject is not eligible to enter study extension 2. Once discontinued from study extension 2, a subject is not eligible to enter study extension 3.

5.9 Subject Replacement Strategy

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

5.10 Beginning and End of the Trial

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

5.11 Clinical Criteria for Early Trial Termination

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

1. The External Data Monitoring Committee (eDMC) recommends that the trial be terminated and the Executive Oversight Committee 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 applies to all subjects in the base study from screening through follow-up after the Week 96 visit. Flow Chart B applies to those subjects continuing into study extension 1 from Week 96 through follow-up after the Week 192 visit. Flow Chart C applies to those subjects continuing into study extension 2 from Week 208 through follow-up after the Week 288 visit. Flow Chart D applies to those subjects continuing into study extension 3 from Week 304 through follow-up after the Week 384 visit.

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

Visit Number/Title:	1	2	3	4	5	6	7	8	9		10	11	12	13	U (Virologic Failure Confirmation)	U (Early Discon)	99
Trial Period	Screening		Treatment														
TRIAL PROCEDURES	Screen	Fasting (Day1)[a]	WK 2	WK 4	WK 8	WK 16	Fasting WK 24	WK 36	Fasting WK 48		W K6 0	WK 72	WK 84	Fasting WK 96[r]	≥1 week to ≤ 4 weeks after the time virologic failure is first identified	At time of Discon	Post-study 14 day follow-up[p]
Administrative Procedures																	
Informed Consent	X													X[q]			
Informed Consent for Future Biomedical Research (optional)[b]	X																
Inclusion/Exclusion Criteria	X	X												X[q]			
Provide Subject Identification Cards	X																
Medical History[o]	X																
Concomitant Medication Review	X	X	X	X	X	X	X	X	X		X	X	X	X		X	X
Treatment Allocation/Randomization		X															
Register Study Visit and/or Dispense Study Therapy via Interactive Voice Response System (IVRS)[c]	X[d]	X	X[d,e]	X	X	X	X	X	X		X	X	X	X[c]		X[d]	
Provide/Review Study Medication Diary		X	X	X	X	X	X	X	X		X	X	X	X		X	
Clinical Procedures/Assessments																	
Full Physical Examination	X																
Directed Physical Examination		X	X	X	X	X	X	X	X		X	X	X	X		X	X
Height	X																
Weight	X								X					X			

Visit Number/Title:	1	2	3	4	5	6	7	8	9		10	11	12	13	U (Virologic Failure Confirmation)	U (Early Discon)	99
Trial Period	Screening	Treatment															
TRIAL PROCEDURES	Screen	Fasting (Day1) [a]	WK 2	WK 4	WK 8	WK 16	Fasting WK 24	WK 36	Fasting WK 48		W K60	WK 72	WK 84	Fasting WK 96[r]	≥1 week to ≤ 4 weeks after the time virologic failure is first identified	At time of Discon	Post-study 14 day follow-up [p]
Vital Signs (including pulse rate, blood pressure, respiratory rate, & body temperature)	X	X	X	X	X	X	X	X	X		X	X	X	X		X	X
Adverse Events Monitoring	X	X	X	X	X	X	X	X	X		X	X	X	X		X	X
12-lead ECG (local) [m]		X															
Laboratory Procedures/Assessments [n]																	
Serum Pregnancy Test	X [f,]																
Urine Pregnancy test [f]		X[g]		X	X	X	X	X	X		X	X	X	X		X	X
Collected Blood for Safety Laboratory Tests Hematology/Chemistry [h]	X	X[n]	X	X	X	X	X[n]	X	X[n]		X	X	X	X[n]	X	X[n]	X
Hemostatic Function Test [i]	X																
Human Leukocyte Antigen Test	X																
HIV/Hepatitis Screening [j]	X																
Virology Test Plasma HIV viral RNA quantification test (Abbott RealTime HIV-1)	X	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 PK [k]		X		X	X		X		X								
Collect Plasma for Viral Resistance Test	X						X								X	X[l]	
Collect Blood (DNA) for Future Biomedical Research (optional)[b]		X															
Collect Plasma for Future Biomedical Research (optional)[b]		X							X					X			

a. Prior to first dose on Day 1.
b. The optional informed consent for future biomedical research samples must be obtained before the FBR samples for DNA and plasma are collected. The FBR sample for DNA analysis should be obtained pre-dose, on Day 1 (or with the next scheduled blood draw), as the last sample drawn, on randomized subjects only, or at a later date as soon as the informed consent is obtained. The plasma samples for FBR should be collected at Day 1, Weeks 48 and 96.
c. Site personnel will access IVRS to register subjects at the screening visit. IVRS will be used to allocate drug and to manage distribution of clinical supplies; for Week 96, drug will be dispensed only to subjects who enter study extension 1, after providing informed consent.
d. At these visits, IVRS will be called to register the subject visit but no drug will be dispensed.
e. At the Week 2 (Visit 3) visit, the IVRS will be called to register the subject visit but no drug will be dispensed. In addition, the study coordinator will visually examine the bottles/container dispensed at Day 1 (Visit 2) for compliance (pills will not be counted), and drug will be returned to the subject following evaluation.

Visit Number/Title:	1	2	3	4	5	6	7	8	9		10	11	12	13	U (Virologic Failure Confirmation)	U (Early Discon)	99
Trial Period	Screening		Treatment														
TRIAL PROCEDURES	Screen	Fasting (Day1)[a]	WK 2	WK 4	WK 8	WK 16	Fasting WK 24	WK 36	Fasting WK 48		W K6 0	WK 72	WK 84	Fasting WK 96[r]	≥1 week to ≤ 4 weeks after the time virologic failure is first identified	At time of Discon	Post-study 14 day follow-up[p]

f. For women of childbearing potential.
g. Results of test need to be available prior to randomization.
h. Refer to Table 4 for listing of specific blood safety and chemistry tests.
i. Hemostatic Function Test includes: Prothrombin time (PT), Activated Partial Thromboplastin Time (APTT), and International Normalized Ratio (INR).
j. HIV/hepatitis Screening test 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.
k. Sample(s) for population PK will be collected at Day 1 and Weeks 4, 8, 24, 48. At Week 4, the sample must be collected predose. At weeks 24 and 48, the samples must be collected predose and within 0.5 to 2 hours postdose; and at Week 8, the samples may be collected irrespective of time of dose.
l. If virologic failure is confirmed (with a confirmatory HIV-1 RNA at least one week following the initial assessment), and the decision is made to discontinue the subject, plasma for resistance should still be collected at the discontinuation visit.
m. A local ECG should be performed prior to the subject's first dose of study medication.
n. Subjects will fast for at least 8 hours prior to the study visits at Day 1, Week 24, Week 48 and Week 96 and, if applicable, at the Discontinuation Visit. Fasting is required at these visits for lipids measurements.
o. Include smoking history in Medical History.
p. The follow-up visit 14 days after the Week 96 visit in the base study applies only to subjects who do not enter study extension 1.
q. If the subject is eligible and elects to enter study extension 1, he/she will be considered to have completed the base study and will, after providing informed consent for study extension 1, immediately enter study extension 1.
r. The visit window for Week 96 is approximately +/- 7 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.

Flow Chart B (Study Extension 1): Week 100 Through Week 192 Plus 14 Days Follow-up

Visit Number/Title:	14 [a]	15	16	17	18	19	20	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) [c]	X	X	X	X	X	X	X		X	
Dispense Study Therapy	X	X	X	X	X	X	X[d]			
Provide/Review Study Medication Diary	X	X	X	X	X	X	X		X	
Assess Subject Eligibility for Study Extension 2[e]							X			
Informed Consent for Study Extension 2[e]							X			
Clinical Procedures/Assessments										
Directed Physical Examination	X	X	X	X	X	X	X		X	X
Weight				X			X			
Vital Signs (including pulse rate, blood pressure, respiratory rate, & body temperature)	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 [f]	X	X	X	X	X	X	X		X	X
Collect Blood for Safety Laboratory Tests Hematology/Chemistry [g]	X	X	X	X[g]	X	X	X[g]	X	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[i]	

a. Subjects who enter study extension 1 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.

Visit Number/Title:	14 [a]	15	16	17	18	19	20	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

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 will be used to allocate drug and to manage distribution of clinical supplies.
d. Study drug for extension 2 will be dispensed at Week 192, if subject is continuing into extension 2
e. If the subject is eligible and elects to enter study extension 2, he/she will be considered to have completed study extension 1 and will, after providing informed consent, immediately enter study extension 2 and be dispensed MK-1439.
f. For women of childbearing potential
g. Subjects will fast for at least 8 hours prior to the study visits at Week 148 and Week 192 and, if applicable, at the Discontinuation Visit. Fasting is required at these visits for lipids measurements. Refer to Table 4 for listing of specific blood safety and chemistry tests.
h. If virologic failure is confirmed (with a confirmatory HIV-1 RNA at least one week following the initial assessment), and the decision is made to discontinue the subject, plasma for resistance testing should still be collected at the discontinuation visit..

Flow Chart C (Study Extension 2): Week 208 Through Week 288 Plus 14 Days Follow-up

Visit Number/Title:	21 [a]	22	23	24	25	26	U (Extension Early Discontinuation)	99
Trial Period:	**Extension: Treatment [b,c]**							**Post-Treatment [d]**
TRIAL PROCEDURES	**Wk 208**	**Wk 224**	**Wk 240**	**Wk 256**	**Wk 272**	**Wk 288**	**At time of Discontinuation**	**14 Day Follow-up**
Administrative Procedures								
Register Study Visit via Interactive Voice/Web Response System (IVRS/IWRS)	x	x	x	x	x	x	x	
Dispense Study Therapy [e]	x	x	x	x	x	x[f]		
Assess Subject Eligibility for Study Extension 3						x[g]		
Informed Consent for Study Extension 3						x[g]		
Clinical Procedures/Assessments								
Serious Adverse Events Monitoring	x	x	x	x	x	x	x	x
Birth Control Confirmation	x	x	x	x	x	x	x	x
Laboratory Procedures/Assessments								
Urine Pregnancy Test (if applicable) [h]	x	x	x	x	x	x	x	x

a. Subjects who enter study extension 2 are considered enrolled in the extension upon providing written informed consent at the Week 192 study visit.
b. The total duration is dependent on when MK-1439 becomes locally available, with a maximum total duration of treatment of 288 weeks. Subjects should discontinue at the next scheduled visit after MK-1439 becomes locally available in the market.
c. The visit windows are approximately +/- 14 days for all visits from Week 208 through Week 288. The timing of each visit is relative to the randomization (Day 1) visit. Every attempt must be made to keep subjects on schedule
d. The visit window for the post-study 14-day follow-up visit is approximately – 2 to 0 days.
e. IVRS/IWRS will be used to allocate drug and to manage distribution of MK-1439.
f. Study drug for extension 3 will be dispensed at Week 288, if subject is continuing into extension 3.
g. If the subject is eligible and elects to enter study extension 3, he/she will be considered to have completed study extension 2 and will, after providing informed consent, immediately enter study extension 3 and be dispensed MK-1439.
h. For women of childbearing potential.

