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TITLE:

A Phase III Multicenter, Open-Label, Randomized Study to Evaluate a Switch to MK-1439A in HIV-1-Infected Subjects Virologically Suppressed on a Regimen of a Ritonavir-boosted Protease Inhibitor and Two Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

SUBTITLE: Amendment to Include Switches From Additional Antiretroviral Regimens

IND NUMBER: 124,997
EudraCT NUMBER: 2014-005550-18

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SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
1.0 2.1 2.2 3.3 4.2.3.2 4.2.4 5.1.2 5.2 5.2.1.2 5.8	Trial Summary Trial Design Trial Diagram Exploratory Objectives Rationale for Safety Endpoints Rationale for Study Extensions Subject Inclusion Criteria Trial Treatments Dose Modification/Interruption Subject Withdrawal/ Discontinuation Criteria	Multiple changes in the sections noted to update the trial summary and design (including designation of the first study extension as study extension 1) and to describe the rationale for study extension 2, the criteria for enrollment into study extension 2, procedures for visits in study extension 2, and summary of data for this extension period.	The trial is being extended to (1) provide continued access to MK-1439A for participants who are deriving benefit from MK-1439A 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-1439A.

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
6.0	Trial Flow Chart		
7.1.1.2	Inclusion/Exclusion Criteria		
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8.4	Analysis Endpoints		
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8.11	Compliance (Medication Adherence)		
12.4	Approximate Blood Volumes Drawn		

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
4.1.1.	Pharmaceutical and Therapeutic Background	The term combination antiretroviral therapy (cART) replaced the term Highly Active Antiretroviral Therapy (HAART) in a few sentences.	To make the protocol consistent with current usage.
5.5	Concomitant Medications/Vaccinations (Allowed & Prohibited)	Added oxcarbazepine and rifapentine to the list of prohibited medications/therapy due to MK-1439 interaction.	To make the protocol consistent with the current label.
7.1.2.5	Adverse Events	Deleted evaluation of immune reconstitution inflammatory syndrome (IRIS) causality when evaluating an adverse event (AE).	IRIS is not expected to occur in this study population hence this requirement has been removed.
8.6.1	Statistical Methods for Efficacy Analyses	The visit windows in Table 7 have been changed for Week 24 (end of baseline period for Delayed Switch group), Week 28, Week 48 (end of base study), Week 64, and Week 144 (end of study extension 1).	In order to correctly capture data pertinent to the specific milestones, the relative day windows were changed to be based on when the subject completed a milestone rather than specific study days.
Several sections		Minor changes to correct typographic errors.	

1.0 TRIAL SUMMARY

Abbreviated Title	Switch to MK-1439A from PI-, EVG- or NNRTI-based regimen for HIV-1 infection
Trial Phase	Phase III
Clinical Indication	Treatment of HIV-1 infection (therapy switch in virologically-suppressed subjects).
Trial Type	Interventional
Type of control	Active control without placebo
Route of administration	Oral
Trial Blinding	Unblinded Open-label
Treatment Groups	Immediate Switch Group: Immediate Switch (at Study Day 1) to MK-1439A from a stable antiretroviral baseline regimen of a ritonavir- or cobicistat-boosted protease inhibitor (PI), specifically, atazanavir, darunavir, or lopinavir, or cobicistat-boosted elvitegravir, or a non-nucleoside reverse transcriptase inhibitor (NNRTI), specifically, efavirenz, nevirapine, or rilpivirine, each administered with 2 nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs). Delayed Switch Group: Delayed Switch (at Study Week 24) to MK-1439A from a baseline regimen as described above.
Number of trial subjects	Approximately 660 subjects will be enrolled.
Estimated duration of trial	The Sponsor estimates that the trial will require approximately 7 years from the time the first subject signs the informed consent until the last subject's last study-related phone call or visit.
Duration of Participation	For subjects who participate in the base study but do not continue into study extension 1, these subjects will participate in the trial for approximately 55 weeks, from the time they sign the Informed Consent Form (ICF) through the final contact. For subjects who continue into study extension 1 but who do not continue into study extension 2, these subjects will participate for approximately 151 weeks (approximately 3 years total) from the time the subject signs the ICF in the base study through the final contact. For subjects who continue into study extension 2, these subjects will participate for approximately 247 weeks (approximately 5 years total) from the time they sign the ICF in the base study through the final contact. After a screening phase of up to 30 days, each subject will be receiving assigned treatment for approximately 48 weeks in the base study. For subjects who continue into study extension 1, study treatment will continue for an additional 96 weeks, approximately, through a total of approximately 144 weeks of treatment. For subjects who continue into study extension 2, study treatment with MK-1439A will continue until locally available or for an additional 96 weeks (whichever comes first), through a maximum of approximately 240 weeks of total treatment. After the end of treatment, each subject will be followed for 14 days.
Randomization Ratio	2:1 with ~440 subjects in the Immediate Switch Group to MK-1439A on Study Day 1 and ~220 subjects in the Delayed Switch Group to MK-1439A at Study Week 24.

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

2.0 TRIAL DESIGN

2.1 Trial Design

This is a multicenter, open-label, randomized, active-controlled study to evaluate a switch from a stable antiretroviral regimen of a ritonavir- or cobicistat-boosted protease inhibitor (PI) (specifically, atazanavir, darunavir, or lopinavir), or cobicistat-boosted elvitegravir (an integrase strand transfer inhibitor [InSTI]), or a non-nucleoside reverse transcriptase inhibitor (NNRTI) (specifically, efavirenz, nevirapine, or rilpivirine), each administered with two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) to MK-1439A in virologically-suppressed, human immunodeficiency virus type 1 (HIV-1)-infected subjects. The study consists of a 48-week base study, followed by a 96-week open-label study extension (study extension 1) in which all subjects receive MK-1439A. Subjects who have completed the base study and are considered eligible for entering study extension 1 must provide consent in order to enroll in this study extension. This current amendment (024-07), includes a second study extension (study extension 2). Subjects who have completed study extension 1 and are considered eligible for entering study extension 2 must provide consent in order to enroll in this study extension. Eligible subjects will have the opportunity to continue to receive MK-1439A until MK-1439A becomes locally available or for up to an additional 96 weeks (whichever occurs first) via study extension 2. The study is to be conducted in conformance with Good Clinical Practice.

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

Subjects who have been virologically suppressed for at least 6 months and have HIV-1 RNA below the limit of quantification (BLoQ) by the Abbott RealTime HIV-1 Assay (<40 copies/mL) at screening on a stable antiretroviral regimen consisting of one of the ritonavir- or cobicistat-boosted PIs or one of the NNRTIs specified above, or cobicistat-boosted elvitegravir, each on a backbone of 2 NRTIs, will be eligible for enrollment, provided they have no prior history of virologic failure on any regimen or resistance to the components of MK-1439A. For the purpose of historical documentation of virologic suppression, undetectable HIV-1 RNA is considered a result below the level of quantification using a validated (local) assay with lower limit of quantification of 50 copies/mL or less.

Subjects should be on their first or second antiretroviral regimen prior to enrollment. Subjects who complete the base study, as specified below, will be eligible to enter study extension 1 and if they remain eligible at the end of study extension 1, will be eligible to enroll in study extension 2.

Approximately 660 subjects will be stratified in the base study by their regimen at screening (one of the PIs specified above boosted with ritonavir vs. one of the PIs specified above boosted with cobicistat vs. elvitegravir boosted with cobicistat or one of the NNRTIs specified above); subjects in the ritonavir-boosted PI stratum will be further stratified by use of lipid-lowering therapy at Study Day 1 (yes/no). Subjects will be randomized in a 2:1 ratio to an immediate switch to MK-1439A on Study Day 1 (Immediate Switch Group) or delayed switch to MK-1439A at Study Week 24 (Delayed Switch Group). The Delayed Switch Group will continue their baseline regimen until the time of the switch to MK-1439A at Study Week 24.

At Study Week 48, subjects who meet the following criteria will be eligible to enter study extension 1: (1) completed the Week 48 study visit, (2) considered by the investigator to have derived benefit from study participation, (3) further treatment with MK-1439A is considered clinically appropriate by the investigator, and (4) have provided informed consent to continue into the study extension, thus continuing for approximately 2 years beyond the base study.

Similarly, at Study Week 144, subjects who meet the following criteria will be eligible to enter study extension 2: (1) completed the Week 144 study visit, (2) considered by the investigator to have derived benefit from treatment with MK-1439A, (3) further treatment with MK-1439A is considered clinically appropriate by the investigator, and (4) have provided informed consent, thus continuing until MK-1439A becomes locally available or up to approximately 2 years beyond the first extension (whichever comes first).

The total duration of treatment for a given subject in the base study is 48 weeks; for subjects who continue into study extension 1, the total duration of treatment is 144 weeks. For subjects who continue into study extension 2, the total duration is dependent on when MK-1439A becomes locally available, with a maximum total duration of treatment of 240 weeks. Subjects should discontinue at the next scheduled visit after MK-1439A becomes locally available in the market.

The primary endpoint is the proportion of subjects maintaining HIV-1 RNA <50 copies/mL by the Abbott RealTime HIV-1 Assay at Study Week 48 in the Immediate Switch Group and the proportion of subjects with HIV-1 RNA <50 copies/mL by the Abbott RealTime HIV-1 Assay at Study Week 24 in the Delayed Switch Group. Thus, in the primary efficacy assessment, the Immediate Switch Group will have received MK-1439A for *48 weeks*, and the Delayed Switch Group will have received their baseline regimen for *24 weeks on-study* (though they will have received the same regimen for at least 6 months prior to the study [note that the primary endpoint will be assessed before the Delayed Switch Group switches to MK-1439A]). This endpoint compares the ability of MK-1439A to maintain virologic suppression for 48 weeks in previously suppressed subjects with the ability of the continued PI-based, elvitegravir-based, or NNRTI-based treatment regimen, as specified above, to maintain suppression for at least 24 weeks in previously-suppressed subjects (who will have received their baseline regimen for ≥48 weeks in total at the time of the primary assessment).

Long-term efficacy data will be collected during study extension 1 and summarized descriptively. Efficacy data will not be collected for study extension 2.

The open-label design of the study will reduce complexity and allow observation of the simplicity and acceptability of a complete fixed-dose regimen as an aspect of switching therapy. Because the study, by design, allows a switch from multiple ART regimens, including multiple backbone agents, blinding of all of these agents would be operationally challenging.

Randomized subjects who meet virologic failure criteria during the study (base study or study extension 1) (see Section 4.2.3.1) will return to the site for repeat viral RNA testing between 1 and 4 weeks (≥1 and ≤ 4 weeks) later (at a virologic failure confirmation visit). If virologic failure is confirmed and the viral load meets the criterion for resistance testing (>400 copies/mL) in the base study or study extension 1, viral resistance testing will be performed. For subjects in the base study with confirmed virologic failure, plasma samples collected for resistance testing from the virologic failure visit and from the confirmation visit will be sent for resistance testing. For subjects in study extension 1 with confirmed virologic failure, the plasma sample from the virologic failure confirmation visit will be sent for resistance testing. In addition, plasma samples for resistance testing collected at the discontinuation visit from subjects who discontinue, from either the base study or study extension 1, for reasons other than virologic failure will be sent for testing. (Note that if a sample from the discontinuation visit is not available, a sample from the most recent previous visit [if available] will be sent.)