Flow Chart D (Study Extension 3): Week 304 Through Week 384 Plus 14 Days Follow-up

Visit Number/Title:	**27** [a]	**28**	**29**	**30**	**31**	**32**	**U (Extension Early Discontinuation)**	**99**
Trial Period:	**Extension: Treatment** [b, c]							**Post-Treatment** [d]
TRIAL PROCEDURES	**Wk 304**	**Wk 320**	**Wk 336**	**Wk 352**	**Wk 368**	**Wk 384**	**At time of Discontinuation**	**14 Day Follow-up**
Administrative Procedures								
Register Study Visit via Interactive Voice/Web Response System (IVRS/IWRS)	x	x	x	x	x	x	x	
Dispense Study Therapy [e]	x	x	x	x	x			
Clinical Procedures/Assessments								
Serious Adverse Events Monitoring	x	x	x	x	x	x	x	x
Birth Control Confirmation	x	x	x	x	x	x	x	x
Laboratory Procedures/Assessments								
Urine Pregnancy Test (if applicable) [f]	x	x	x	x	x	x	x	x

a. Subjects who enter study extension 3 are considered enrolled in the extension upon providing written informed consent at the Week 288 study visit.
b. The total duration is dependent on when MK-1439 becomes locally available, with a maximum total duration of treatment of 384 weeks. Subjects should discontinue at the next scheduled visit after MK-1439 becomes locally available in the market.
c. The visit windows are approximately +/- 14 days for all visits from Week 304 through Week 384. The timing of each visit is relative to the randomization (Day 1) visit. Every attempt must be made to keep subjects on schedule.
d. The visit window for the post-study 14-day follow-up visit is approximately – 2 to 0 days.
e. IVRS/IWRS will be used to allocate drug and to manage distribution of MK-1439.
f. For women of childbearing potential.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

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

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

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

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

7.1.1.1.1 General Informed Consent

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

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

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

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

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

7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial. A review of these criteria should occur at the Screening visit and on the Day 1 visit (prior to randomization). For subjects who wish to continue into study extension 1, the additional inclusion criteria (9 to 12, Section 5.1.2) are to be reviewed at the Week 96 study visit of the base study. For subjects who wish to continue into study extension 2, the additional inclusion criteria (13 to 16, Section 5.1.2) are to be reviewed at the Week 192 study visit. For subjects who wish to continue into study extension 3, the additional inclusion criteria (17 to 20, Section 5.1.2) are to be reviewed at the Week 288 study visit.

7.1.1.3 Subject Identification Card

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

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

7.1.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee at the Screening visit. The medical history should include information pertaining to the diagnosis of HIV infection and Acquired Immune Deficiency Syndrome (if applicable) 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 medications use and record all medication taken by the subject within 30 days before starting the study.

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

7.1.1.5.2 Concomitant Medications

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

7.1.1.6 Assignment of Screening Number

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

The site must call the IVRS system to register each screening subject.

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 for the base study and study extension 1.

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 (allocation number), visit number, and visit dates 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 2 visits to ascertain problems with non-compliance as early as possible, taking study medication as directed and to ensure that subjects experiencing difficulties are re-educated, as appropriate.

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

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

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Physical Examination

All physical examinations should be performed as indicated in the study flow charts (Section 6.0). All physical examinations must be performed by the principal investigator or subinvestigator (physician, physician assistant or nurse practitioner).

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

Physical examinations after the Screening visit will be directed exams and will include vital signs. Any significant changes between the Screening and 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 Weight and Height Assessment

The subject's height and weight should be assessed as indicated in the study flow charts (Section 6.0). If height is measured after the Screening visit, the site should indicate whether or not the result is clinically significant and the result should be documented in the subject’s chart. If the result is clinically significant, it should be captured as an adverse event on the eCRF.

7.1.2.3 Vital Signs

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

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

After the Screening visit, the site should indicate whether or not the result is clinically significant and document the result in the subject's chart. If any result is clinically significant, it should be captured as an 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, as indicated in the study flow chart (Section 6.0), and any abnormalities documented.

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 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 the subject 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

The principal investigator or subinvestigator (physician, physician assistant or nurse practitioner) must determine the severity and relationship to study medication(s) of all adverse events. A physician investigator must review, initial and date any assessment of severity or relationship to study medication when the initial assessment of an adverse event is made by a physician assistant or nurse practitioner. Designated medical practitioners must be licensed and the responsibilities transferred to them must be documented in the site file. Details on assessing and recording adverse events can be found in Section 7.2.

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

When assessing the relationship of an AE to study medication during the base study, the investigator should indicate whether the relationship is to:

- Blinded therapy (MK-1439 or darunavir/ritonavir) or

- TRUVADA™ or
- EPZICOM™/KIVEXA™ or
- Combination ART (Blinded therapy combined with TRUVADA™ or EPZICOM™/KIVEXA™).

When assessing the relationship of an AE to study medication during the study extensions, the investigator should indicate whether the relationship is to:

- MK-1439 (open-label) alone or in combination with other background regimen.

7.1.2.6 Toxicity Management

Guidelines for grading the severity of adverse experiences are based on Division of Acquired Immunodeficiency Syndrome (DAIDS) criteria for grading severity of adverse events (Appendix 12.5). 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 MSD Clinical Director or Designee and the Independent Ethics Committee/Institutional Review Board and a re-challenge consent is needed prior to re-initiation of study therapy.

If, after re-initiation of study therapy, there is a recurrence of the laboratory abnormality or clinical adverse event, consideration should be given to permanently discontinuing all study therapy. In general, when a clinical or laboratory adverse event occurs which requires interruption of study therapy, all study drugs should be interrupted to avoid having a subject receive suboptimal therapy which may predispose them to the development of resistance. In general, all study medications should be restarted concomitantly at full dose. **Whenever study drugs are interrupted, the MSD Clinical Director or Designee should be notified.**

7.1.2.7 Birth Control Confirmation

Care must be taken to avoid pregnancy in female subjects of childbearing potential and in the female partners of 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 Screening to the 14 days post-study visit), including approximate blood/tissue volumes drawn/collected by visit and by sample type per subject can be found in Section 12.4.

7.1.3.1 Serum /Urine Pregnancy Test

For women of childbearing potential, a pregnancy test must be performed at all study visits except Week 2. A serum pregnancy is to be done at the Screening visit and a urine pregnancy test is to be done at all other visits of both the base study (except the Week 2 visit) and the study extensions, including the Day 1 visit prior to randomization, at the discontinuation visit and the 14-day post-study visit. A subject found to be pregnant must be discontinued from the study.

7.1.3.2 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests (hematology, chemistry and other) which are to be performed during the base study and study extension 1 of the trial are specified in Table 4.

Table 4 Laboratory Tests

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

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

1. Perform lipid analyses at Randomization (Day 1), Week 24, Week 48, and Week 96 in the base study and, for subjects who continue into study extension 1, at Week 148 and Week 192, and, as applicable, at the Early Discontinuation visit if possible. Subjects should be fasting for 8 hours prior to the visit. Perform non-fasting glucose at Screening and at Weeks 2, 4, 8, 16, 36, 60, 72 and 84 in the base study and, for subjects who continue into study extension 1, at Weeks 110, 116, 132, 164 and 180.
2. Perform at screening visit only.
3. If result of the hepatitis C Antibody testing is positive, then a plasma hepatitis C virus PCR quantitative test will also be performed.
4. Serum β hCG test at the Screening visit to be performed by central laboratory.
5. Urine β hCG test to be performed at the investigator site at Day 1 and every study visit thereafter (with the exception of Week 2).
6. Creatinine clearance will be computed at every visit by the central laboratory and provided to the site in the report that the site receives from the central laboratory.

7.1.3.3 HIV/ Hepatitis Screening

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

7.1.3.4 Human Leukocyte Antigen

At the screening visit, a blood sample will be collected to screen for the HLA-B*5701 allele to potentially avoid a hypersensitivity reaction to EPZICOM™/KIVEXA™.

7.1.3.5 Virology Test

Plasma HIV-1 RNA quantification will be performed at all visits in both the base study and study extension 1, except for Week 2. The testing will be performed at the central laboratory using the Abbott RealTime HIV-1 assay.

7.1.3.6 Viral Resistance Testing

Blood samples will be collected for HIV viral resistance testing at the Screening visit to determine MK-1439, darunavir, ritonavir, emtricitabine, tenofovir, abacavir and lamivudine resistance. Blood samples will also be collected for HIV viral resistance testing at Week 24 and, where applicable, at the Virologic Failure Confirmation visit and at the Early Discontinuation Visit. All resistance testing in the base study and in study extension 1 will be performed by the central laboratory.

7.1.3.7 CD4 Cell Counts

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

7.1.3.8 Pharmacokinetic/Pharmacodynamic Evaluations

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.

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
4	Week 4	Sample to be collected predose
5	Week 8	Sample to be collected pre or postdose
7	Week 24	Sample to be collected predose and within 0.5 to 2 hours postdose (Patient should remain fasting until postdose PK sample is collected).
9	Week 48	Sample to be collected predose and within 0.5 to 2 hours postdose (Patient should remain fasting until postdose PK sample is collected).

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

7.1.3.9 Future Biomedical Research

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

- Blood for genomics 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.

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

1. The reason the subject discontinued.

2. The date of the last dose of study medications from the trial.

3. The date of the last assessment and/or contact.

4. All adverse events (including any serious adverse events) in the base study and study extension 1.

5. Only serious adverse events in study extension 2 and study extension 3.

6. Final Assessments: Every effort should be made to ensure that all procedures and evaluations scheduled for the final study visit are performed.

In addition all investigative products must be retrieved from the subject.

7.1.4.1.1 Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.com), and a form will be provided by the Sponsor to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. A letter will be sent from the Sponsor to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the

subject's personal information and their specimens. In this situation, the request for specimen destruction cannot be processed.

7.1.4.2 Blinding/Unblinding

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

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

For emergency situations where the investigator or subinvestigator needs to identify the drug used by a subject and/or the dosage administered in case of emergency, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or subinvestigator 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 subinvestigator 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.

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

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

7.1.4.3 Calibration of Equipment

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

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

7.1.5 Visit Requirements

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

7.1.5.1 Screening

Written informed consent/assent must be obtained from the subject prior to performing any study-specific procedures. Potential subjects will be evaluated to determine if they fulfill the Inclusion/Exclusion entry requirements 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 Study Flow Chart (Section 6.0) must be completed and the subject's eligibility confirmed by the investigator prior to the subject's randomization and drug administration on Day 1.

- Blood will be collected at the Screening visit (Visit 1) as per the Trial Flow Chart (section 6.0). 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 to Visit 13)

Randomization Day 1 (Visit 2)

- Procedures listed for Day 1 (Visit 2) on the Study Flow Chart (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.

- Blood will be collected on Day 1 (Visit 2) as per the Trial Flow Chart (section 6.0). These samples will be sent to the appropriate central laboratories following the procedure(s) set forth in the manual(s).

- The investigator should also have selected the optimal NRTI backbone (either TRUVADA™ or EPZICOM™/KIVEXA™) to be given in combination with the blinded study therapy. Pharmacogenetic testing for potential hypersensitivity to EPZICOM™/KIVEXA™ will have been completed at the Screening Visit.

- Following completion of the Day 1 pretreatment procedures and confirmation of eligibility, the site pharmacist or study coordinator will contact the IVRS for assignment of the drug to be administered. Sites should not call IVRS 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 (4 bottles/containers labeled A, B, C, and D or E) on Day 1 (Visit 2) (see Section 7.1.5.2.1). 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/Container (A, B, C, and either D or E) Components

Bottle Label	Component
Bottle A	MK-1439 or placebo
Bottle B	Darunavir or placebo
Bottle C	Ritonavir or placebo
Bottle D	TRUVADA™†
Container E	EPZICOM™/KIVEXA™†
†Subject will take either bottle D (TRUVADA™) or container E (EPZICOM™/KIVEXA™) based on Investigator decision.	

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

All Subjects will take one tablet once daily from each of 4 bottles/containers as follows:

Note: In general study medication should be taken directly from the study bottle/container.

Bottle A (MK-1439 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 light and moisture sensitive.

Bottle B and Bottle C (darunavir/ ritonavir or placebo):

Subjects will be instructed to take one tablet from Bottle B and one tablet from Bottle C, once a day (q.d.) orally, together, with food at approximately the same time each day.

All subjects will take one tablet once daily from EITHER Bottle D or Container E as follows:

Bottle D (TRUVADA™)

Subjects will be instructed to take one tablet from Bottle D once a day (q.d.) orally, with food at approximately the same time each day.

OR

Container E (EPZICOM™/KIVEXA™)

Subjects will be instructed to take one tablet from Container E once a day (q.d.) orally, with or without food at approximately the same time each day.

Week 2 (Visit 3) to Week 96 (Visit 13)

- All procedures for treatment Week 2 (Visit 3) to Week 96 (Visit 13) listed on Study 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 Study Flow Chart. These samples will be sent to the appropriate central laboratory(ies) following the procedure(s) set forth in the manual(s).

- For a female subject who is of childbearing potential, a urine pregnancy test will be performed at all study visits (except Week 2). 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.

- Except as noted below, all bottles/containers 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 recorded in the source documentation. The primary source of adherence data, however, will be the subjects study medication diary.

  Note: At Week 2 (Visit 3), the study coordinator will visually examine the bottles/containers dispensed at Day 1 (Visit 2) for compliance (bottles will not be opened, pills will not be counted). Day 1 drug will be returned to the subject following evaluation. If the study coordinator suspects the patient has been non-compliant based on visual inspection, a pill count can be done at their discretion to verify study drug compliance, but new unopened drug will then need to be dispensed to the patient.

- Subjects will receive a 4-week supply of study drug (4 bottles labeled Bottle A, Bottle B, Bottle C, and Bottle D or Container E) at Day 1 (Visit 2) and Week 4 (Visit 4); an 8-week supply (8 bottles/containers; 2 each of bottles labeled Bottle A, Bottle B, and Bottle C, and 2 bottles/containers of either Bottle D or Container E) at Week 8 (Visit 5) and Week 16 (Visit 6); a 12-week supply (12 bottles/containers; 3 each of bottles labeled Bottle A, Bottle B, Bottle C, and 3 bottles/containers of either Bottle D or container E) beginning from Week 24 (Visit 7) through Week 84 (Visit 12).

- At Week 96 (Visit 13), subjects who continue into study extension 1 will receive a 4-week supply of unblinded study drug: this will consist, for all subjects, of MK-1439, packaged in a single bottle labeled 'Bottle F' or 'Bottle G', plus investigator-selected backbone therapy consisting of the following NRTIs as single entities or as an FDC, and provided by individual sites in commercial packaging: either tenofovir (as tenofovir disoproxil fumarate [TDF] or tenofovir alafenamide fumarate [TAF]) or abacavir (ABC), each administered with either emtricitabine (FTC) or lamivudine (3TC).

- 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 1 (Visit 14 to Visit 20)

- All procedures listed in the Study 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 100, Week 148 and Week 192 visits.

- Subjects will receive a 16-week supply of unblinded study drug, i.e., MK-1439 and either tenofovir (as TDF or TAF) or ABC, each administered with either FTC or 3TC, and

provided by individual sites in commercial packaging at each visit through Week 180. Study drug for extension 2 will be dispensed at Week 192 for subjects continuing into extension 2.

- All containers 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 container 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 Treatment Visits in Study Extension 2 (Visit 21 to Visit 26)

- All procedures for Study Week 208 (Visit 21), Week 224 (Visit 22), Week 240 (Visit 23), Week 256 (Visit 24), Week 272 (Visit 25), and Week 288 (Visit 26) listed on the Study Flow Chart C (Section 6.0) should be performed.
- For a female subject who is of childbearing potential, a urine pregnancy test will be performed at all study visits. If the urine pregnancy test result is positive, the subject must be discontinued.
- All bottles of study drug will be returned to the study coordinator at each visit, at which time the drug supplies for the following time period will be dispensed. The number of tablets remaining in the bottle will be counted and recorded in the source documentation. Only first dose, last dose, overdose (if applicable) and study drug interruption (if applicable) due to any toxicity, ECI or (S)AE will be collected in the database.
- Site staff will access the IVRS/IWRS for registration of visits. Subjects will receive a 16-week supply of study drug at each study visit through Week 272. Subjects continuing into study extension 3, if applicable, will receive a 16-week supply of study drug for study extension 3 at Week 288 (Visit 26).

7.1.5.5 Treatment Visits in Study Extension 3 (Visit 27 to Visit 32)

- All procedures for Study Week 304 (Visit 27), Week 320 (Visit 28), Week 336 (Visit 29), Week 352 (Visit 30), Week 368 (Visit 31), and Week 384 (Visit 32) listed on the Study Flow Chart D (Section 6.0) should be performed.
- For a female subject who is of childbearing potential, a urine pregnancy test will be performed at all study visits. If the urine pregnancy test result is positive, the subject must be discontinued.
- All bottles of study drug will be returned to the study coordinator at each visit, at which time the drug supplies for the following time period will be dispensed. The number of tablets remaining in the bottle will be counted and recorded in the source documentation.

Only first dose, last dose, overdose (if applicable) and study drug interruption (if applicable) due to any toxicity, ECI or (S)AE will be collected in the database.

- Site staff will access the IVRS/IWRS for registration of visits. Subjects will receive a 16-week supply of study drug at each study visit through Week 368.

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

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

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

1) Confirmed (2 consecutive measures at least one week apart) HIV-1 RNA ≥200 copies/mL at week 24 or week 36, or confirmed (2 consecutive measures at least one week apart) HIV-1 RNA ≥50 copies/mL at week 48;

   OR

2) Confirmed (2 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**.

The protocol allows a subject to switch from one of the study backbone NRTI regimens to the other (either from TRUVADA™ to EPZICOM™/KIVEXA™ or from EPZICOM™/KIVEXA™ to TRUVADA™) in the base study for management of toxic effects. If the switch occurs prior to the Week 2 visit, the subject will not be counted as a failure in the primary efficacy analysis; however if the switch occurs after Week 2 and the subject has HIV-1 RNA ≥50 copies/mL at the time of the switch, the subject will be regarded as a failure for the primary efficacy analysis as specified by FDA's snapshot approach in the base study.

During the open-label study extension 1, in order to address issues of drug access, tolerability, or subject convenience, single-drug or FDCs of the 4 permitted NRTIs may be used, and both TAF and TDF formulations of tenofovir may be used. (Permitted combinations are tenofovir [as TDF or TAF] or ABC, each administered with either FTC or 3TC). A switch to another NRTI backbone regimen during study extension 1 for drug access, tolerability, or subject convenience reasons will not be counted as a failure in the efficacy analysis in open-label extension 1, regardless of viral load at the time of the switch.

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

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

- 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.

- Refer to Section 7.1.4.1 for the list of information which must be collected when a subject discontinues.

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

7.1.5.8 Post-Trial

- Following the completion of study therapy in the base study (at 96 weeks) or in the study extensions (at 192, 288, or 384 weeks), or at the time of early discontinuation, subjects will be required to return to the clinic approximately 14 days after the last dose of study drug for the post-study visit as outlined in the Study Flow Charts (Section 6.0).

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

7.2 Assessing and Recording Adverse Events

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

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

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

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

All adverse events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. From the time of treatment allocation/randomization through 14 days following cessation of treatment, all adverse events must be reported by the investigator during the base study and study extension 1 as specified in Section 2. During study extension 2 and study extension 3, serious adverse events must be reported by the investigator as specified in Section 2; and if an investigator chooses to report a non-serious adverse event (NSAE), it should be submitted using the same process used to submit NSAEs in the base study and study extension 1. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

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

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

In this trial, an overdose is any dose higher than 2 times the recommended daily dose in a calendar day for any of the study medications provided.

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

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

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

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial.

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but

not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. Pregnancies and lactations that occur from the time of treatment allocation/randomization through 14 days following cessation of Sponsor's product must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

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

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

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

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

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

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

Refer to Table 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).

7.2.3.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events with respect to the elements outlined in Table 7. The investigator's assessment of causality is required for each adverse event. Refer to Appendix 12.5 for instructions in 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 an MSD product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect (**in offspring of subject taking the product regardless of time to diagnosis); or	
	Is a cancer (although not serious per ICH definition, is reportable to the Sponsor within 24 hours to meet certain local requirements); **or**	
	Is associated with an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Sponsor's product to be discontinued?	
Relationship to Sponsor's Product	Did the Sponsor's product cause the adverse event? The determination of the likelihood that the Sponsor's product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information **The following components are to be used to assess the relationship between the Sponsor's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the adverse event:	
	Exposure	Is there evidence that the subject was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Sponsor's Product (continued)	**The following components are to be used to assess the relationship between the Sponsor's product and the AE: (continued)**	
	Dechallenge	Was the Sponsor's product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the Sponsor's product in this trial? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time.) NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AND, IF REQUIRED, BY THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.
	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 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 DMC will monitor the trial at an appropriate frequency, with suggested periodic reviews to occur every ~4-6 months during the base study; there will be no involvement of the DMC in study extension 1. Details regarding the DMC 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 8.2.9 - 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.

A DMC recommendation will be communicated to the Sponsor as agreed to in the Collaboration agreement.

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, along with an explanation as to when and why they occurred, will be listed in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR. No separate Statistical Analysis Plan (SAP) will be issued for this study.

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 study extension 1, for those subjects who continue into extension 1, will be summarized separately using descriptive statistics only. Serious adverse event data from study extension 2 and study extension 3 will be summarized separately.

8.1 Statistical Analysis Plan Summary

This section contains a brief summary of the statistical analyses for this trial. Full detail is in the Statistical Analysis Plan (SAP) (Section 8.2).

8.1.1 Efficacy Analyses

The efficacy endpoints, primary analysis population, and statistical methods that will be employed for the efficacy analyses are presented in Table 8 below.

The primary hypothesis will be assessed based upon the proportion of subjects achieving HIV-1 RNA <50 copies/mL at Week 48 using the Full Analysis Set (FAS), which includes all randomized subjects who have taken at least one dose of study medication and have baseline data (for those analyses that require baseline data). The Non-Completer=Failure approach (NC=F) as defined by the 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, HIV-1 RNA <40 copies/mL, HIV-1 RNA < 200 copies/mL). All missing data will be treated as failures regardless of the reason.

For the analysis at time points 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.

A margin of 10 percentage points is used to define the non-inferiority of MK-1439 100 mg q.d. versus darunavir/ritonavir (800 mg/100 mg) q.d., each in combination with TRUVADA™ or EPZICOM™/KIVEXA™. This non-inferiority margin is consistent with current regulatory agency guidelines for evaluation of drugs in treatment-naïve subjects with HIV-1 infection. MK-1439 100 mg q.d. will be concluded non-inferior to darunavir/ritonavir (800 mg/100 mg) q.d., each in combination with TRUVADA™ or EPZICOM™/KIVEXA™, 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-1439 100 mg q.d. minus darunavir/ritonavir [800 mg/100 mg] q.d.) is greater than -10 percentage points. Provided non-inferiority is established, it can be further concluded that MK-1439 100 mg q.d. is superior to darunavir/ritonavir (800 mg/100 mg) q.d. if the lower bound of the two-sided 95% CI for the difference in response rate (MK-1439 100 mg q.d. minus darunavir/ritonavir [800 mg/100 mg] q.d.) is greater than zero. The superiority will be tested only if the non-inferiority is demonstrated. Due to the principles of closed testing, no adjustment for multiplicity is required for the superiority test since non-inferiority can always be concluded whenever the data also support superiority. The non-inferiority and superiority of MK-1439 100 mg q.d. versus darunavir/ritonavir (800 mg/100 mg) q.d. at Week 96 will be assessed using the same approach as for Week 48.

A sensitivity analysis will be performed using the Observed Failure (OF) approach under which non-intermittent missing data for subjects who prematurely discontinued their assigned treatment due to lack of efficacy are considered as failures thereafter.

The treatment difference in changes from baseline in CD4 cell count at time points of interest will be estimated between the 2 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.

Time to loss of virologic response (TLOVR) will be estimated using Kaplan-Meier product-limit estimates and graphically displayed. Log rank tests and Cox Proportional Hazards models may also be applied to this time-to-event data.