Pharmacokinetic (PK) samples to be assayed for MK-1439 plasma concentrations will be collected in all subjects in both treatment groups at Study Day 1 (randomization visit) as a pre-drug sample and at Study Week 48. In addition, blood samples for PK will also be collected from subjects in the Immediate Switch Group at Study Weeks 4, 12, and 24.

During study extension 1, subjects will continue to be monitored for safety, including fasting lipids, and maintenance of virologic suppression. Long-term safety data will be collected during study extension 1 and summarized. During study extension 2, serious adverse events (SAEs) and pregnancy for female subjects will be monitored and collected.

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

2.2 Trial Diagram

The trial design is depicted in Figure 1.

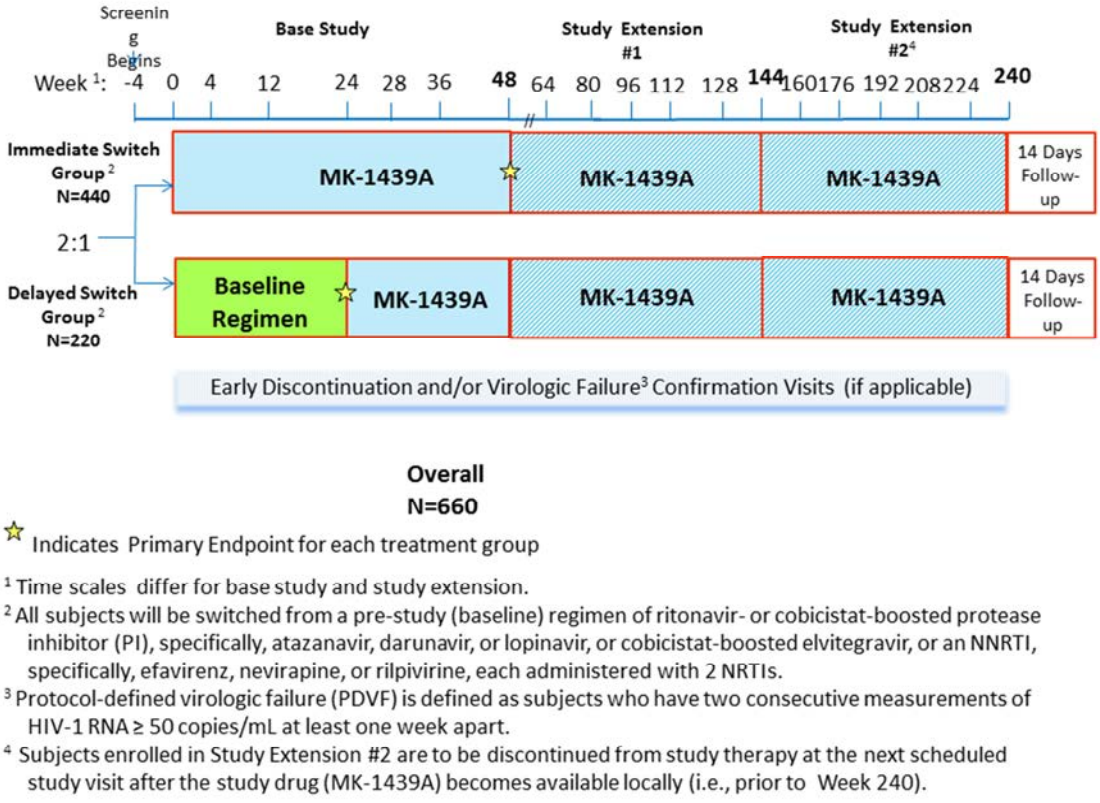

Figure 1 Trial Design

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

In HIV-1 positive subjects who have been virologically suppressed for at least 6 months and have HIV-1 RNA below the limit of quantification (BLoQ) by the Abbott RealTime HIV-1 Assay (<40 copies/mL) at screening on a stable antiretroviral regimen of a ritonavir- or cobicistat-boosted PI (specifically, atazanavir, darunavir, or lopinavir), or cobicistat-boosted elvitegravir, or an NNRTI (specifically, efavirenz, nevirapine, or rilpivirine), each administered with 2 NRTIs:

1) **Objective:** To evaluate the non-inferior antiretroviral activity of an immediate switch to MK-1439A on Study Day 1 compared with continuation of a ritonavir- or cobicistat-boosted PI-based or cobicistat-boosted elvitegravir-based or NNRTI-based regimen for 24 weeks, as measured by the proportion of subjects maintaining HIV-1 RNA <50 copies/mL by the Abbott RealTime HIV-1 Assay at Study Week 48 in the Immediate Switch Group and at Study Week 24 in the Delayed Switch Group.

   Hypothesis: An immediate switch to MK-1439A on Study Day 1 is non-inferior to continuation of a ritonavir- or cobicistat-boosted PI-based or cobicistat-boosted elvitegravir-based or NNRTI-based regimen for 24 weeks, as assessed by the proportion of subjects maintaining HIV-1 RNA <50 copies/mL by the Abbott RealTime HIV-1 Assay at Study Week 48 in the Immediate Switch Group and at Study Week 24 in the Delayed Switch Group. A margin of 8 percentage points is used to define non-inferiority.

3.2 Secondary Objective(s) & Hypothesis(es)

In HIV-1 positive subjects who have been virologically suppressed for at least 6 months and have HIV-1 RNA below the limit of quantification (BLoQ) by the Abbott RealTime HIV-1 Assay (<40 copies/mL) at screening on a stable antiretroviral regimen of a ritonavir-boosted PI administered with 2 NRTIs:

1) **Objective:** To evaluate the effect on fasting LDL-C of an immediate switch to MK-1439A on Study Day 1 compared with continuation of a ritonavir-boosted, PI-based regimen for 24 weeks, as measured by mean change from baseline at Study Week 24 in each treatment group.

   Hypothesis: An immediate switch to MK-1439A on Study Day 1 is superior to the continuation of a ritonavir-boosted, PI-based regimen for 24 weeks, as assessed by the mean change from baseline in fasting LDL-C at Study Week 24 in each treatment group.

2) **Objective:** To evaluate the effect on fasting non-HDL-C of an immediate switch to MK-1439A on Study Day 1 compared with continuation of a ritonavir-boosted, PI-based regimen for 24 weeks, as measured by mean change from baseline at Study Week 24 in each treatment group.

   Hypothesis: An immediate switch to MK-1439A on Study Day 1 is superior to the continuation of a ritonavir-boosted, PI-based regimen for 24 weeks, as assessed by the mean change from baseline in fasting non-HDL-C at Study Week 24 in each treatment group.

In HIV-1 positive subjects who have been virologically suppressed for at least 6 months and have HIV-1 RNA below the limit of quantification (BLoQ) by the Abbott RealTime HIV-1 Assay (<40 copies/mL) at screening on a stable antiretroviral regimen of a ritonavir- or cobicistat-boosted PI (specifically, atazanavir, darunavir, or lopinavir), or cobicistat-boosted elvitegravir, or an NNRTI (specifically, efavirenz, nevirapine, or rilpivirine), each administered with 2 NRTIs:

3) **Objective:** To evaluate the non-inferior antiretroviral activity of an immediate switch to MK-1439A on Study Day 1 compared with continuation of a ritonavir- or cobicistat-boosted PI-based or cobicistat-boosted elvitegravir-based or NNRTI-based regimen for 24 weeks, as measured by the proportion of subjects maintaining HIV-1 RNA <50 copies/mL by the Abbott RealTime HIV-1 Assay at Study Week 24 in each treatment group.

   Hypothesis: An immediate switch to MK-1439A on Study Day 1 is non-inferior to the continuation of a ritonavir- or cobicistat-boosted PI-based or cobicistat-boosted elvitegravir-based or NNRTI-based regimen for 24 weeks, as assessed by the proportion of subjects maintaining HIV-1 RNA <50 copies/mL by the Abbott RealTime HIV-1 Assay at Study Week 24 in each treatment group. A margin of 8 percentage points is used to define non-inferiority.

4) **Objective:** To evaluate the superior antiretroviral activity of an immediate switch to MK-1439A on Study Day 1 compared with continuation of a ritonavir- or cobicistat-boosted PI-based or cobicistat-boosted elvitegravir-based or NNRTI-based regimen for 24 weeks, as measured by the proportion of subjects maintaining HIV-1 RNA <50 copies/mL by the Abbott RealTime HIV-1 Assay at Study Week 48 in the Immediate Switch Group and at Study Week 24 in the Delayed Switch Group.

   Hypothesis: An immediate switch to MK-1439A on Study Day 1 is superior to continuation of a ritonavir- or cobicistat-boosted PI-based or cobicistat-boosted elvitegravir-based or NNRTI-based regimen for 24 weeks, as assessed by the proportion of subjects maintaining HIV-1 RNA <50 copies/mL by the Abbott RealTime HIV-1 Assay at Study Week 48 in the Immediate Switch Group and at Study Week 24 in the Delayed Switch Group.

5) **Objective:** To evaluate the superior antiretroviral activity of an immediate switch to MK-1439A on Study Day 1 compared with continuation of a ritonavir- or cobicistat-boosted PI-based or cobicistat-boosted elvitegravir-based or NNRTI-based regimen for 24 weeks, as measured by the proportion of subjects maintaining HIV-1 RNA <50 copies/mL by the Abbott RealTime HIV-1 Assay at Study Week 24 in each treatment group

   Hypothesis: An immediate switch to MK-1439A on Study Day 1 is superior to the continuation of a ritonavir- or cobicistat-boosted PI-based or cobicistat-boosted elvitegravir-based or NNRTI-based regimen for 24 weeks, as assessed by the proportion of subjects maintaining HIV-1 RNA <50 copies/mL by the Abbott RealTime HIV-1 Assay at Study Week 24 in each treatment group.

6) **Objective:** To evaluate the antiretroviral activity of an immediate switch to MK-1439A on Study Day 1 compared with continuation of a ritonavir- or cobicistat-boosted PI-based or cobicistat-boosted elvitegravir-based or NNRTI-based regimen for 24 weeks, as measured by the proportion of subjects maintaining HIV-1 RNA below the limit of quantification (BLoQ) by the Abbott RealTime HIV-1 Assay (<40 copies/mL) at Study Week 48 in the Immediate Switch Group vs Study Week 24 in the Delayed Switch Group and at Study Week 24 in both treatment groups.

7) **Objective**: To evaluate the immunological effect of an immediate switch to MK-1439A on Study Day 1 compared with continuation of a ritonavir- or cobicistat-boosted PI-based or cobicistat-boosted elvitegravir-based or NNRTI-based regimen for 24 weeks, as measured by the change from baseline in CD4 cell count at Study Week 48 in the Immediate Switch Group and at Study Week 24 in the Delayed Switch Group.