Table 8 Summary of Analysis Strategy for Efficacy Endpoints

Endpoint/Variable (Description, Timepoint)	Statistical Method	Analysis Population	Missing Data Approach
Primary Hypothesis			
Proportion of subjects achieving HIV-1 RNA <50 copies/mL at Week 48	Stratum-adjusted Mantel-Haenszel†	Full Analysis set	NC=F approach
Supportive to the Primary Hypothesis			
Proportion of subjects achieving HIV-1 RNA <50 copies/mL at Week 48	Stratum-adjusted Mantel-Haenszel†	Full Analysis set	OF approach
Secondary Hypothesis			
Proportion of subjects achieving HIV-1 RNA <50 copies/mL at Week 96	Stratum-adjusted Mantel-Haenszel†	Full Analysis set	NC=F approach
Supportive to the Secondary Hypothesis			
Proportion of subjects achieving HIV-1 RNA <50 copies/mL at Week 96	Stratum-adjusted Mantel-Haenszel†	Full Analysis set	OF approach
Secondary Objective			
Change from baseline in CD4 cell counts at Week 48 and Week 96	Two sample t-test	Full Analysis set	OF approach assuming baseline-carried-forward
Proportion of subjects achieving HIV-1 RNA <40 copies/mL at Week 48 and 96	Stratum-adjusted Mantel-Haenszel †	Full Analysis set	NC=F approach
Exploratory Objectives			
Proportion of subjects achieving HIV-1 RNA <200 copies/mL at Week 48 and 96	Stratum-adjusted Mantel-Haenszel †	Full Analysis set	NC=F approach
Time to Loss of Virological Response (TLOVR)	Kaplan-Meier product-limit estimates; Log-rank tests; Cox modeling	Full Analysis set	Not applicable

† Stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of the sample size per arm for each stratum.

8.1.2 Safety Analyses

The All Subjects as Treated population will be employed for safety analyses. For this study, there are safety hypotheses (i.e., Tier 1 events) regarding the change from baseline in fasting LDL-C and non-HDL-C (non-HDL-C = total cholesterol – fasting HDL-C) at Week 48. The change from baseline in fasting lipids (LDL-C, non-HDL-C, total cholesterol, HDL-C and triglycerides) will be analyzed using ANCOVA models adjusted by baseline fasting lipids level and treatment group. The treatment differences and 95% confidence intervals will be provided for all lipids parameters and a p-value for the between treatment comparison will be provided for LDL-C and non-HDL-C. The significance of the treatment difference for LDL-C will be tested first. Sequential testing for non-HDL-C will be done only if superiority is established for LDL-C.

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) discontinuation from study therapy due to an adverse experience. 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 method, an unconditional, asymptotic method.

Time to discontinuation from study due to an adverse experience will be estimated using Kaplan-Meier product-limit estimates and graphically displayed. A log rank test may also be applied to analyze this time-to-event data.

Data Monitoring Committee

To supplement the routine safety monitoring outlined in this protocol, an external Data Monitoring Committee will monitor ongoing safety data and provide recommendations to ensure the safety of study participants and the integrity of the trial. The eDMC will also review the interim efficacy data and make a recommendation on study conduct based on the pre-defined futility rule. The voting members of the committee are external to the Sponsor. The members of the eDMC 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 voting members of the eDMC will include clinicians and an external statistician experienced in HIV-1 infection; in addition, an unblinded trial statistician who will help prepare the analyses for the eDMC will serve as a non-voting member of the committee. Details regarding the eDMC will be described in a charter document.

8.1.3 Power and Sample Size

Efficacy

The study will randomize 340 subjects into each treatment arm to achieve 90% power to demonstrate the primary hypothesis that MK-1439 100 mg q.d. is non-inferior to darunavir/ritonavir (800 mg/100 mg) q.d., each in combination with TRUVADA™ or EPZICOM™/KIVEXA™, 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 using the Abbott RealTime HIV-1 Assay. The power calculation assumes a true response rate of 80% at Week 48 for both MK-1439 100 mg q.d. arm and darunavir/ritonavir (800 mg/100 mg) 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-1439 100 mg q.d. versus darunavir/ritonavir (800 mg/100 mg) q.d., each in combination with TRUVADA™ or EPZICOM™/KIVEXA™.

Safety

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

With 340 subjects in each treatment group, the study has >99% power to detect a between treatment difference of 14 mg/dL for mean change from baseline in fasting LDL-C. The study also has >99% power to detect a between treatment difference of 20 mg/dL for mean change from baseline in fasting non-HDL-C.

With 340 randomized subjects in each treatment group, the study has 90% power to declare, with 95% confidence, that the true difference between group proportions is no more than 9.9 percentage points for a reasonably common adverse experience which occurs in 20% of subjects receiving either MK-1439 100 mg q.d. or darunavir/ritonavir (800 mg/100 mg) q.d., each in combination with TRUVADA™ or EPZICOM™/KIVEXA™.

8.1.4 Interim Analysis

Two interim analyses will be performed in this study. The endpoints, timing, and purpose of the interim analyses are summarized in Table 9 below.

Although the assessment of neuropsychiatric adverse experiences is not a key objective in this study, a low rate of neuropsychiatric AEs associated with MK-1439 is expected to be an important attribute for the drug. Therefore, for administrative reasons, the Sponsor has an interest in comparing the neuropsychiatric AE profile of MK-1439 with that of darunavir early in the study to determine if the profiles of the 2 drugs are observationally similar. Thus, the first interim analysis will occur after 200 subjects have completed Week 8 and will assess the overall neuropsychiatric adverse event profile for the MK-1439 group versus the control. A selected list of neuropsychiatric adverse events will be examined. These include terms in the following 5 subcategories of events (1) dizziness, (2) sleep disorders and disturbances, (3) altered sensorium, (4) depression and suicide/self-injury, and (5) psychosis and psychotic disorders. All such events will be pooled and evaluated as neuropsychiatric events. Events in each separate subcategory will also be evaluated. MK-1439 and the control are expected to have similar neuropsychiatric AE profiles, and high rates of neuropsychiatric AEs are not expected in this study. Therefore, this analysis is not expected to lead to a termination of the study for safety reasons, and this interim analysis will be considered an administrative look at the data for purposes of making a program decision.

The second interim analysis will be an efficacy analysis, which will be performed for the sole purpose of stopping the study for a lack of efficacy (futility). This interim analysis will be conducted when complete Week 24 data are available for ~ 340 subjects (i.e. 50% of subjects randomized in this study). Details of analysis and futility rule are described in Section 8.2.9.1.

The eDMC will review the results for these 2 interim analyses and make a recommendation based on the data.

Table 9 Summary of Interim Analysis Strategy

Key Endpoints for Interim Analysis	Timing of Interim Analysis	Purpose of Interim Analysis
Proportion of Subjects with Neuropsychiatric Adverse Events by Week 8	Approximately 200 of randomized subjects (~100 subjects on each treatment group) have either completed the Week 8 visit or discontinued before Week 8.	Administrative look
Proportion of Subjects Achieving HIV-1 RNA <50 copies/mL at Week 24	Approximately 340 of randomized subjects (~170 subjects on each treatment group) have either completed the Week 24 visit or discontinued before Week 24.	Stop for futility

8.2 Statistical Analysis Plan

8.2.1 Responsibility for Analyses/In-House Blinding

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

The base study will be conducted as a double-blind study under in-house blinding procedures; study extensions 1, 2, and 3, for eligible subjects who elect to continue into these extensions, will be conducted as open-label studies. 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. 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. All personnel who are unblinded at the subject level 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 study extension 1), 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 Week 96 (base study) and from study extension 1 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 response system (IVRS).

The planned interim analyses are described in Section 8.2.9. Study enrollment is likely to be ongoing at the time of the interim analyses. Blinding to treatment assignment will be

maintained at all investigational sites. The results of the interim analysis will not be shared with the investigators prior to the completion of study extension 1. Subject-level unblinding will be restricted to the designated external unblinded statistician and scientific programmer performing the interim analysis, who will have no other responsibilities associated with the study and are otherwise unaffiliated with the program.

Treatment-level results of the interim analysis will be provided by the designated external unblinded statistician to the eDMC. Limited Sponsor personnel may be unblinded to the treatment-level results of the interim analysis, if required, in order to act on the recommendations of the eDMC. The extent to which individuals are unblinded with respect to results of the interim analysis will be documented by the designated external unblinded statistician.

The eDMC will serve as the primary reviewer of the results of the interim analyses and will make recommendations for discontinuation of the study or protocol modifications to an Executive Oversight Committee (EOC) of the Sponsor, who will be responsible for implementing the recommendations of the eDMC. Additional logistical details will be provided in the eDMC Charter. Key aspects of the planned interim analyses are described in Section 8.2.9.

Separate functional unblinding for pharmacokinetics will be done independent of the above interim analyses. Pharmacokinetic measurements will be conducted in support of pharmacokinetic evaluations. A small team as specified in a separate Modeling and Simulation (M&S) Modeling Analysis Plan, and who are separate from the study team, will be unblinded for the purpose of preparing the pharmacokinetic analyses. No interim data or results will be shared with the study team before the primary analyses at Week 48 have been completed. No decisions will be made based on this functional unblinding that will influence the conduct of the trial.

8.2.2 Hypotheses/Estimation

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

8.2.3 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated for within- and/or between-treatment differences for the base study and study extension 1 are listed below, followed by the descriptions of the derivations of selected endpoints.

8.2.3.1 Efficacy/Pharmacokinetics Endpoints

8.2.3.1.1 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

The proportions of subjects achieving HIV-1 RNA <50 copies/mL, <40 copies/mL 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.

Time to Loss Of Virologic Response (TLOVR)

For subjects who achieve HIV-1 RNA <50 copies/mL and subsequently have 2 consecutive HIV-1 RNA values (measured at least 1 week apart) ≥50 copies/mL, time to loss of virologic response is the time between Day 1 and the date of the first of the 2 consecutive values ≥50 copies/mL. For subjects who achieve and sustain HIV-1 RNA <50 copies/mL, time to loss of virologic response is censored at the time of the last available measurement. For subjects who do not achieve HIV-1 RNA values <50 copies/mL, time to loss of virologic response is 0 weeks.

Protocol-Defined Virologic Failure (PDVF)

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

Resistance

Subjects with protocol-defined virologic failure and those who discontinue for any reason, who have blood samples available and potentially amplifiable (>400 copies/mL) for resistance testing, will be assessed for resistance to study drugs. Resistance data from subjects with protocol-defined virologic failure and from subjects who discontinue from the study will be summarized.

8.2.3.1.2 Pharmacokinetic Endpoints

For the population PK analysis, descriptive statistics will be provided for C_{min} (defined as the minimum concentration for an individual subject collected predose). A population PK model has been developed utilizing the sparse PK data from Phase 2 and PK data from Phase 1 studies. This model will be updated with data from this study in order to assess individual exposure to MK-1439 (AUC, C_{max} and C_{24hr}) based on the sparse sampling data.

8.2.3.2 Safety Endpoints

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

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 fasting 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 (Appendix 12.5). A listing of the subjects who meet the criteria will be provided.

8.2.4 Analysis Populations

8.2.4.1 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 and
- 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 8.2.5 (Statistical Methods).

8.2.4.2 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.

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 8.2.5 (Statistical Methods).

8.2.5 Statistical Methods

Statistical testing and inference for safety analyses are described in Section 8.2.5.2. Efficacy results that will be considered to be statistically significant after consideration of the strategy for controlling the Type-I error are described in Section 8.2.6 (Multiplicity). Nominal p-values may be computed for other efficacy analyses as a measure of strength of association between the endpoint and the treatment effect rather than formal tests of hypotheses. Unless otherwise stated, all statistical tests will be conducted at the α=0.05 (2-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 study extension 1, for those subjects who continue into extension 1, will be summarized separately using descriptive statistics only. Serious adverse

event data will be collected and summarized for study extension 2 and study extension 3 separately.

8.2.5.1 Statistical Methods for Efficacy Analyses

Time Window

Table 10 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 10 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	Week 2	≥2 and ≤21	15	Week 2
		Week 4	≥22and ≤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 ≤ the last day of double-blind treatment period	673	Week 96
Treatment	Open-label Study Extension 1	Week 100	≥ first day of open-label extension 1 treatment period 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 and ≤ last day of open-label extension 1 treatment period	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 11). 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 those subjects who 1) are on study assigned double-blind-treatment; 2) have HIV-1 RNA measurement(s) within the time window specified in Table 10; and 3) have the measurement closest to the target date of the time point <50 copies/mL, can be classified as virologic success at that time point. The other subjects, either with 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.

In addition, the protocol allows a subject to switch from one of the study backbone NRTI regimens to the other (either from TRUVADA™ to EPZICOM™/KIVEXA™ or from EPZICOM™/KIVEXA™ to TRUVADA™) for management of toxic effects in the base study. If the switch occurs after Week 2 and the subject has HIV RNA ≥50 copies/mL at the time of switch, the subject will be regarded as a failure at all timepoints after the switch in the base study. During the open-label study extension, in order to address issues of drug access, tolerability, or subject convenience, a subject is allowed to switch from the NRTI backbone therapy used during the base study to another one of the allowed NRTI regimens permitted during the extension. A switch to another NRTI backbone regimen during study extension 1 for drug access, tolerability, or subject convenience reasons will not be counted as a failure in the efficacy analysis in the open-label extension, regardless of viral load at the time of the switch.

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 copies/mL and <200 copies/mL.

Table 11 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 Discontin-uation 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.

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-1439 100 mg q.d. to darunavir/ritonavir (800 mg/100 mg) q.d., each in combination with TRUVADA™ or EPZICOM™/KIVEXA™. MK-1439 100 mg q.d. will be concluded non-inferior to darunavir/ritonavir (800 mg/100 mg) 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-1439 100 mg q.d. minus darunavir/ritonavir [800 mg/100 mg] q.d) is greater than -10 percentage points. It can be further concluded that MK-1439 100 mg q.d. is superior to darunavir/ritonavir (800 mg/100 mg) q.d. if the lower bound of the two-sided 95% CI for the difference in response rates (MK-1439 100 mg q.d. minus darunavir/ritonavir [800 mg/100 mg] q.d.) is greater than zero.

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.

Proportion of Subjects Achieving HIV-1 RNA <40 copies/mL and <200 copies/mL

The proportion of subjects achieving HIV-1 RNA <40 copies/mL and < 200 copies/mL will be analyzed using the same approach as described above for the proportion of subjects achieving HIV-1 RNA <50 copies/mL with the exception that no hypothesis will be assessed for these endpoints.

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 2 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.

Time to Loss Of Virologic Response (TLOVR)

TLOVR will be estimated using Kaplan-Meier product-limit estimates and graphically displayed. Log rank tests and Cox Proportional Hazards models may also be applied to this time-to-event data.

Table 8 summarizes the key efficacy analyses of the study. The strategy to address multiplicity issues with regard to multiple treatment comparisons, multiple efficacy endpoints, multiple timepoints, and/or interim analyses is described in Section 8.2.6 (Multiplicity) and Section 8.2.9 (Interim Analyses).

Protocol-Defined Virologic Failure (PDVF)

The number of subjects with PDVF will be summarized for each treatment group.

Resistance

Resistance data from subjects with protocol-defined virologic failure and from subjects who discontinue from the study will be summarized.

8.2.5.2 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 12). 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 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 Tier 1 events are the change from baseline in fasting LDL-C and non-HDL-C. Change from baseline in other fasting lipids (total cholesterol, HDL-C, triglycerides) will be Tier 2 events. The change from baseline in fasting lipids will be analyzed using ANCOVA models adjusted by baseline fasting lipids level and treatment group. The treatment differences and 95% confidence intervals will be provided for all lipid parameters, and p-value for the between treatment comparison will be provided for LDL-C and non-HDL-C. The significance of treatment difference for LDL-C will be tested first. Sequential testing for non-HDL-C will be done only if superiority is established for LDL-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 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 [1].

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 (1985) [1], an unconditional, asymptotic method.

The time to discontinuation from study due to an adverse experience will be estimated using Kaplan-Meier product-limit estimates and graphically displayed.

Table 12 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint†	p-Value	95% CI for Treatment Comparison	Descriptive Statistics
Tier 1	Change from baseline in fasting LDL-C, non-HDL-C	X	X	X
Tier 2	Change from baseline in other fasting lipids (total cholesterol, HDL-C, triglycerides)		X	X
	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 subjects in one of the treatment groups)		X	X
	Time to discontinuation from study due to AE			X
Tier 3	Specific AEs, SOCs or PDLCs (incidence <4of 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.
Note: SOC=System Organ Class; PDLC=Pre-Defined Limit of Change; X = results will be provided.

8.2.5.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

8.2.5.3.1 Demographic and Baseline Characteristics

The comparability of the treatment groups for each relevant characteristic will be assessed by the use of descriptive statistics. 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 using descriptive statistics for continuous or categorical variables, as appropriate. Summary statistics for baseline disease characteristics to be used as efficacy measures such as HIV-1 RNA and CD4 cell count will also be provided by treatment.

8.2.5.3.2 Population PK and PK/PD Analyses

Summary statistics will be presented for sparsely sampled MK-1439 plasma concentrations. PK samples will also be used to update a previously developed population PK model and to explore possible PK/PD associations.

8.2.6 Multiplicity

No multiplicity adjustment is needed in this study to account for multiple efficacy endpoints or multiple opportunities to declare success based on the test of the primary efficacy hypothesis. Efficacy analyses other than the primary hypothesis test at Week 48 will be considered supportive and/or explanatory. The superiority of MK-1439 to darunavir/ritonavir with respect to the primary efficacy endpoint will be tested only if non-inferiority is first demonstrated. Due to the principles of closed testing, no adjustment for multiplicity is required for the superiority test since non-inferiority can always be concluded whenever the data also support superiority.

The safety hypotheses on fasting LDL-C and non-HDL-C will be tested sequentially. The hypothesis for LDL-C will be tested first. Sequential testing for non-HDL-C will be done only if superiority is established for LDL-C. Due to the principles of closed testing, no adjustment for multiplicity is needed.

However, there are 2 interim analyses planned in the study (see Section 8.1.4). The first interim analysis of neuropsychiatric adverse events is not related to efficacy or fasting lipids and is considered an administrative look at the data for the purposes of making a program decision. Therefore, it does not affect the Type-I error for the testing of the primary efficacy hypothesis or secondary lipid hypotheses. Although the second interim analysis is an efficacy analysis, the plan is to stop the study only for lack of efficacy; therefore, there is no need to adjust for multiplicity in this setting. However, as it is customary to spend a small amount of alpha for interim analyses, an alpha level of 0.00001 will be allocated for each interim analysis before testing the primary efficacy hypothesis or secondary lipid hypotheses. Thus, both tests will be conducted at the 2-sided α=0.049998 level.

8.2.7 Sample Size and Power Calculations

8.2.7.1 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-1439 100 mg q.d. is non-inferior to darunavir darunavir/ritonavir (800 mg/100 mg) q.d., each in combination with TRUVADA™ or EPZICOM™/KIVEXA™, 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 using the Abbott RealTime HIV-1 Assay. The power calculation assumes a true response rate of 80% at Week 48 for both the MK-1439 100 mg q.d. arm and darunavir/ritonavir (800 mg/100 mg) 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-1439 100 mg q.d. versus darunavir/ritonavir (800 mg/100 mg) q.d., each in combination with TRUVADA™ or EPZICOM™/KIVEXA™. Given the non-inferiority margin of 10%, the assumed response rates in darunavir/ritonavir (800 mg/100 mg) q.d. group and the chosen sample size, non-inferiority may be established when the observed difference in response rates (MK-1439 100 mg q.d. minus darunavir/ritonavir [800 mg/100 mg] 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. The power calculation is based on an asymptotic method proposed by Farrington and Manning (1990) [2] and is carried out using SAS v9.3. Table 13 summarizes the power for the primary comparison under various assumptions for the control response rate and underlying difference in response rates.

Table 13 Power (%) Under Various Assumptions (With 340 Subjects Randomized in Each Treatment Group)

Response Rate (%) in Darunavir/ritonavir (800 mg/100mg) q.d.	**Underlying Difference in Response Rates (%) (MK-1439 100 mg q.d. – Darunavir/ritonavir [800 mg/100mg] 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							

8.2.7.2 Sample Size and Power for Safety Analyses

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 fasting lipids level and treatment group. MK-1439 100 mg q.d. will be concluded to be superior to darunavir/ritonavir (800 mg/100 mg) q.d. if the mean change from baseline in fasting LDL-C for the MK-1439 group is significantly lower than that for the darunavir/ritonavir group (the p-value for the between

treatment comparison is less than 0.04998). If superiority for LDL-C is established, sequential testing for non-HDL-C will be conducted at the same α level.

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. If we assume that darunavir/ritonavir has an effect on lipids at least as large as efavirenz, the treatment difference in mean change from baseline in fasting 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 14 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 14 mg/dL for mean change from baseline in fasting LDL-C. The study also has >99% power to detect a between treatment difference of 20 mg/dL for mean change from baseline in fasting 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) [3].

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).		

Table 15 gives the difference in the incidence of adverse experience (MK-1439 100 mg q.d. – darunavir/ritonavir [800 mg/100mg] 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 2 treatment groups. For a reasonably common adverse experience which occurs in 20% of subjects either in the MK-1439 100 mg q.d. arm or darunavir/ritonavir (800 mg/100mg) 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) [2].

Table 15 Differences in Incidences of AEs (MK-1439 100 mg q.d. minus Darunavir/ritonavir [800 mg/100mg] 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.					

8.2.8 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) 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)
- NRTI background therapy (TRUVADA™, EPZICOM™/KIVEXA™)

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

8.2.9 Interim Analyses

8.2.9.1 Efficacy Interim Analyses

One efficacy interim analysis will be performed for the sole purpose of stopping the study for a lack of efficacy (futility). Key aspects of this interim analysis are described in this section. Additional logistical details will be provided in the eDMC Charter.

Interim Futility Analysis at Week 24

The interim analysis will be performed when approximately 340 subjects randomized in the study (~170 subjects per treatment group) either complete Week 24 visit or discontinue before Week 24. There will be no pause in the enrollment for this interim analysis. Based on the observed proportion of subjects with HIV-1 RNA <50 copies/mL at Week 24, if the conditional power for demonstrating non-inferiority in the final analysis of the primary

hypothesis at Week 48 is <20%, the study may be stopped and all subjects in the MK-1439 100 mg q.d. group will be switched to standard therapy. For example, if at Week 24, the response rate in MK-1439 100 mg q.d. group is <74.4% and the response rate in the darunavir/ritonavir (800 mg/100 mg) q.d. group is 80%, the conditional probability of demonstrating non-inferiority in the final analysis will be <20% (assuming similar response rates are seen at Week 48) and the study may be stopped. There is approximately a 9.8% chance of stopping the study based on Week 24 data from 170 subjects per treatment group when in fact the true response rate in both treatment groups is 80%.

Type-I/II Error Control for Interim Analyses

As the only purpose of the planned interim analyses is to stop the study for lack of efficacy, no adjustment for Type-I error is necessary. However, as it is customary to spend a small amount of alpha for interim analyses, an alpha level of 0.00001 will be allocated to this interim analysis. On the other hand, as there is a chance that the study may be stopped early for lack of efficacy, albeit small, there is a reduction in the overall power (i.e., inflation of the Type II error) of the study. Using conditional power <20% as the stopping criterion at interim analysis, the overall power of the study will reduce to 86%. If the stopping criterion is not met at the interim analysis, the conditional probability of demonstrating non-inferiority in the final analysis will increase to 94% (assuming 80% response rates for both treatment groups).