8) **Objective**: To evaluate the immunological effect of an immediate switch to MK-1439A on Study Day 1 compared with continuation of a ritonavir- or cobicistat-boosted PI-based or cobicistat-boosted elvitegravir-based or NNRTI-based regimen for 24 weeks, as measured by the change from baseline in CD4 cell count at Study Week 24 in each treatment group.

9) **Objective**: To evaluate the safety and tolerability of an immediate switch to MK-1439A on Study Day 1 compared with continuation of a ritonavir- or cobicistat-boosted PI-based or cobicistat-boosted elvitegravir-based or NNRTI-based regimen for 24 weeks, as assessed by review of the accumulated safety data by Study Week 24 in each treatment group.

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

11) **Objective:** To evaluate the antiretroviral activity of an immediate switch to MK-1439A on Study Day 1 compared with continuation of a ritonavir- or cobicistat-boosted PI-based or cobicistat-boosted elvitegravir-based or NNRTI-based regimen for 24 weeks, as measured by the proportion of subjects with HIV-1 RNA ≥50 copies/mL at Study Week 48 in the Immediate Switch Group and at Study Week 24 in the Delayed Switch Group based on the FDA snapshot approach.

3.3 Exploratory Objectives

In HIV-1 positive subjects who have been virologically suppressed for at least 6 months and have HIV-1 RNA below the limit of quantification (BLoQ) by the Abbott RealTime HIV-1 Assay (<40 copies/mL) at screening on a stable antiretroviral regimen of a ritonavir- or cobicistat-boosted PI (specifically, atazanavir, darunavir, or lopinavir), or cobicistat-boosted elvitegravir, or an NNRTI (specifically, efavirenz, nevirapine, or rilpivirine), each administered with 2 NRTIs:

1) **Objective**: To describe patient-reported outcomes related to health-related quality of life, self-reported HIV symptoms, work productivity/activity impairment and gastrointestinal symptoms at Study Day 1, Study Weeks 24 and 48 in subjects who switch to MK-1439A at Study Day 1 relative to those who continue a ritonavir- or cobicistat-boosted PI-based or cobicistat-boosted elvitegravir-based or NNRTI-based regimen for 24 weeks.

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

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

4) **Objective**: To assess data on long-term efficacy and safety of MK-1439A administered for up to 144 weeks in subjects enrolled in study extension 1 of the study.

4.0 BACKGROUND & RATIONALE

4.1 Background

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

4.1.1 Pharmaceutical and Therapeutic Background

HIV infection, which causes Acquired Immunodeficiency Syndrome (AIDS) and for many years was associated with substantial morbidity and mortality, has now become a chronic disease that can be controlled through life-long combination antiretroviral therapy (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 five distinct mechanistic classes known as reverse transcriptase inhibitors [nucleos(t)ide reverse transcriptase inhibitors (N(t)RTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs)], protease inhibitors (PIs), fusion inhibitors, entry inhibitors (CCR5 co–receptor antagonists), and integrase strand transfer inhibitors (InSTIs). Successful combinations of antiretroviral medications generally utilize 3 agents from at least 2 different mechanistic classes. The goal of cART is to suppress HIV to undetectable levels so that immune function is preserved or restored. Yet, while cART can delay disease progression and death, as well as reduce the risk of HIV transmission, it does not cure the infection. As a result, lifelong treatment must be maintained, which may lead to therapy fatigue and to noncompliance if the treatment regimen is difficult to adhere to (e.g. pill burden, frequency of treatment) and associated with intolerable side-effects. This can potentially lead to treatment failures with possible development of resistant virus. Additionally, there is currently still significant concern regarding toxicities of some widely-used antiretroviral agents, including neuropsychiatric toxicities associated with efavirenz (EFV, an NNRTI), gastrointestinal toxicities such as diarrhea associated with multiple protease inhibitors (PIs), and serum lipid abnormalities associated with multiple mechanistic classes. Thus, potent treatment regimens that have an excellent safety and tolerability profile and are convenient to take are still highly desirable.

Currently available therapies for HIV infection include PIs, a diverse class of potent agents with a high genetic barrier to resistance, but generally requiring boosting by ritonavir or cobicistat to achieve appropriate drug exposure. As a class, PIs are highly efficacious, and several are recommended as preferred agents for first-line therapy for treatment-naïve HIV-infected subjects; however, they are also associated with a variety of toxicities including gastrointestinal adverse experiences (AEs) (especially diarrhea), serum lipid abnormalities, and lipodystrophy, 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, MK-1439A could be a valuable treatment option for subjects switching from a PI-containing regimen, providing that virologic suppression can be maintained on the new regimen after the switch.

Elvitegravir boosted with cobicistat, in the InSTI mechanistic class, is recommended as a fixed-dose combination with two NRTIs for treatment of ART-naïve patients, as long as their CrCl is ≥70 mL/min [1], and as a single agent, combined with a ritonavir-boosted PI and other antiretroviral drugs, in ART-experienced patients. As with PIs, elvitegravir requires boosting by ritonavir or cobicistat to achieve appropriate drug exposure; the most frequently reported AEs are nausea and diarrhea.

For initiation of combination antiretroviral therapy for HIV infection, currently available NNRTIs constitute an important option for use as anchor agents, along with two NRTIs. Efavirenz and rilpivirine have been among the recommended therapies for treatment initiation according to multiple guidelines [1] [2]; however, each has limitations. For example, while efavirenz has shown excellent efficacy over many years of use, it is associated with substantial neuropsychiatric intolerance and skin rash, as well as lipid abnormalities. In addition it can be a perpetrator of drug-drug interactions as a mixed inducer or inhibitor of CYP3A and CYP2B6 enzymes. Rilpivirine has shown suboptimal efficacy in patients with high viral load or low baseline CD4 cells, and thus is not indicated in patients with baseline viral load above 100,000 copies/mL or CD4 count below 200/µL. 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. Furthermore, supratherapeutic doses of rilpivirine (≥75 mg QD) have been shown to prolong the QTc interval [3]. Importantly, high level resistance may occur in response to a single mutation for all currently available NNRTIs except etravirine which must be dosed twice daily. Therefore, new agents of the NNRTI class that offer high potency, a distinct resistance profile, dosing convenience and a favorable safety and tolerability profile are needed.

MK-1439 is a novel NNRTI being studied for treatment of HIV-1 infection in antiretroviral-naïve HIV-infected subjects. MK-1439 is a potent inhibitor of HIV-1 replication in vitro and is active against both wild type virus and the most common NNRTI resistant variants at concentrations achieved with once daily dosing. MK-1439 displays excellent potency against wild type virus with an IC_{50} of 12 nM in the presence of 100% normal human serum (NHS). Preclinical studies also indicate a favorable in vitro resistance profile that is distinct from other NNRTIs, with IC_{50}'s of 21, 31, and 55 nM against mutants containing the most frequently transmitted NNRTI mutations, K103N, Y181C and G190A, respectively, under the same conditions. The potency against viruses containing the double mutant K103N + Y181C is 33nM. The preclinical toxicity profile of MK-1439 is favorable in rats up to 6 months in duration at 3, 30, and 450 mg/kg/day, and in dogs up to 9 months in duration at 1, 10, and 1000 mg/kg/day. Clinical pharmacology studies indicate that MK-1439 can be dosed once daily, without regard to food, and MK-1439 is not a metabolic inducer or inhibitor, reducing the likelihood of significant drug-drug interactions. Furthermore, the available data from a Phase 2 study in treatment-naive HIV-infected patients demonstrate that MK-1439 in combination with TDF/emtricitabine has favorable safety and tolerability profile and potent efficacy, with ~76% of patients receiving MK-1439 achieving undetectable viral load (see section 4.2.2). These data provide key support for the initiation of the Phase 3 program, which includes evaluations of both MK-1439 as a single agent and MK-1439A as a fixed dose regimen.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Factors that impact HIV treatment success include efficacy, safety and tolerability, barrier to resistance, simplicity/convenience of administration and drug-drug interactions. There is a clear medical need for new regimens that are highly effective, have a high barrier to resistance development, are very well tolerated, and are simple to administer (and thus facilitate increased adherence and prevent treatment fatigue). This need is further driven by the necessity for life-long treatment of HIV infection as many HIV patients become increasingly older with co-morbid diseases/conditions.

Recent advances in HIV therapeutics have included the development of complete fixed-dose regimen pills. HIV-infected patients who are suppressed on complex, multi-pill regimens may benefit from treatment simplification. This strategy is supported in recent iterations of treatment guidelines which recommend regimen simplification to improve a patient's quality of life, increase medication adherence, reduce the likelihood of virologic non-suppression, and improve tolerability [1]. The key principles of regimen switch in this setting are to maintain viral suppression without compromising future options and to consider a patient's prior treatment history and responses to ART, resistance profiles, and drug tolerance when contemplating a regimen switch.

With current antiretroviral therapy (ART) regimens, HIV-infected patients have a high likelihood of achieving and maintaining undetectable HIV RNA levels, however it is estimated that 25% of those patients receiving ART are not virologically suppressed. Drug adverse effects and toxicities, food requirements, high pill burden and/or dosing frequency and drug-drug interactions with concomitant medications are among the reasons cited for virologic failure due to ART regimens. Earlier patient cohorts suggested that suboptimal adherence and drug intolerance/toxicity accounted for 28% to 40% of virologic failure and regimen discontinuations [4]. These are the same reasons patients and prescribers consider switching components of a patient's antiretroviral therapy in the setting of viral suppression, before failure occurs.

With the aging of the HIV-infected population, it is anticipated that switches will become even more common with increased concerns for the risks of long term toxicity, drug-drug interactions and co-morbid conditions (i.e. neuropsychiatric, cardiovascular).

MK-1439 has the potential to be an ideal agent in the switch setting due to its favorable efficacy and safety profile, anticipated lack of food requirements, and favorable drug-drug interaction profile observed to date.

4.2.1.1 Rationale for Expansion of Subject Population (Amendment 06)

Amendment 06 allows individuals to enter the study whose ART regimens at screening include a third agent from either of two mechanistic classes (InSTIs and NNRTIs) in addition to the originally allowed PI class; it also allows individuals with a baseline PI regimen using cobicistat as a boosting agent in addition to the originally allowed ritonavir.

The expansion of the subject population in this amendment better reflects the real-world use of antiretroviral agents and current HIV treatment guidelines. Initial ART regimens are now less likely to be PI-based. For example, the most recent update of the US Department of Health and Human Services (DHHS) guideline for ART in adults and adolescents, released while this study was ongoing, includes multiple InSTI-based regimens, with PI-based regimens moved into the alternative category [1]. A majority of patients whose initial ART regimen was PI-based and who had tolerability issues have already switched to another regimen that is more tolerable. Those patients remaining on PI-based regimens are now less likely to switch. Recently completed and ongoing switch studies of other HIV-1 therapies have also allowed multiple mechanistic classes as a third agent. Note that the primary hypothesis, non-inferiority of MK-1439A to baseline regimens with regard to antiretroviral activity, remains unchanged and applies to the expanded list of baseline regimens. All other hypotheses and objectives also apply to all baseline regimens with the following exception: the two secondary hypotheses that a switch to MK-1439A is superior to maintenance of baseline regimen with respect to fasting LDL-C and fasting non-HDL-C, respectively, apply only to regimens of a ritonavir-boosted PI, as in the original protocol. The rationale for restricting the lipid-related objectives to this subset of subjects is the known adverse effect of ritonavir-boosted PIs, as a class, on lipid profiles, and the expectation that relatively few subjects on a cobicistat-boosted PI regimen will be enrolled compared with the number of already-enrolled subjects on a ritonavir-boosted PI, such that statistical analysis of these subjects would not be feasible.

For individuals whose regimen at screening is based on an NNRTI, the inclusion criterion requiring documentation of pre-treatment HIV genotyping has been removed. This is because individuals who are virologically suppressed on a regimen of an NNRTI plus 2 NRTIs are unlikely to have major drug resistance mutations to the NRTI components, since NNRTI monotherapy is not sufficient to maintain complete suppression. Therefore, for individuals to be suppressed on an NNRTI-based regimen at screening, NRTI efficacy would need to be robust, indicating lack of NRTI resistance, such that absence of baseline genotype information would not increase the risk of failure on MK-1439A due to NRTI resistance.

Documentation of pre-treatment HIV genotype in subjects on a regimen at screening of a ritonavir- or cobicistat-boosted PI or cobicistat-boosted elvitegravir is required since these drugs in combination with NRTIs may mask the presence of NRTI resistance that could potentially affect the activity and efficacy of MK-1439A. Boosted-PI regimens are commonly used as second-line regimens, even in the presence of resistance to emtricitabine or lamivudine, due to the potency of PIs. Cobicistat-boosted elvitegravir is also a potent third agent with the potential to mask the presence of NRTI resistance.

4.2.2 Rationale for Dose Selection/Regimen

The investigational FDR, MK-1439A, contains 100 mg of MK-1439, a potent investigational NNRTI, and standard doses of 2 commercially-available and commonly used NRTIs, lamivudine (300 mg) and TDF (300 mg). A 100 mg dose of MK-1439 was selected for Phase 3 development based on Phase 1b and 2 data and several other factors.

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

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

In Protocol 007 (Part 1) 208 treatment-naïve HIV-1 infected subjects were treated with study drug (MK-1439 or efavirenz). At Week 24, all MK-1439 doses had rates of virologic suppression comparable to efavirenz for the key efficacy endpoints including the proportion of subjects with HIV-1 RNA levels <40 copies/mL (primary) or <200 copies/mL (secondary). All MK-1439 doses showed numerically higher response rates compared to efavirenz (80.0%, 76.2%, 71.4%, 78.0% versus 64.3% of patients with <40 copies/mL for the MK-1439 25 mg, 50 mg, 100 mg, 200 mg versus efavirenz arms, respectively [5, 6]). The treatment differences (MK-1439 minus efavirenz) were not significant, and there was no dose-response for efficacy observed. Overall 76.4% of patients receiving MK-1439 (at any dose) achieved <40 copies/mL compared with 64.3% for efavirenz. In addition, approximately 30% of subjects in the study had baseline HIV RNA above 100,000 copies/mL, and, in this subgroup, MK-1439 at all dosing levels showed virologic responses comparable to efavirenz. It should be acknowledged that this high viral load subgroup was relatively small, with approximately 12 subjects per dosing group. However, the totality of these efficacy data strongly support that the dose range studied (25-200 mg daily) was on the plateau of the dose response curve.

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

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

Patients receiving MK-1439 at 25, 50 or 200 mg in Part 1 of Protocol 007 were switched to 100 mg after dose selection. An additional 132 patients were randomized in Part 2, 66 to receive MK-1439 100 mg and 66 to receive EFV 600 mg. Combining Part 1 and 2, a total of 108 patients received MK-1439 100 mg, and 108 patients received EFV. By week 8, at least one CNS AE was reported in 22.2% of the MK1439 group and 43.5% of the EFV group ($p<0.001$). The most commonly-reported CNS AEs were dizziness (in 9.3% of patients receiving MK-1439 and 27.8% of patients receiving EFV), insomnia (in 6.5% of patients receiving MK-1439 and 2.8% of patients receiving EFV), abnormal dreams (in 5.6% of patients receiving MK-1439 and 16.7% of patients receiving EFV), and nightmares (in 5.6% of patients receiving MK-1439 and 8.3% of patients receiving EFV).

The rationale for selection of the 100 mg daily dose of MK-1439 in treatment-naïve HIV-1 infected subjects is considered to also be applicable to subjects eligible for the current study, since they are required to be virologically suppressed for at least 6 months prior to entry, to have no history of prior virologic failure, and, where applicable depending on the regimen at screening (see inclusion criteria in Section 5.1.2), to have documented pre-treatment HIV resistance testing showing no resistance mutations to any of the components of the MK-1439A regimen. The 100-mg dose is expected to provide sufficient coverage for subjects entering this study whose pre-treatment HIV resistance testing shows those NNRTI mutations that confer < 3-fold increase in IC_{95} to MK-1439; therefore these subjects will be permitted to enroll in this study, as specified in Section 5.1.2, inclusion criterion 7. Standard marketed doses of lamivudine and TDF were selected for inclusion in MK-1439A because these dose levels have demonstrated efficacy and safety in treatment-naive subjects, and no antagonism was observed between MK-1439 and either of these drugs in in vitro studies.

There is no dose modification for MK-1439A permitted in this study.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

The primary efficacy parameter in the study is viral load as measured by HIV-1 RNA, which is consistent with other clinical trials in HIV-infected patients and the current regulatory guidance. Suppressing HIV RNA to low levels preserves the immune system and prevents the development of opportunistic infections and progression of the disease. Clinical trials of antiretroviral agents in multiple classes have demonstrated that suppression of HIV RNA to levels below 50 copies/mL is a clinically meaningful endpoint. Therefore, the primary efficacy hypothesis of this study compares the proportion of subjects maintaining HIV-1 RNA <50 copies/mL at Study Week 48 in the Immediate Switch Group with the proportion of subjects maintaining HIV-1 RNA <50 copies/mL at Study Week 24 in the Delayed Switch Group. Note that the time points for the assessment of the primary efficacy hypothesis are defined as per agreement with regulatory agencies. It is acknowledged that the longer assessment period in the Immediate Switch Group may lead to more non-treatment related dropouts in that group. Therefore, an additional efficacy comparison will be performed based on Study Week 24 assessments for both groups, as this represents the last available time point at which the immediate switch to MK-1439A can be directly compared to those subjects continuing on their previous ART regimen with the same follow-up time for each treatment group.

Secondary and exploratory measurements for efficacy include the proportion of subjects maintaining HIV-1 RNA <40 copies/ mL (BLoQ), the proportion of subjects with HIV-1 RNA ≥50 copies/mL based on the FDA snapshot approach, change from baseline in CD4 cell counts, time to loss of virologic response (TLVOR), and viral resistance for subjects who meet the virologic failure criteria and whose virus can be amplified.

Protocol-defined virologic failure (PDVF) is defined as subjects who have two consecutive measurements of HIV-1 RNA ≥50 copies/mL at least one week apart. Subjects should be discontinued, regardless of compliance to study therapy, if they meet the protocol defined virologic failure criteria.

4.2.3.2 Safety Endpoints

Key safety endpoints include change from baseline in fasting serum lipids, clinical and laboratory adverse experiences and predefined limits of change in laboratory parameters. While lipid data will be evaluated as part of the general safety assessment for all subjects (through predefined limits of change or summary of laboratory values), primary analyses related to change from baseline in fasting lipids will include data only from subjects whose regimen at screening is a ritonavir-boosted PI (see Table 10).

Safety evaluations in the base study will include physical examinations (including vital signs) and laboratory tests (blood) performed at the screening visit, randomization (Study Day 1), Study Weeks 4, 12, 24, 28, 36, 48, a virologic failure confirmation visit (no physical exam or vital signs), an early discontinuation visit (for subjects who discontinue the study early), and,

for subjects who do *not* enter study extension 1, a 14-day follow-up visit. For subjects who continue into study extension 1, safety evaluations will be performed at each of the study visits in the extension (Study Weeks 64, 80, 96, 112, 128 and 144 and, if applicable, an early discontinuation visit and/or a virologic failure confirmation visit) and at a 14-day follow-up visit. Adverse experiences will be evaluated at each visit and graded according to the guidelines provided in Section 7.2. Subjects may be asked to return for unscheduled visits in order to perform additional safety monitoring.

During study extension 2, SAEs and pregnancies will be collected at each study visit (Week 160, 176, 192, 208, 224, and 240 as applicable, depending on when MK-1439A is available locally, and, if applicable, at early discontinuation visit).

4.2.3.3 Pharmacokinetic Endpoints

Pharmacokinetic (PK) samples to be assayed for MK-1439 plasma concentrations will be collected in all subjects in both treatment groups at the Study Day 1 (randomization) visit as a pre-drug sample and at Study Week 48. In addition, blood samples for PK will also be collected from subjects in the Immediate Switch Group at Study Weeks 4, 12, and 24.

At Study Day 1 and Study Week 4 the samples must be collected predose. At Study Weeks 24 and 48, the samples must be collected predose and within 0.5 to 2 hours postdose (subjects should remain fasting until post dose sample is collected); at Study Week 12, 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 Patient Reported Outcome Endpoints

Subjects will complete 4 patient-reported outcome questionnaires at Study Day 1, Study Weeks 4, 24, 28, 48 and/or the discontinuation visit. The questionnaires are designed to capture patient-reported assessments for health domains that may be affected by the use of currently available PIs: 1) general quality of life, 2) symptoms associated with HIV and its treatment, 3) the impact of health conditions on productivity and 4) gastrointestinal-related impact on quality of life. The specific questionnaires to be used are the Irritable Bowel Syndrome-Quality of Life (IBS-QOL) questionnaire, the HIV Symptom Index (HIV-SI or SDM) questionnaire, Work Productivity and Activity Impairment Questionnaire (WPAI) and the EuroQol five dimensional descriptive system, five level version (EQ-5D-5L).

4.2.3.5 Planned Exploratory Biomarker

Understanding genetic determinants of drug response is an important endeavor during medical research. This research will evaluate whether genetic variation within a clinical trial population correlates with response to the treatment(s) under evaluation. If genetic variation is found to predict efficacy or adverse events, the data might inform optimal use of therapies in the patient population. This research contributes to understanding genetic determinants of efficacy and safety associated with the treatments in this study.

4.2.3.6 Future Biomedical Research

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

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

4.2.4 Rationale for Study Extensions

Because HIV infection is chronic, with treatment generally lasting for years, collection of long-term safety and efficacy data in study extension 1 will provide useful information, although these data will not be subject to inferential analyses.

The rationale for study extension 2 is to avoid interruption of treatment by providing continued study drug, until it becomes locally available, for subjects who are eligible and deemed by the investigator to have benefited from treatment with study drug. An additional rationale is that any change from a successfully suppressive and tolerated cART regimen carries with it a well-recognized but small risk of treatment failure on a new regimen.