8.2.9.2 Safety Interim Analyses

To supplement the routine safety monitoring outlined in this protocol, the eDMC will monitor ongoing safety data and provide recommendations to ensure the safety of study participants and the integrity of the trial to the EOC (see Section 7.3.3). The eDMC will monitor the trial at an appropriate frequency, with suggested periodic reviews to occur every ~4-6 months. Details regarding the eDMC will be described in a charter document.

One interim analysis will occur after 200 subjects (~100 subjects per treatment group) have completed Week 8 and will assess the overall neuropsychiatric adverse event profile for the MK-1439 group versus control. A selected list of neuropsychiatric adverse events will be examined. These include terms in the following 5 subcategories of events (1) dizziness, (2) sleep disorders and disturbances, (3) altered sensorium, (4) depression and suicide/self-injury, and (5) psychosis and psychotic disorders. All such events will be pooled and evaluated as neuropsychiatric events. Events in each subcategory will also be evaluated separately.

MK-1439 and the control are expected to have similar neuropsychiatric AE profiles, and high rates of neuropsychiatric AEs are not expected in this study. Therefore, this analysis is not expected to lead to a termination of the study for safety reasons, and this will be considered an administrative look at the data for purposes of making a program decision. No adjustment for Type-I error is necessary. However, as it is customary to spend a small amount of alpha for interim analyses, an alpha level of 0.00001 will be allocated to this interim analysis.

8.2.10 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 4 bottles/containers 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/container 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 using a different definition of compliance will also be conducted for the base study. 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/containers provided for this study (as noted in Section 7.1.5.2.1) will also be summarized.

During study extension 1, MK-1439 will be provided as study medication by the sponsor and 2 NRTIs will be selected and supplied by investigator. Compliance with MK-1439 administration will be summarized for study extension 1. A day within the study will be considered an "On-Therapy" day if the subject takes 1 tablet of MK-1439.

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

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

8.2.11 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 Extensions

Product Name & Potency	Dosage Form
Base Study	
MK-1439 100 mg	Oral Compressed Tablet
Placebo to match MK-1439 100 mg	Oral Compressed Tablet
Darunavir 800 mg	Film-coated Tablet
Placebo to match darunavir 800 mg	Film-coated Tablet
Ritonavir 100 mg	Film-coated Tablet
Placebo to ritonavir 100 mg	Film-coated Tablet
TRUVADA™ (emtricitabine 200 mg and tenofovir disoproxil fumarate 300 mg)	Film-coated Tablet
EPZICOM™/KIVEXA™ (abacavir sulfate 600 mg and lamivudine 300 mg)	Film-coated Tablet
Study Extensions	
MK-1439 100 mg	Oral Compressed or Film-coated 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 both blinded (Bottles A, B and C) and open label (Bottle D or Container E) bottles in accordance with the dispensing schedule. No kitting will be required. During the study extensions, subjects will receive Bottle F (oral compressed tablets) or, if subsequently available, Bottle G (film-coated tablets).

9.3 Clinical Supplies Disclosure

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

electronic treatment allocation/randomization system (IVRS/IWRS) should be used in order to unblind subjects and to unmask treatment/vaccine identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

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

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

9.4 Storage and Handling Requirements

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

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

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

9.5 Discard/Destruction/Returns and Reconciliation

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

9.6 Standard Policies

For trials using Controlled Substances, all Federal, State, Province, Country, etc. regulations must be adhered to in regard to the shipping, storage, handling and dispensing of controlled substances. Additionally, the investigator should have the appropriate controlled drug license(s) as mandated by Federal, State, Province, Country, etc. laws in which the trial is being conducted.

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 drugs PREZISTA™ (darunavir 800 mg) and NORVIR™ (ritonavir 100 mg) as much as possible. You did not receive the active drugs PREZISTA™ (darunavir 800 mg) and NORVIR™ (ritonavir 100 mg) as manufactured by Janssen Pharmaceuticals, Inc. and AbbVie, Inc., respectively."

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

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

10.1.2 Confidentiality of Subject Records

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

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

10.1.3 Confidentiality of Investigator Information

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

1. name, address, telephone number and e-mail address;

2. hospital or clinic address and telephone number;

3. curriculum vitae or other summary of qualifications and credentials; and

4. other professional documentation.

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

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

10.1.4 Confidentiality of IRB/IEC Information

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

10.2 Compliance with Financial Disclosure Requirements

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

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

10.3 Compliance with Law, Audit and Debarment

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

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

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

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

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

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

The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. By signing this protocol, the investigator agrees that documentation shall be retained until at least 2 years after the last approval of a marketing application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed

since the formal discontinuation of clinical development of the investigational product. Because the clinical development and marketing application process is variable, it is anticipated that the retention period can be up to 15 years or longer after protocol database lock. The Sponsor will determine the minimum retention period and notify the investigator when documents may be destroyed. The sponsor 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 discarding trial and/or subject files.

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

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

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

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

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

10.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Amendments Act (FDAAA) of 2007 and the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to

the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. MSD, as Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

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

10.5 Quality Management System

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

10.6 Data Management

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

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

10.7 Publications

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

primary outcome, 12 months after the decision to discontinue development, or product marketing (dispensed, administered, delivered or promoted), whichever is later.

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

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

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

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

11.0 LIST OF REFERENCES

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

2. 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.

3. 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 Code of Conduct for Clinical Trials

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

I. Introduction

A. Purpose

MSD, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (including all applicable data protection laws and regulations), and International Council for Harmonisation Good Clinical Practice (ICH-GCP), and also in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

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

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

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish the primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the pre-specified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing; in such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

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

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

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

B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care.

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Participants may withdraw from an MSD trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices.

V. Investigator Commitment

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

12.2 Collection and Management of Specimens for Future Biomedical Research

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The DNA and plasma specimen(s) collected in the current trial will be used to study various causes for how subjects may respond to a drug/vaccine. The DNA and plasma specimen(s) will be stored to provide a resource for future trials conducted by MSD 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 MSD 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 Future Biomedical Research.

b. Informed Consent

Informed consent for specimens (ie, DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all participants or legal guardians, at a study visit by the investigator or his or her designate. Informed consent for future biomedical research should be presented to the participants on the visit designated in the SoA. If delayed, present consent at next possible Participant Visit. Consent forms signed by the participant will be kept at the clinical study site under secure storage for regulatory reasons.

A template of each study site's approved informed consent will be stored in the Sponsor's clinical document repository.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of participant consent for future biomedical research will be captured in the eCRFs. 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, and plasma specimens 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 MSD 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, MSD 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 MSD 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 MSD designated facility to an Entrusted Keyholder at MSD. The second code will be logged into the primary biorepository database at MSD 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 MSD Entrusted Keyholder under strict security policies and procedures. The MSD 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 Sponsor will be used for analyses using good scientific practices. Analyses utilizing the future biomedical research specimens may be performed by the Sponsor, or an additional third party (eg, a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third party analyses will conform to the specific scope of analysis outlined in future biomedical research protocol and consent. Future biomedical research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact MSD using the designated mailbox (clinical.specimen.management@MSD.com) and a form will be provided by MSD 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 MSD 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 MSD 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 MSD policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated study administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards to protect against unauthorized access.

9. Reporting of Future Biomedical Research Data to Subjects

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 MSD 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 MSD) 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, MSD will publish the results without revealing specific subject information, inform all trial sites who participated in the MSD 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 MSD 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.

MSD 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 MSD 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.