4.3 Benefit/Risk

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

MK-1439 is a promising new NNRTI for the treatment of HIV-1 infection. It is a potent inhibitor of HIV-1 replication in vitro and is active against both wild type virus and most common NNRTI-resistant variants at concentrations achieved with once daily dosing. In

early studies, MK-1439 has been shown to be efficacious in combination with other ARTs in treatment naïve patients. MK-1439 is not expected to have many of the safety/tolerability concerns associated with boosted PIs or boosted elvitegravir, the neuropsychiatric effects associated with EFV, or the food requirements of rilpivirine. Therefore, MK-1439 could represent a valuable addition to the HIV armamentarium as a treatment which could be used in patients who are virologically suppressed on a regimen containing a ritonavir- or cobicistat-boosted PI, cobicistat-boosted elvitegravir, or a traditional NNRTI, but needing a switch due to tolerability-based considerations.

Additionally, the FDR, MK-1439A, which is used in this protocol, is a simplified regimen that could result in increased adherence, thereby potentially decreasing the risk of virologic failure. Thus, the fixed dose regimen, MK-1439A, may improve quality of life.

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

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male/female subjects 18 years of age or older who are HIV-1 positive and who, at study entry, have had HIV RNA at an undetectable level for at least 6 months on a stable antiretroviral regimen consisting of a ritonavir- or cobicistat-boosted PI (specifically, atazanavir, darunavir, or lopinavir) or cobicistat-boosted elvitegravir or an NNRTI (specifically, efavirenz, nevirapine, or rilpivirine) on a backbone of 2 NRTIs will be enrolled in this trial.

5.1.2 Subject Inclusion Criteria

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

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

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

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

4. have been receiving antiretroviral therapy with a ritonavir- or cobicistat-boosted PI (specifically atazanavir, darunavir or lopinavir) or cobicistat-boosted elvitegravir or an NNRTI (specifically, efavirenz, nevirapine or rilpivirine), each given in combination with 2 NRTIs (and no other ART) continuously with HIV-1 RNA at undetectable levels for ≥6 months prior to the screening visit (as measured at ≥2 sequential time points) and have no history of prior virologic failure. See table in inclusion criterion (5).

   Note: The more recent of the 2 sequential time points must be within the 6 months immediately prior to screening.

   Note: For the purpose of historical documentation of virologic suppression, undetectable HIV-1 RNA is considered a result below the level of quantification using a validated (local) assay with lower limit of quantification of 50 copies/mL or less.

5. be receiving his/her first or second antiretroviral regimen

   Note:

   - Subjects receiving an NNRTI-based regimen must be on their first antiretroviral regimen.

   - Subjects receiving a boosted PI-based or boosted elvitegravir-based regimen may be on their first or second antiretroviral regimen. If subjects are on their second regimen, HIV-1 RNA **must** have been below the limit of quantification (BLoQ) at the time of the first change in antiretroviral agents. See table below.

   - A change in NRTI background therapy due to tolerability or toxicity while virologically suppressed prior to enrollment in the trial will not be considered an additional regimen change.

Mechanistic Class	Permitted as first regimen (in combination w/2 NRTIs)	Permitted as second regimen (in combination w/2 NRTIs)[a]
PIs	ATV/r, ATV/c DRV/r, DRV/c LPV/r	ATV/r, ATV/c DRV/r, DRV/c LPV/r
NNRTIs	EFZ NVP RPV	None
InSTIs	EVG/c only	EVG/c only

Abbreviations:
PIs = protease inhibitors: ATV = atazanavir; DRV = darunavir; LPV = lopinavir; /c = boosted with cobicistat; /r = boosted with ritonavir.
NNRTIs = non-nucleoside reverse transcriptase inhibitors: EFZ = efavirenz; NVP = nevirapine; RPV = rilpivirine.
InSTIs = integrase strand transfer inhibitors: EVG = elvitegravir.
[a] If a subject is on a second regimen, he/she must have had HIV-1 RNA at a level below the limit of quantification (BLoQ) before the second regimen was begun.

6. have no history of using any experimental NNRTI for any length of time.

   Note: No history of use is defined as having received no (0 days of) NNRTI therapy for the treatment of HIV infection.

7. have had a genotype prior to starting his/her initial antiretroviral regimen and have no known resistance to any of the study agents (MK-1439, TDF, or lamivudine).

   Note: Subjects on their first NNRTI-based regimen are not required to have documentation of pre-treatment HIV genotyping. If, however, a subject on an NNRTI-based regimen has had documented HIV genotyping at any time before or during treatment, and if any subject on another ART regimen has had additional documented genotyping after beginning initial treatment, the same criteria apply, i.e., the subject must have no known resistance to any of the study agents: MK-1439, TDF, or lamivudine.

   Note: Subjects with selected NNRTI-class mutations that confer resistance to other NNRTIs, but are considered susceptible to MK-1439, are eligible for the study.

   Reverse transcriptase mutations K103N, Y181C, and G190A as well as the K103N+Y181C double-mutant constitute the majority of transmitted NNRTI-resistant variants. Each of these mutations confers less than a 3-fold reduction in sensitivity to MK-1439, and PK/PD modeling indicates that the 100mg q.d. dose of MK-1439 should be able to inhibit these variants in vivo. Therefore, a subject whose virus harbors any of these mutations would be eligible for the study.

8. be on either no lipid-lowering therapy or on a stable dose of lipid-lowering therapy at the time of enrollment

9. have the following laboratory values at screening within 30 days prior to the treatment phase of this study:

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

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

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

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

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

    For Men:

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

    For Women:

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

11. 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).

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

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

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

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

Single method (one of the following is acceptable):

- intrauterine device (IUD)
- vasectomy of a female subject's male partner
- contraceptive rod‡ implanted into the skin (not acceptable for the subjects in the Delayed Switch Group until they switch to MK-1439A at Study Week 24)

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

- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- cervical cap with spermicide (nulliparous women only)
- contraceptive sponge (nulliparous women only)
- male condom or female condom (cannot be used together)↑
- hormonal contraceptive‡: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection (not acceptable for the subjects in the Delayed Switch Group until they switch to MK-1439A at Study Week 24)

*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. In addition, more restrictive contraceptive methods must be used if required by local ethics or regulatory authorities.

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

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

[‡]Contraceptives containing ethinyl estradiol (including contraceptive rods and hormonal contraceptives) cannot be used as a method of birth control for subjects who are taking ritonavir in this study (applicable to subjects in the Delayed Switch Group until they switch to MK-1439A at Study Week 24) due to an interaction between ethinyl estradiol and ritonavir that may reduce the effectiveness of the contraceptives. Therefore, it is recommended that a condom or other non-hormonal method of contraception should be used instead.

In order to be eligible for participation in study extension 1 at the Week 48 visit, the subject must:

13. have completed the Week 48 visit.

14. be considered, in the opinion of the investigator, to have derived benefit from study participation through Week 48.

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-1439A.

16. understand the procedures in the study extension 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 study treatment in study extension 2 at the Week 144 visit the subject must:

17. have completed the Week 144 visit.

18. be considered, in the opinion of the investigator, to have derived benefit from MK-1439A by Week 144 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-1439A.

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

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, emtricitabine, entecavir, lamivudine or tenofovir.

   Note: Subjects may be enrolled if treatment occurred prior to the diagnosis of HIV or in the context of a complete regimen for HIV

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

   a. Resistance to MK-1439 for the purpose of this study is considered to include the following NNRTI mutations (as single mutations or components of double or triple mutations): L100I, K101E, K101P, K103S, V106A, V106I, V106M, V108I, E138A, E138G, E138K, E138Q, E138R, V179L, Y181I, Y181V, Y188C, Y188H, Y188L, G190S, H221Y, L234I, P225H, F227C, F227L, F227V, M230L, M230I.

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

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

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

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

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

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

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

   Note: Subjects with chronic hepatitis B and C may enter the study as long as they fulfill all entry criteria, have stable liver function tests, and have no significant impairment of hepatic synthetic function (significant impairment of hepatic synthetic function is defined as a serum albumin <2.8 mg/dL or an INR >1.7 in the absence of another explanation for the abnormal laboratory value).

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

    or

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

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

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

12. is female and is expecting to donate eggs (at any time during the study) or is male and is expecting to donate sperm (at any time during the study).

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

5.2 Trial Treatment(s)

Following completion of the Study Day 1 procedures and confirmation of eligibility, the site will contact the IVRS/IWRS for assignment of the drug to be administered. For subjects in the Immediate Switch Group, the study drug will be MK-1439A. For subjects assigned to the Delayed Switch Group, study treatment consists of maintaining therapy with the baseline regimen until a switch to MK-1439A at Study Week 24. Trial treatment for the Immediate Switch Group should begin on the day of randomization. Sites should not contact IVRS/IWRS for drug administration until the subject has met all criteria for the study and is ready to receive the first dose of study medication on Study Day 1. The two treatment regimens/groups to be used in this trial are outlined in Table 1.

Table 1 Treatment Regimens During Base Study

Immediate Switch Group	n = ~440	MK-1439A PO q.d.†
Delayed Switch Group	n = ~220	Ritonavir- or cobicistat-boosted PI (specifically, atazanavir, darunavir, or lopinavir) or cobicistat-boosted elvitegravir or an NNRTI (specifically, efavirenz, nevirapine, or rilpivirine) each administered with 2 NRTIs from Study Day 1 to Study Week 24 and MK-1439A PO q.d. † from Study Week 24 to Study Week 48
† MK-1439A is a single-tablet FDR containing MK-1439 100 mg, lamivudine 300 mg and TDF 300 mg.		

Table 2 Treatment Regimen During Study Extensions

Immediate Switch Group	n = ~440	MK-1439A PO q.d.†
Delayed Switch Group	n = ~220	
† MK-1439A is a single-tablet FDR containing MK-1439 100 mg, lamivudine 300 mg and TDF 300 mg.		

For subjects in the Immediate Switch Group, the first dose of study treatment (MK-1439A) should be taken on Study Day 1 (Visit 2). Subsequent dosing will be performed once daily by the subject at approximately the same time each day.

Subjects in the Delayed Switch Group will continue their baseline regimen (provided by the trial site) until the switch to MK-1439A at the Study Week 24 visit. The first dose of MK-1439A study treatment for this Group should be taken on the day of Study Week 24 visit (Visit 5). Subsequent dosing will be performed once daily by the subject at approximately the same time each day.

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

Please refer to the product circulars for all allowed ART therapies for recommendations regarding the administration of these agents.

MK-1439A for the base study and for the extensions (provided that development of MK-1439A is continuing) will be provided centrally by the Sponsor. The PIs, ritonavir, cobicistat, elvitegravir, NNRTIs and NRTIs used during the trial in subjects randomized to the Delayed Switch Group will be provided by the trial site.

All supplies indicated in Table 1 and Table 2 above will be provided centrally by the Sponsor or locally by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements.

For any commercially available product that is provided by the trial site, subsidiary or designee every attempt will be made to source these supplies from a single lot/batch number. The trial site will be responsible for recording the lot number, manufacturer and expiry date of any locally purchased 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 trial treatments in accordance with the protocol and any applicable laws and regulations.

5.2.1 Dose Selection

5.2.1.1 Dose Selection (Preparation)

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background & Rationale. There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each subject.

5.2.1.2 Dose Modification/Interruption

Dose Modification:

No dose modification is allowed during the study or the extensions.

Dose Interruption:

Consideration should be given to interrupting study therapy for toxicity management.

For subjects in the Delayed Switch Group, during the 1st 24 weeks of the study while subjects are continuing on their baseline regimens, if study therapy is interrupted, all ARTs should be interrupted to minimize the 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.

5.2.2 Timing of Dose Administration

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

Please refer to the product circulars for all allowed ART therapies for recommendations regarding the administration of these agents.

If a subject misses a dose of study drug (MK-1439A) and it is less than 12 hours before the next dose, the missed dose should be skipped and the normal dosing schedule resumed. The subject should not double the next dose in order to compensate for what has been missed. If a subject misses a dose and it is greater than 12 hours before the next dose, the missed dose should be taken and the normal dosing schedule resumed.

5.2.3 Trial Blinding/Masking

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

5.3 Randomization or Treatment Allocation

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 2:1 ratio to an immediate switch to MK-1439A on Study Day 1 (Immediate Switch Group) or a delayed switch to MK-1439A at Study Week 24 (Delayed Switch Group). With ~660 subjects enrolled, ~440 and ~220 will be randomized to the Immediate Switch Group and the Delayed Switch Group, respectively.

Subjects will be assigned randomly according to a computer-generated allocation schedule.

5.4 Stratification

Randomization will be stratified according to the following factors:

1. The ART class used in the subject's regimen at screening (a ritonavir-boosted PI vs. cobicistat-boosted PI vs. cobicistat-boosted elvitegravir or an NNRTI)

2. For subjects whose regimen at screening includes a ritonavir-boosted PI: Use of lipid-lowering therapy at Study Day 1 (yes/no)

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

Table 3 Stratification

Stratum	
I	Ritonavir-boosted PI **with** the use of lipid-lowering therapy at Study Day 1
II	Ritonavir-boosted PI **without** the use of lipid-lowering therapy at Study Day 1
III	Cobicistat-boosted PI
IV	Cobicistat-boosted elvitegravir or an NNRTI
Note: Allowed protease inhibitors (PIs) are atazanavir, darunavir, or lopinavir. Note: Allowed non-nucleoside reverse transcriptase inhibitors (NNRTIs) are efavirenz, nevirapine, or rilpivirine.	

5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

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

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

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

Permitted Concomitant Medications/Therapies

The concomitant use of other medications/therapies is allowed unless specifically prohibited in the Prohibited Concomitant Medication/Therapies section below. Before placing a subject on a specific medication/therapy, it is the responsibility of the investigator to check on potential drug-drug interactions between that medication/therapy and all applicable study therapies being administered to a given subject, i.e., the PIs atazanavir, darunavir, or lopinavir, elvitegravir, the NNRTIs efavirenz, nevirapine, or rilpivirine), the boosting agents ritonavir or cobicistat, and the appropriate NRTIs.

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

Prohibited Concomitant Medications/Therapies

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

- Short courses of corticosteroids and inhaled corticosteroids (e.g., in the setting of exacerbation of chronic respiratory ailments or for prophylaxis for these ailments) **are allowed**.
- Intralesional or localized electron beam therapy for cutaneous Kaposi's sarcoma **is permitted**.

- If a subject develops a malignancy (for example lymphoma) after randomization, the subject **may receive** chemotherapy (including cancer immunotherapy) and remain in the study if, in the opinion of the investigator, the benefits outweigh the risks. Depending on the type of chemotherapy, study medication may need to be interrupted until completion of the chemotherapy.

- 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 benefits outweigh the risks. If it is possible, interferon-based therapy should be deferred until the completion of the study.

Antiretroviral therapies other than those used in the study (MK-1439A and the specific baseline regimens used by patients in the Delayed Switch Group) 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 also not permitted during the course of the study.

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

MK-1439 is expected to be eliminated mainly via CYP (cytochrome)3A-mediated oxidation.

The medications and/or substances below are prohibited in this study because they are moderate or potent inducers of CYP3A, and their coadministration with MK-1439A could possibly result in reduced drug levels of MK-1439 or has the potential for additional drug-drug interactions. Since this list is not comprehensive, the investigator should use his/her medical judgment when a subject presents with a medication not on the list or call the Sponsor Clinical Director or Designee for clarification.

Prohibited Medication/ Therapy Due to MK1439 Interaction
Carbamazepine
Oxcarbazepine
Rifapentine
Phenobarbital
Phenytoin
Rifabutin
Rifampin
Herbal remedies
St. John's Wort
Modafinil
Bosentan
Nafcillin

Prohibited Concomitant Therapy Due to Potential Interactions with PIs, Ritonavir, Cobicistat, Elvitegravir or NNRTIs

The following medications are prohibited for subjects in the Delayed Switch Group, while receiving baseline medication, because competition for CYP3A4 by a PI (including ritonavir used as a boosting agent), cobicistat, elvitegravir or an NNRTI could result in inhibition of metabolism of these drugs and create the potential for serious and/or life-threatening adverse events. For complete information, refer to the most recent package circulars for all allowed ART therapies (as appropriate).

Prohibited Medication/ Therapy Due to PI Interaction
Alfuzosin
Amiodarone
Astemizole
Bepridil
Cisapride
Dronedarone
Ergot alkaloids (eg, ergotamine, ergonovine)
Irinotecan
Lidocaine, systemic
Lovastatin
Midazolam administered orallyPimozide
Quetiapine
Quinidine
Ranolazine
Rifampin/Rifampicin
Sertindole
Sildenafil (for treatment of pulmonary arterial hypertension)
Simvastatin
St. John's Wort
Terfenadine
Ticagrelor
Triazolam

Prohibited Medication/ Therapy Due to Ritonavir or Cobicistat Interaction	
Prohibited Due to Ritonavir Interaction (see combined list below)	**Prohibited Due to Cobicistat Interaction** (see combined list below)
Astemizole	Carbamazepine
Avanafil	Dronedarone
Bepridil	Irinotecan
Clorazepate	Phenobarbital
Clozapine	Phenytoin
Diazepam	Rifampin/Rifampicin
Eletriptan	
Encainide	
Estazolam	
Flecainide	
Flurazepam	
Fusidic acid	
Pethidine	
Piroxicam	
Propafenone	
Propoxyphene	
Quetiapine	
Rifabutin	
Terfenadine	
Vardenafil	
Voriconazole	

Prohibited Due to Ritonavir and Cobicistat Interaction
Alfuzosin
Amiodarone
Cisapride
Ergot alkaloids (eg, ergotamine, ergonovine)
Lovastatin
Midazolam administered orally
Pimozide
Quinidine
Rivaroxaban
Simvastatin
St. John's Wort
Sildenafil (for treatment of pulmonary arterial hypertension)
Triazolam administered orally

Prohibited Medication/ Therapy Due to Elvitegravir Interaction
Carbamazepine
Phenobarbital
Phenytoin
Rifampin/Rifampicin
St. John's Wort

Prohibited Medication/ Therapy Due to NNRTI Interaction
Astemizole
Bepridil
Boceprevir
Carbamazepine
Cisapride
Dexamethasone (if >1 dose)
Ergot derivatives (eg, ergotamine, ergonovine)
Itraconazole
Ketoconazole
Midazolam
Oxcarbazepine
Phenobarbital
Phenytoin
Pimozide
Proton pump inhibitors (eg, omeprazole, pantoprazole)
Rifampin/Rifampicin
Rifapentine
St. John's Wort
Telaprivir
Triazolam
Voriconazole

It is the responsibility of the investigator to review the current product circulars for the NRTIs used in his/her patients to ensure that contraindicated and prohibited medications are not concomitantly administered.

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

Concomitant Therapy to be used With Caution

For complete information, please refer to the product circulars for all allowed ART therapies (i.e., the PIs atazanavir, darunavir, or lopinavir, elvitegravir, the NNRTIs efavirenz, nevirapine, or rilpivirine, the boosting agents ritonavir or cobicistat, and the relevant NRTIs) for drugs that are permitted in the protocol but that should be used with caution because they have established drug interactions with any of these agents.

Lipid Lowering Therapy

For subjects requiring initiation or modification to lipid-lowering therapy due to toxicity, a fasting blood sample should be drawn prior to initiation or modification. This could be done via an unscheduled visit.

5.6 Rescue Medications & Supportive Care

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

5.7 Diet/Activity/Other Considerations

Diet:

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

Please refer to the product circulars for all allowed ART therapies for recommendations regarding the diet requirements for administration of these agents.

Alcohol/Substance Abuse

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

5.8 Subject Withdrawal/Discontinuation Criteria

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

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

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

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

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

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

- The subject has a confirmed positive serum/urine pregnancy test.

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

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

  Male:

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

  Female:

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

- Subject has serum phosphorous < 0.32 mmol/L.

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

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

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

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

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.

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:

There are no pre-specified criteria for terminating the trial early.

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

6.0 TRIAL FLOW CHART

Flow chart A applies to the base study from screening through follow-up after the Week 48 visit, flow chart B applies to those subjects continuing into study extension 1 from Week 48 through follow-up after the Week 144 visit, and flowchart C applies to those subjects continuing into study extension 2 from Week 160 through follow-up after the last extension 2 treatment visit.