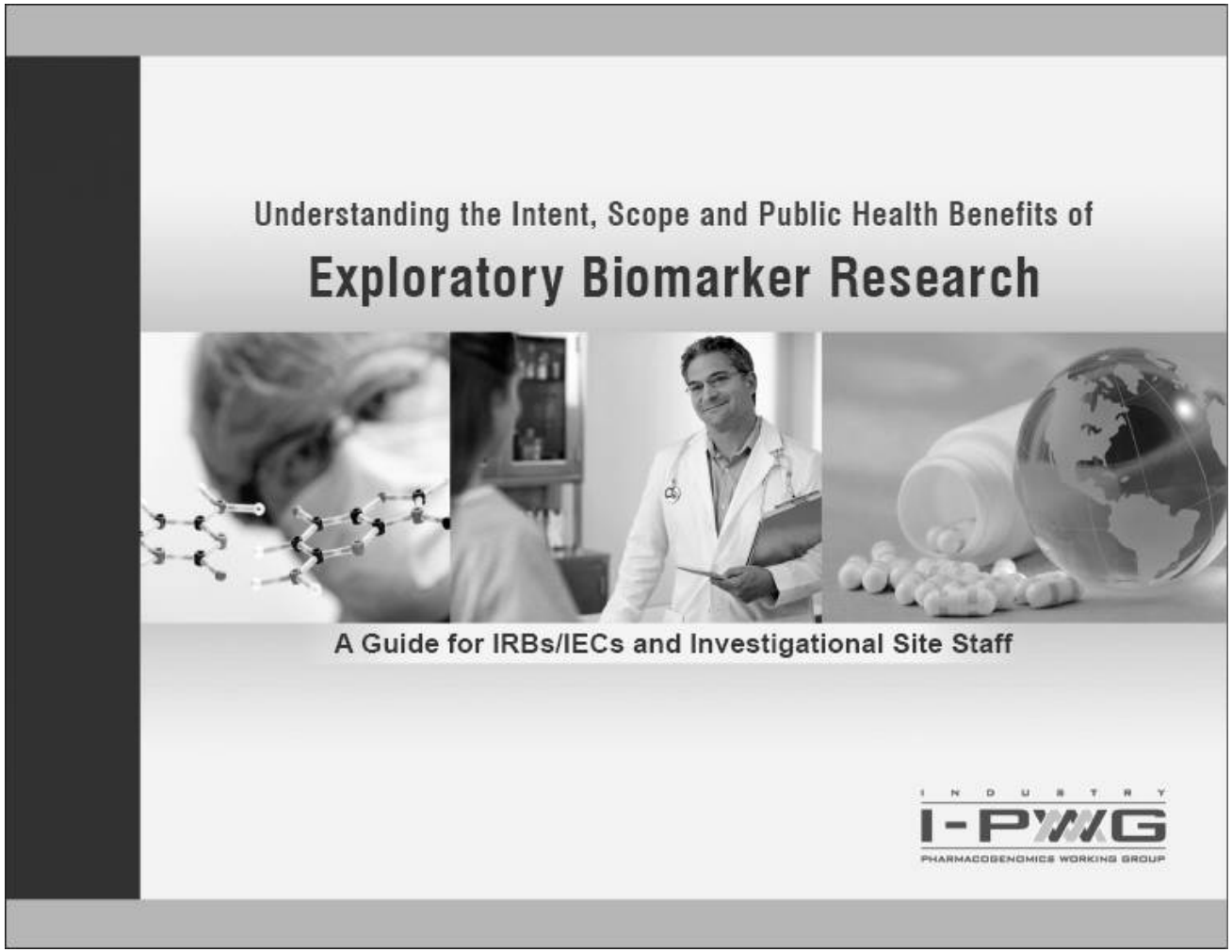
13. Questions

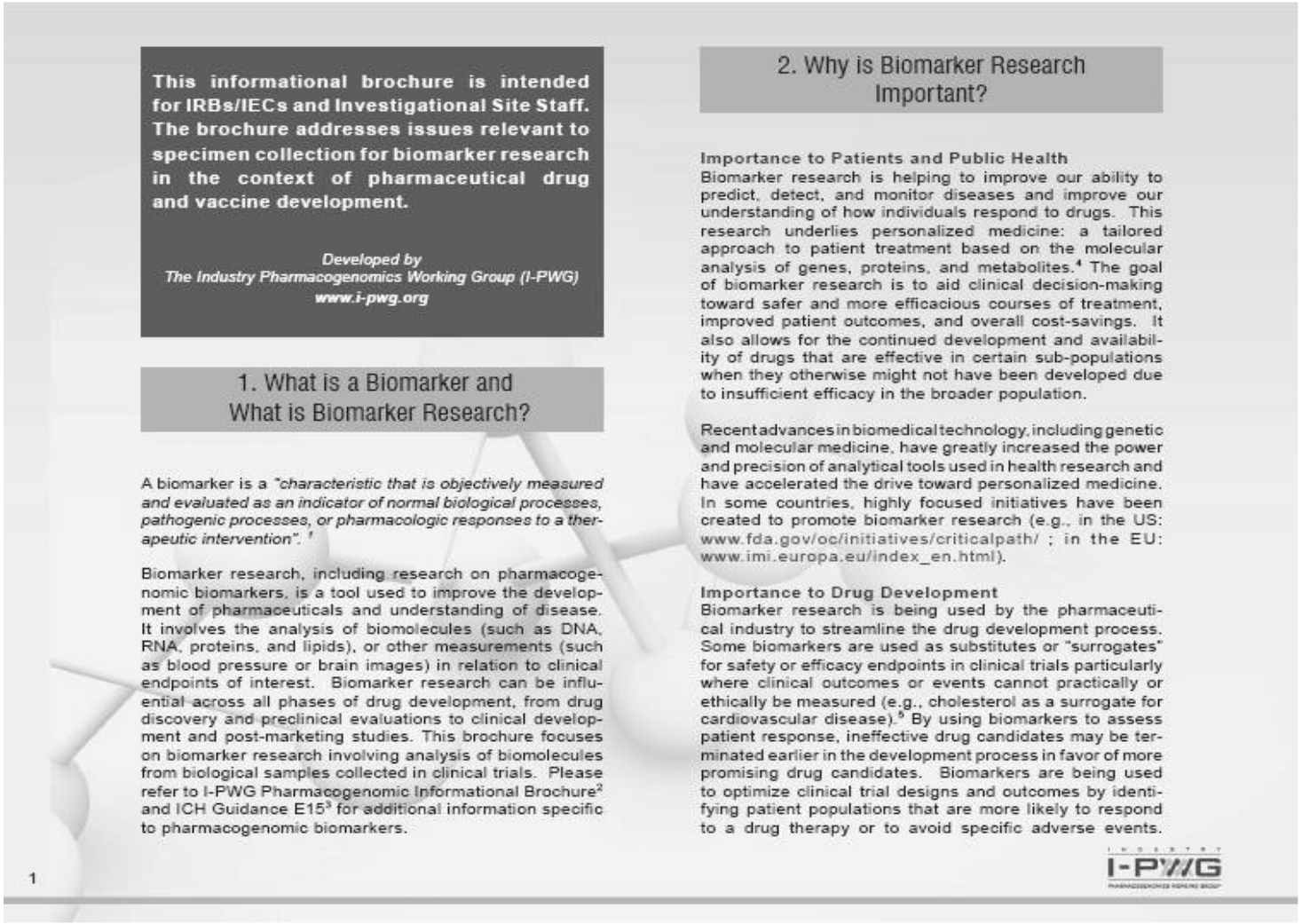
Any questions related to the future biomedical research should be e-mailed directly to clinical.specimen.management@MSD.com.

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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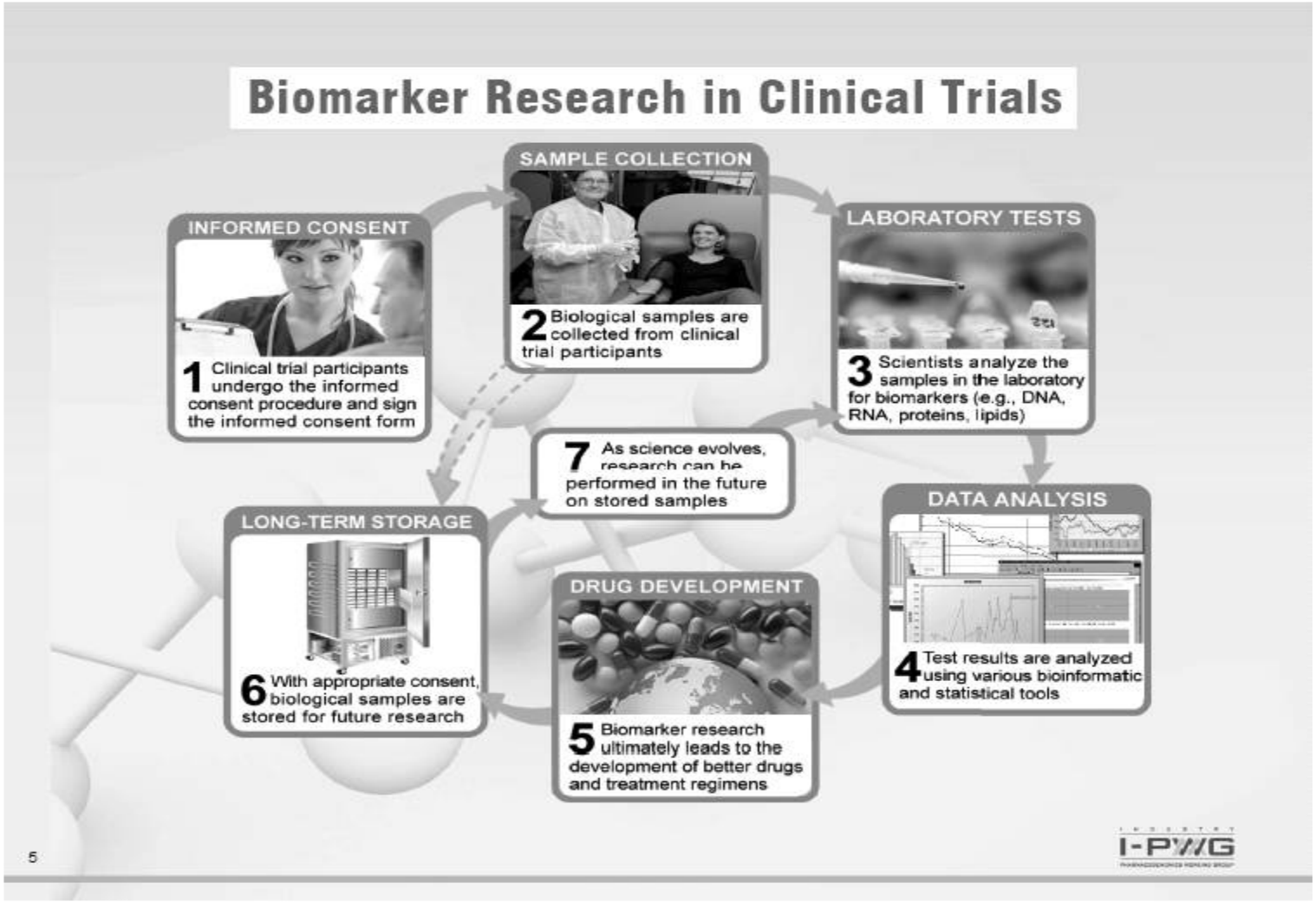
Biomarker Research in Clinical Trials
SAMPLE COLLECTION
2 Biological samples are collected from clinical trial participants
INFORMED CONSENT
1 Clinical trial participants undergo the informed consent procedure and sign the informed consent form
LABORATORY TESTS
3 Scientists analyze the samples in the 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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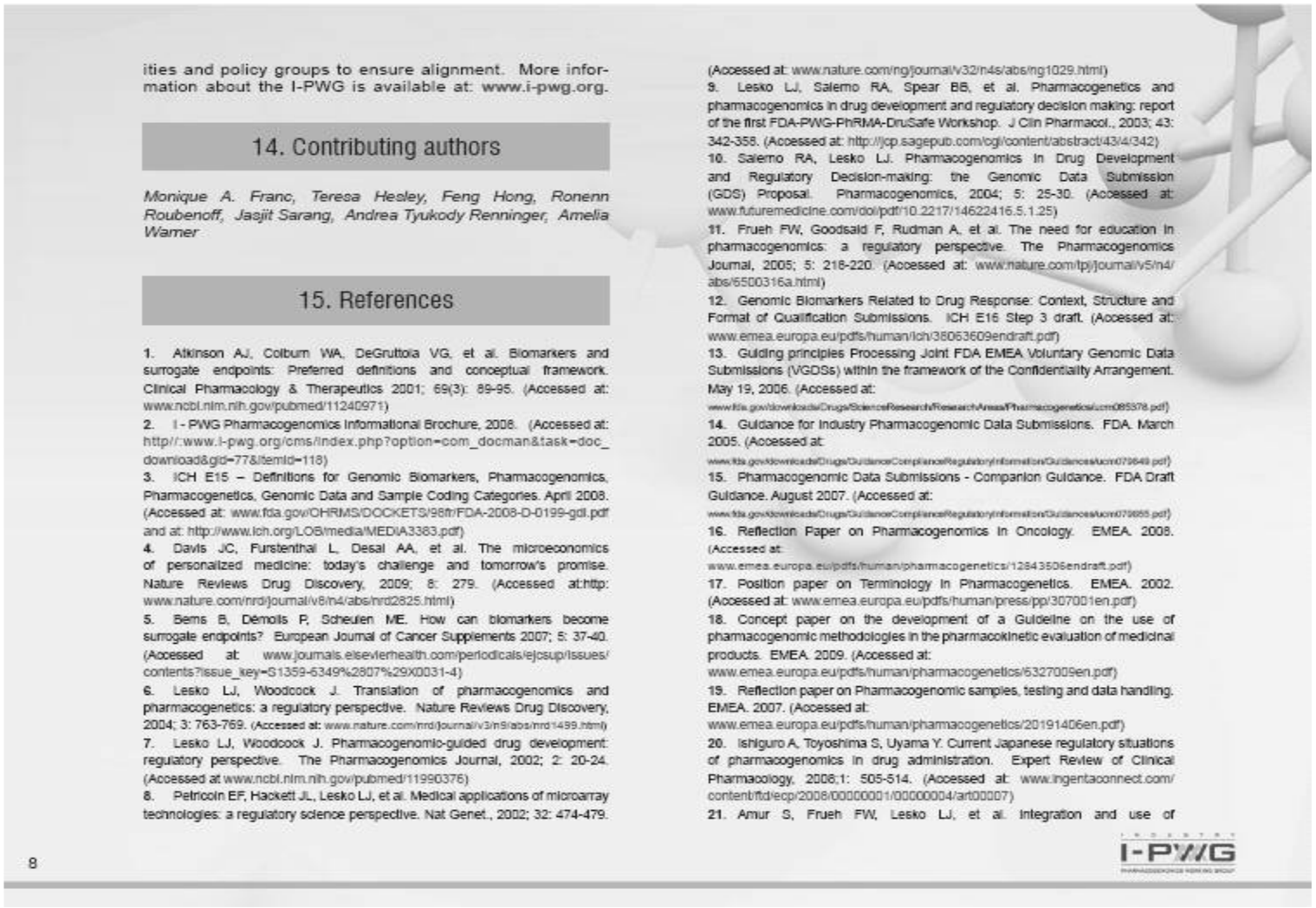

ities and policy groups to ensure alignment. More information about the I-PWG is available at: www.i-pwg.org.