Flow Chart A: Screening Through Week 48 Plus 14 Days Follow-up (Base Study)

Visit Number/Title:	1	2 Randomization	3	4	5	6	7	8	U (Virologic Failure Confirmation)	U (Early Discontinuation)	99
Trial Period:	Screening	Treatment[p]									Post-treatment[q]
TRIAL PROCEDURES	Screen	Fasting Day 1 [a]	WK 4	WK 12	Fasting WK 24	WK 28	WK 36	Fasting WK 48	≥ 1 to ≤4 weeks after initial virologic failure	At time of Discontinuation	14 Day Follow-up
Administrative Procedures											
Informed Consent	x							x [r]			
Informed Consent for Future Biomedical Research [b]	x										
Inclusion/Exclusion Criteria	x	x									
Medical History [c]	x										
Provide Subject Identification Card	x										
Concomitant Medication Review	x	x	x	x	x	x	x	x		x	x
Treatment Allocation/Randomization		x									
Register Study Visit via Interactive Voice/Web Response System (IVRS/IWRS)	x	x	x	x	x	x	x	x		x	
Dispense Study Therapy[d]		x [e]	x [e]	x [e]	x	x	x	x [r]			
Provide/Review Study Medication Diary		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
Height	x										
Vital Signs (including pulse rate, blood	x	x	x	x	x	x	x	x		x	x

Visit Number/Title:	1	2 Randomization	3	4	5	6	7	8	U (Virologic Failure Confirmation)	U (Early Discontinuation)	99
Trial Period:	**Screening**	**Treatment[p]**									**Post-treatment[q]**
TRIAL PROCEDURES	**Screen**	**Fasting Day 1 [a]**	**WK 4**	**WK 12**	**Fasting WK 24**	**WK 28**	**WK 36**	**Fasting WK 48**	**≥ 1 to ≤4 weeks after initial virologic failure**	**At time of Discontinuation**	**14 Day Follow-up**
pressure, respiratory rate, and body temperature) and weight											
Adverse Events Monitoring		x	x	x	x	x	x	x		x	x
Birth Control Confirmation	x	x	x	x	x	x	x	x		x	x
12-Lead Electrocardiogram (ECG) (local)		x [f o]									
Patient Reported Outcomes [g]		x	x		x	x		x		x	
Assess Subject Eligibility for Extension 1 [r]								x			
Laboratory Procedures/Assessments											
Collect Blood for Safety Laboratory Tests (Hematology/Chemistry) [h]	x	x [i]	x	x	x [i]	x	x	x [i]	x	x	x
Serum Pregnancy Test [j]	x										
Urine Pregnancy Test (if applicable) [j]		x [f]	x	x	x	x	x	x		x	x
Hemostatic Function Test [k]	x										
HIV/Hepatitis Screen [l]	x										
Virology Test Plasma HIV viral RNA quantification test (Abbott Real Time HIV-1)	x	x	x	x	x	x	x	x	x	x	x
Collect Blood for CD4 Cell Count		x		x	x		x	x			
Viral Resistance Test (Plasma)		x	x	x	x	x	x	x	x	x [m]	
Collect Blood for MK1439 PK [n]		x	x	x	x			x			
Collect Blood for Genetics[b]		x									
Collect Plasma for Future Biomedical Research [b]		x			x			x			

a. Prior to the first dose on Day 1.
b. This sample should be drawn for planned genetic analysis of DNA and drug response unless there is either a documented law or regulation prohibiting collection, or unless the IRB/IEC does not approve of the collection of the sample for these purposes. If the sample is collected, any leftover extracted DNA will be stored for future biomedical research if the subject signs the FBR consent. Plasma samples for FBR should be collected at Study Day 1, and Study Weeks 24 and 48.
c. Includes smoking history, pretreatment HIV RNA, and, for subjects whose regimen at screening includes a boosted PI or cobicistat-boosted elvitegravir, historical genotype.
d. IVRS/IWRS will be used to allocate drug and to manage distribution of MK-1439A.

Visit Number/Title:	1	2 Randomization	3	4	5	6	7	8	U (Virologic Failure Confirmation)	U (Early Discontinuation)	99
Trial Period:	Screening	Treatment[p]									Post-treatment[q]
TRIAL PROCEDURES	Screen	Fasting Day 1 [a]	WK 4	WK 12	Fasting WK 24	WK 28	WK 36	Fasting WK 48	≥ 1 to ≤4 weeks after initial virologic failure	At time of Discontinuation	14 Day Follow-up

e. For the subjects in the Delayed Switch Group IVRS/IWRS will be called to register the subject's visit; no MK-1439A will be dispensed at these visits since they will continue on their ongoing baseline regimen.
f. Results of test must be available prior to randomization and prior to the subject's first dose of medication.
g. Patient Reported Outcomes will be done on Study Day 1, Study Weeks 4, 24, 28, 48 and at discontinuation (if applicable) for all subjects (Immediate and Delayed Switch Treatment Groups). There are a total of four questionnaires in the study (IBS-QOL, HIV-SI, WPAI and EuroQol EQ-5D-5L). Only at sites in the United States (US), subjects, whose native language is either English or Spanish, will be eligible to complete all four questionnaires. At all other sites outside the US, subjects will be eligible to complete the questionnaires only if language translations are available in the subject's native language for all four questionnaires. The questionnaires will be administered in the following sequential order: IBS-QOL, HIV-SI, WPAI and EuroQol EQ-5D-5L.
h. Refer to Table 4 for listing of specific blood safety tests.
i. Fasting for at least 8 hours. Fasting is required at these visits for lipids measurement. For subjects requiring initiation or modification to lipid lowering therapy due to toxicity, a fasting blood sample should be also drawn prior to initiation or modification via an unscheduled visit.
j. For women of childbearing potential.
k. Hemostatic Function Test includes: Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT) and International Normalized Ratio (INR).
l. HIV/Hepatitis Screening Tests include: Enzyme Immunoassay HIV Antibody Screen, Serum Hepatitis B Surface Antigen, Serum Hepatitis B Surface Antibody, Serum Hepatitis B e-Antigen and Serum Hepatitis C Antibody. A plasma Hepatitis C virus PCR quantitative test will be performed if the Hepatitis C antibody test is positive.
m. If viral failure or relapse is confirmed (with a confirmatory HIV-1 RNA at least one week later), and the decision is made to discontinue the subject, plasma for resistance need not be collected again at the discontinuation visit. All other early discontinuation tests should be performed at the early discontinuation visit.
n. Blood samples will be collected from all subjects in both treatment groups at Randomization (Study Day 1) and at Study Week 48. In addition, blood samples for PK will also be collected from subjects in the Immediate Switch Group at Study Weeks 4, 12, and 24. At Study Day 1 and Study Week 4, sample must be collected predose. At Study Week 12, the sample may be collected irrespective of time of dose. At Study Weeks 24 and 48, samples must be collected predose, and within 0.5 to 2 hours postdose (subjects should remain fasting until postdose PK sample is collected).
o. A local ECG should be performed prior to the subject's first dose of study medication (within 7 days prior to the Study Day 1 visit).
p. Visit window periods are approximately +/- 3 days for the Week 4 to Week 28 visits and approximately +/- 7 days for the Week 36 and Week 48 visits. The timing of each visit is relative to the randomization (Day 1) visit. Every attempt must be made to keep subjects on schedule.
q. The visit window period for the Post study 14 day follow up visit is approximately – 2 to 0 days. This follow-up assessment applies only to subjects who complete (or discontinue from) the base study and do not enter study extension 1.
r. 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, immediately enter study extension 1 and be dispensed MK-1439A.

Flow Chart B: Week 64 Through Week 144 Plus 14 Days Follow-up (Study Extension 1)

Visit Number/Title:	**9** [a]	**10**	**11**	**12**	**13**	**14**	**U (Virologic Failure Confirmation)**	**U (Extension Early Discontinuation)**	**99**
Trial Period:		**Extension: Treatment** [b]							**Post-Treatment** [c]
TRIAL PROCEDURES	**Wk 64**	**Wk 80**	**Fasting Wk 96**	**Wk 112**	**Wk 128**	**Fasting Wk 144**	**≥ 1 to ≤4 weeks after initial virologic failure**	**At time of Discontinuation**	**14 Day Follow-up**
Administrative Procedures									
Informed Consent						x [d]			
Concomitant Medication Review	x	x	x	x	x	x		x	x
Register Study Visit via Interactive Voice/Web Response System (IVRS/IWRS)	x	x	x	x	x	x		x	
Dispense Study Therapy [e]	x	x	x	x	x	x			
Provide/Review Study Medication Diary	x	x	x	x	x	x		x	
Assess Subject Eligibility for Study Extension 2 [d]						x			
Clinical Procedures/Assessments									
Directed Physical Examination	x	x	x	x	x	x		x	x
Vital Signs (including pulse rate, blood pressure, respiratory rate, and body temperature) and weight	x	x	x	x	x	x		x	x
Adverse Events Monitoring	x	x	x	x	x	x		x	x
Birth Control Confirmation	x	x	x	x	x	x		x	x
Laboratory Procedures/Assessments									
Collect Blood for Safety Laboratory Tests (Hematology/Chemistry) [f]	x	x	x [g]	x	x	x [g]	x	x	x
Urine Pregnancy Test (if applicable) [h]	x	x	x	x	x	x		x	x
Virology Test Plasma HIV viral RNA quantification test (Abbott Real Time HIV-1)	x	x	x	x	x	x	x	x	x
Collect Blood for CD4 Cell Count			x			x			
Viral Resistance Test (Plasma)							x	x [i]	

Visit Number/Title:	**9** [a]	**10**	**11**	**12**	**13**	**14**	**U (Virologic Failure Confirmation)**	**U (Extension Early Discontinuation)**	**99**
Trial Period:		**Extension: Treatment** [b]							**Post-Treatment** [c]
TRIAL PROCEDURES	**Wk 64**	**Wk 80**	**Fasting Wk 96**	**Wk 112**	**Wk 128**	**Fasting Wk 144**	**≥ 1 to ≤4 weeks after initial virologic failure**	**At time of Discontinuation**	**14 Day Follow-up**

a. Subjects who enter study extension 1 are considered enrolled in the extension upon providing written informed consent at the Week 48 study visit.
b. The visit windows are approximately +/- 14 days for all visits from Week 64 through Week 144. The timing of each visit is relative to the randomization (Day 1) visit. Every attempt must be made to keep subjects on schedule.
c. The visit window for the post-study 14-day follow-up visit is approximately – 2 to 0 days.
d. If the subject is eligible and elects to enter study extension 2, he/she will be considered to have completed study extension 1 and will, after providing informed consent, immediately enter study extension 2 and be dispensed MK-1439A.
e. IVRS/IWRS will be used to allocate drug and to manage distribution of MK-1439A.
f. Refer to Table 4 for listing of specific blood safety tests.
g. Fasting for at least 8 hours. Fasting is required at these visits for lipids measurement. For subjects requiring initiation or modification to lipid-lowering therapy due to toxicity, a fasting blood sample should be also drawn prior to initiation or modification via an unscheduled visit.
h. For women of childbearing potential.
i. If viral failure or relapse is confirmed (with a confirmatory HIV-1 RNA at least one week later), and the decision is made to discontinue the subject, plasma for resistance need not be collected again at the discontinuation visit. All other early discontinuation tests should be performed at the early discontinuation visit.

Flow Chart C: Week 160 Through Week 240 [a] Plus 14 Days Follow-up (Study Extension 2)

Visit Number/Title:	**15** [b]	**16**	**17**	**18**	**19**	**20**	**U (Extension Early Discontinuation)**	**99**
Trial Period:	**Extension: Treatment** [c]							**Post-Treatment** [d]
TRIAL PROCEDURES	**Wk 160**	**Wk 176**	**Wk 192**	**Wk 208**	**Wk 224**	**Wk 240**	**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. The total duration is dependent on when MK-1439A becomes locally available, with a maximum total duration of treatment of 240 weeks. Subjects should discontinue at the next scheduled visit after MK-1439A becomes locally available in the market.
b. Subjects who enter study extension 2 are considered enrolled in the extension upon providing written informed consent at the Week 160 study visit.
c. The visit windows are approximately +/- 14 days for all visits from Week 160 through Week 240. The timing of each visit is relative to the randomization (Day 1) visit. Every attempt must be made to keep subjects on schedule
d. The visit window for the post-study 14-day follow-up visit is approximately – 2 to 0 days.
e. IVRS/IWRS will be used to allocate drug and to manage distribution of MK-1439A.
f. For women of childbearing potential.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

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

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

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

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

7.1.1.1.1 General Informed Consent

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

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

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

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

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

7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial. A review of these criteria should occur at the Screening visit and on the Day 1 visit (prior to randomization). For subjects who wish to continue into study extension 1, the additional inclusion criteria (13 to 16, Section 5.1.2) are to be reviewed at the Week 48 study visit. For subjects who wish to continue into study extension 2, the additional inclusion criteria (17 to 20, Section 5.1.2) are to be reviewed at the Week 144 study visit.