14. Contributing authors

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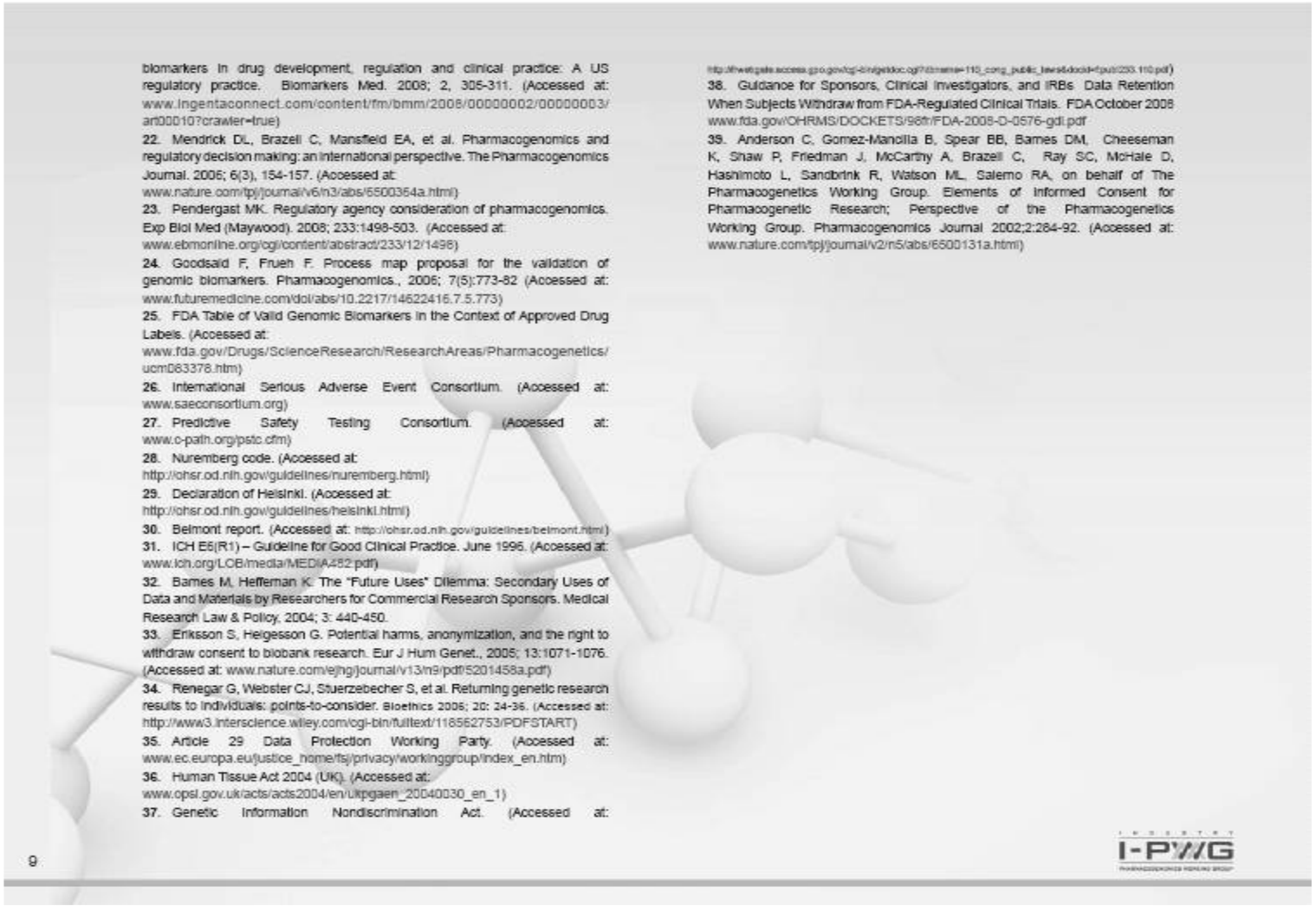


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12.4 Approximate Blood/Tissue Volumes Drawn/Collected by Trial Visit and by Sample Types

12.4.1 Screening through Week 48 (Base Study)

Week (Visit)	Screen (V1)	Randomization Day 1 (V2)	2 (V3)	4 (V4)	8 (V5)	16 (V6)	24 (V7)	36 (V8)	48 (V9)
Hematology	2	2	2	2	2	2	2	2	2
CD4/CD8 cell count	2	2					2		2
Chemistry	12[a]	7	7	7	7	7	7	7	7
PT/INR and APTT	4.5								
HLA	8.5								
HIV-1/HIV-2 Ab screen	8.5								
Hepatitis testing	8.5								
Plasma viral RNA	10	10	10	10	10	10	10	10	10
Plasma for viral resistance	14								
Blood for Pharmacokinetics – Pop PK [b]		4		4	4		8		8
Blood (DNA) for Future Biomedical Research		8.5							
Plasma for Future Biomedical Research		10							10
TOTAL for visit (mL)	**69**	**43.5**	**19**	**23**	**23**	**19**	**29**	**19**	**39**
Total (tablespoons) [c]	**4.6**	**2.9**	**1.3**	**1.5**	**1.5**	**1.3**	**1.9**	**1.3**	**2.6**

[a] Included Serum β-human chorionic gonadotropin (hCG) test
[b] Sample(s) for population PK will be collected. At Day 1 and Week 4 the sample must be collect predose. At weeks 24 and 48, the samples must be collected predose and within 0.5 to 2 hours postdose; and at Week 8, the samples may be collected irrespective of time of dose.
[c] One Tablespoon = 15 mL.

12.4.2 Week 60 Through Post 14 Day Follow- up (Base Study)

Week	60 (V10)	72 (V11)	84 (V12)	96 (V13)	Viral Failure Confirmation (U)	Early Discontinuation (U)	Post 14-Day Follow-up (99)	Total Volume in Base Study
Hematology	2	2	2	2	2	2	2	**30**
CD4/CD8 cell count		2		2				**12**
Chemistry	7	7	7	7	7	7	7	**110**
PT/INR and APTT								**4.5**
HLA								**8.5**
HIV-1/HIV-2 Ab screen								**8.5**
Hepatitis testing								**8.5**
Plasma viral RNA	10	10	10	10	10	10	10	**150**
Plasma for viral resistance					14	14		**42**
Blood for Pharmacokinetics – Pop PK								**28**
Blood (DNA) for Future Biomedical Research								**8.5**
Plasma for Future Biomedical Research				10				**30**
Total for visit (mL)	**19**	**21**	**19**	**31**	**33**	**33**	**19**	**438.5**
Total (tablespoons) [a]	**1.3**	**1.3**	**1.3**	**2.1**	**2.2**	**2.2**	**1.3**	**~29.2**

[a] One tablespoon = 15 mL

12.4.3 Week 100 Through Post-Study 14-Day Follow-up (Study Extension 1)

Week (Visit)	100 (V14)	116 (V15)	132 (V16)	148 (V17)	164 (V18)	180 (V19)	192 (V20)	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	2	18
CD4/CD8 cell count	2			2			2				6
Chemistry	7	7	7	7	7	7	7	7	7	7	63
Plasma viral RNA	10	10	10	10	10	10	10	10	10	10	90
Plasma for viral resistance								14	14		28
Blood (DNA) for Future Biomedical Research											0
Plasma for Future Biomedical Research											0
TOTAL for visit (mL)	**21**	**19**	**19**	**21**	**19**	**19**	**21**	**33**	**33**	**19**	**203**
Total (tablespoons) [b]	**1.4**	**1.3**	**1.3**	**1.4**	**1.3**	**1.3**	**1.4**	**2.2**	**2.2**	**1.2**	**13.5**

[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 study extension 1, but not both, and because there is no post-study follow-up visit after the base study for subjects who continue into the extension, the total volume for both base study and extension is less than the sum.
[b] One tablespoon = 15 mL.

12.5 Guidelines for Grading Severity of Laboratory Adverse Experiences for Toxicity Management

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 10⁹ – 0.650 x 10⁹/L*	500 – 599/mm3 *0.500 x 10⁹ – 0.599 x 10⁹/L*	350 – 499/mm3 *0.350 x 10⁹ – 0.499 x 10⁹/L*	< 350/mm3 < *0.350 x 10⁹/L*
Comment: Values in children ≤ 13 years are not given for the two parameters above because the absolute counts are variable.				
Absolute neutrophil count (ANC)				
Adult and Pediatric, > 7 days	1,000 – 1,300/mm3 *1.000 x 10⁹ – 1.300 x 10⁹/L*	750 – 999/mm3 *0.750 x 10⁹ – 0.999 x 10⁹/L*	500 – 749/mm3 *0.500 x 10⁹ – 0.749 x 10⁹/L*	< 500/mm3 < *0.500 x 10⁹/L*
Fibrinogen, decreased	100 – 200 mg/dL *1.00 – 2.00 g/L* OR 0.75 – 0.99 x LLN	75 – 99 mg/dL *0.75 – 0.99 g/L* OR 0.50 – 0.74 x LLN	50 – 74 mg/dL *0.50 – 0.74 g/L* OR 0.25 – 0.49 x LLN	< 50 mg/dL < *0.50 g/L* OR < 0.25 x LLN OR Associated with gross bleeding
† Use age and sex appropriate values (e.g., bilirubin).				

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

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

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

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

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
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.

12.6 Plasma Assay—Sample Collection, Handling, Labeling, Storage, and Shipment

See Laboratory Manual.

12.7 List of Abbreviations and Acronyms

3TC	Lamivudine
ABC	Abacavir
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ALT	Serum Alanine Aminotransferase
ANCOVA	Analysis of Covariance
APTT	Activated Partial Thromboplastin Time
ART	Antiretroviral Therapy
ASaT	All Subjects as Treated
AST	Serum Aspartate Aminotransferase
BLoQ	Below the Limit of Quantification
CCR5	Chemokine Receptor Type 5
CI	Confidence Interval; or (as in section 10.3 only) Coordinating Investigator
Cl_{cr}	Creatinine Clearance
CNS	Central Nervous System
CSR	Clinical Study Report
CYP	Cytochrome
DAIDS	Division of Acquired Immunodeficiency Syndrome
DILI	Drug-Induced Liver Injury
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
ECI	Event of clinical interest
EFV	Efavirenz
EOC	Executive Oversight Committee
EQ-5D-5L	EuroQol Five Dimensional Descriptive System, Five Level Version
ERC	Ethical Review Committee
FAS	Full Analysis Set
FBR	Future Biomedical Research
FDA	Food and Drug Administration
FDC	Fixed-dose combination
FDR	Fixed-Dose Regimen
FTC	Emtricitabine
GCP	Good Clinical Practice
HAART	Highly Active Antiretroviral Therapy
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HDL-C	High-Density Lipoprotein Cholesterol
HIV-1	Human Immunodeficiency Virus Type 1

IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
INR	International Normalized Ratio
InSTI	Integrase Strand Inhibitors
IRB	Institutional Review Board
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
N(t)RTI	Nucleotide Reverse Transcriptase Inhibitor
NC=F	Non-Completer = Failure
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
OF	Observed Failure
OTC	Over the counter
PCR	Polymerase Chain Reaction
PDLC	Pre-Defined Limit of Change
PDVF	Protocol-Defined Virologic Failure
PGt	Pharmacogenetic
PI	Protease Inhibitors
PK	Pharmacokinetics
PK/PD	Pharmacokinetic/Pharmacodynamic
PO	Per os
PT	Prothrombin Time
q.d.	Once Daily
RBC	Red blood cell
RNA	Ribonucleic acid
SOC	System Organ Class
(s)SAP	(supplemental) Statistical Analysis Plan
SoA	Schedule of Assessments
TAF	Tenofovir Alafenamide Fumarate
TDF	Tenofovir Disoproxil Fumarate
TLOVR	Time to Loss of Virologic Response
ULN	Upper Limit of Normal
US	United States

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

13.2 Investigator

I agree to conduct this clinical trial in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol). I agree to conduct the trial in accordance with generally accepted standards of Good Clinical Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse events as defined in Section 7.0 – Assessing and Recording Adverse Events. I also agree to handle all clinical supplies provided by the Sponsor and collect and handle all clinical specimens in accordance with the protocol. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol and the referenced Investigator's Brochure is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the trial is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure or access by third parties.

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	