7.1.1.3 Subject Identification Card

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

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

7.1.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee at the Screening visit. The medical history should include information pertaining to the diagnosis of HIV infection and Acquired Immunodeficiency Syndrome (if applicable) and the year diagnosed. If the subject has been previously diagnosed with any Acquired Immunodeficiency Syndrome (AIDS) defining conditions, or CD4 <200, the condition as well as a corresponding medical history of Acquired Immunodeficiency Syndrome must be reported. Additionally, the subject's pre-treatment HIV viral load (RNA) and historical genotypes (for those subjects whose ART regimen at screening is a boosted PI or cobicistat-boosted elvitegravir) should be documented, and the subject's history of smoking should be obtained and recorded on the appropriate eCRF.

7.1.1.5 Prior and Concomitant Medications Review

7.1.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, record all prior medication taken by the subject within 30 days before starting the trial and all prior antiretroviral agents taken for treatment of HIV infection.

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

7.1.1.5.2 Concomitant Medications

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

Lipid Lowering Therapy

For subjects requiring initiation or modification to lipid-lowering therapy due to toxicity or improvement, a fasting blood sample should be drawn prior to initiation or modification. This could be done via an unscheduled visit.

7.1.1.6 Assignment of Screening Number

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

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

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

7.1.1.7 Assignment of Randomization Number

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

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

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

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

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

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

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.

7.1.1.9 Patient-Reported Outcomes

Subjects will complete the following 4 questionnaires at Study Day 1, Study Weeks 4, 24, 28, 48 or the Early Discontinuation visit if patient discontinues prior to Study Week 48:

1) Irritable Bowel Syndrome - Quality Of Life (IBS-QoL)

The IBS-QoL is a self-administered questionnaire, initially developed and validated for use in patients with IBS, that has been used in HIV-infected patients where it has been shown to offer specificity for identifying GI-related QoL measures. The IBS-QoL questionnaire consists of 34 items, used to derive an overall score, plus eight sub-scale scores relating to categories of dysphoria, interference with activity, body image, health worry, food avoidance, social reaction, sexual issues, and relationships. The IBS-QOL has been previously been used to measure the impact of gastrointestinal (GI) complications of treatment on patient QoL as related to the effects of boosted protease inhibitor (PI)-based antiretroviral regimens.

2) HIV Symptom Index (HIV-SI or SDM)

The HIV-SI is a validated, self-administered, 20-item health-state questionnaire for use in clinical care and research among patients with HIV infection in order to identify and address common and bothersome symptoms associated with HIV and its treatment. The index was developed based upon prior reports of symptom frequency and bother and expert opinion and has a four-week recall period.

3) Work Productivity and Activity Impairment Questionnaire (WPAI)

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

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

The EuroQol EQ-5D-5L is a validated, standardized 5-item health-state questionnaire applicable to a wide range of health conditions and treatments and used to assess health outcomes [7, 8]. The five health state dimensions include: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems.

Administration

Subjects are to complete the questionnaires on their own at the site using an electronic data capture tool at the beginning of the appropriate study visit (see study flow chart). Every attempt should be made for the subjects to complete the questionnaire prior to receiving study treatment, discussing any medical conditions with the study personnel, or receiving any medical results. Only at sites in the United States (US), subjects, whose native language is either English or Spanish, will be eligible to complete all four questionnaires: IBS-QOL, HIV-SI, WPAI and EQ-5D-5L. At sites outside the US, subjects will be eligible to complete the questionnaires only if language translations are available in the subject's native language for all four of these questionnaires. The questionnaires will be administered in the following sequential order: IBS-QoL, HIV-SI, WPAI, EQ-5D-5L.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Physical Examination

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

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

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

7.1.2.2 Height Assessment

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

7.1.2.3 Vital Signs and Weight

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

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

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

7.1.2.4 12-Lead ECG (performed locally)

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

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

7.1.2.5 Adverse Events

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

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

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

7.1.2.6 Toxicity Management

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

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

If the adverse experience is considered serious and may have been caused by study medication (as defined in Section 7.2.4) or if re-exposure to the test drug poses additional potential significant risk to the subject, then the re-challenge must be approved in advance by the Merck Clinical Director or Designee and, if required, by the Independent Ethics Committee/Institutional Review Board and a re-challenge consent is needed prior to re-initiation of study therapy. If advance approval of re-challenge is not required by local regulations, the Independent Ethics Committee/Institutional Review Board will receive notification for information only. If, after re-initiation of study therapy, there is a recurrence of the laboratory abnormality or clinical adverse event, consideration should be given to permanently discontinuing all study therapy. In general, when a clinical or laboratory adverse event occurs which requires interruption of study therapy, all study drugs should be interrupted to avoid having a subject receive suboptimal therapy which may predispose them to the development of resistance. In general, all study medications should be restarted concomitantly at full dose. **Whenever study drugs are interrupted, the Merck Clinical Director or Designee should be notified.**

7.1.2.7 Birth Control Confirmation

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

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

7.1.3 Laboratory Procedures/Assessments

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

7.1.3.1 Serum /Urine Pregnancy Test

For women of childbearing potential, serum pregnancy is to be done at the Screening visit, and urine pregnancy is to be done at the Study Day 1 visit prior to randomization. Urine pregnancy tests must also be subsequently done at each study visit, including the Discontinuation and Follow up Visits, in both the base study and the study extensions. Results must be documented in the subject's chart. A subject 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)[3]
Hemoglobin	Alanine aminotransferase (ALT, SGPT)	Activated partial thromboplastin time (APTT)[3]
Platelet count	Alkaline phosphatase	International Normalized Ratio (INR)[3]
Red Blood Cell Count	Creatine Kinase	Hepatitis B Virus surface antigen [3]
Erythrocyte Mean corpuscular volume	Total Bilirubin	Hepatitis B Virus surface antibody [3]
CD4% and Absolute CD4/ Lymphocytes	Direct Bilirubin	Hepatitis B e-Antigen [3]
CD8% and Absolute CD8/Lymphocytes	Indirect Bilirubin	Hepatitis C Antibody [3]
CD4/CD8 ratio	Amylase	Plasma hepatitis C virus PCR quantitative[4]
White Blood cell Count	Lipase	Enzyme immunoassay HIV antibody (with confirmation WB)[3]
WBC Differential Leukocytes	Glucose, Fasting [1]	HIV viral RNA Quantification
	Glucose, Non-Fasting [2]	Serum β-human chorionic gonadotropin (hCG) test[5]
	Blood Urea Nitrogen	Urine β-human chorionic gonadotropin (hCG) test[6]
	Creatinine[8]	HIV Viral resistance[7]
	Calcium	
	Phosphorus	
	Magnesium	
	Protein	
	Albumin	
	Sodium	
	Potassium	
	Chloride	
	Bicarbonate	
	High-density lipoprotein cholesterol (HDL-C) (Fasting[1])	
	Low-density lipoprotein cholesterol (LDL-C) (Fasting[1])	
	Triglycerides (Fasting[1])	
	Total Cholesterol (Fasting[1])	

1. Perform at Randomization (Study Day 1) and the Study Weeks 24 and 48 visits and, for subjects who continue into study extension 1, at the Week 96 and 144 visits. Subjects should be fasting for at least 8 hours.
2. Perform at the Screening visit and the Study Weeks 4, 12, 28 and 36 visits and, in study extension 1, at the Study Week 64, 80, 112 and 128 visits.
3. Perform at the Screening visit only.
4. If the result of the Hepatitis C Antibody testing is positive, then a plasma hepatitis C virus PCR quantitative test will also be performed.
5. Serum β hCG test at the Screening visit to be performed by central laboratory.
6. Urine β hCG test to be performed at the investigator site at Day 1 and every study visit thereafter.
7. Perform at Day 1, all scheduled study visits (except the Screening and Post-study 14-day follow up visits), the Virologic Failure Confirmation and the Early Discontinuation visit (if not collected at Virologic Failure Confirmation visit).
8. Creatinine clearance will be computed at every visit by the central laboratory and provided to the site in the report that the site receives from the central laboratory.

7.1.3.3 HIV/ Hepatitis Screening

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

7.1.3.4 Virology Test

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

7.1.3.5 Viral Resistance Testing

Blood samples will be collected for HIV viral resistance testing at the Study Day 1 visit, at all scheduled study visits in the base study (except the Screening and Post-Study 14-day follow up visits), and at the Virologic Failure Confirmation visit or the Early Discontinuation Visit (if not already obtained at Virologic Failure Confirmation visit) in both the base study and study extension 1. Baseline (Day 1) samples will be analyzed in cases of virologic failure and/or discontinuation, provided the viral load meets the criterion for resistance testing (>400 copies/mL). Amplifiable virus to screen for resistance would not be expected for subjects whose viral load was BLoQ at entry. All resistance testing in the base study and in study extension 1 will be performed by a central laboratory.

7.1.3.6 CD4 Cell Counts

CD4 cell count (absolute and percentage) will be determined at Study Day 1, and at Study Weeks 12, 24, 36 and 48; for subjects who continue into study extension 1, CD4 cell count will also be determined at the Study Week 96 and 144 visits. Testing will be performed at the central laboratory using a commercially available assay.

7.1.3.7 Pharmacokinetic/Pharmacodynamic Evaluations

MK-1439 population PK samples will be collected from all subjects as outlined in Table 5. The exact time the dose of study medication (MK-1439A) 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 (MK-1439A) prior to the collection of the PK sample will also be recorded on the appropriate eCRF.

Type of meal is defined as the following:

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

Note: For subjects in the Immediate Switch Group at Study Week 24 (Visit 5) and for both treatment groups at Study Week 48 (Visit 8), two PK samples will be collected, one pre-dose and one 0.5-2.0 hours post dose. Subjects should be fasting for the collection of both samples. Subjects will be given their dose of study drug (MK-1439A) in the office following the collection of the pre-dose sample and may stay in the office or return to the office for the collection of the post dose sample.

Table 5 Pharmacokinetic Sampling Timepoints

Visit Number	Study Day/Week	Time Relative to MK1439-A dose
2	Day 1 (for all subjects)	Sample to be collected predose
3	Week 4 (for subjects in the Immediate Switch group only)	Sample to be collected predose
4	Week 12 (for subjects in the Immediate Switch group only)	Sample to be collected pre or postdose
5	Week 24 (for subjects in the Immediate Switch group only)	Sample to be collected predose and within 0.5 to 2 hours postdose (Patient should remain fasting until postdose PK sample is collected).
8	Week 48 (for all subjects)	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.

7.1.3.8 Future Biomedical Research

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

- Leftover DNA for future research
- 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.

7.1.4.1.1 Withdrawal From Future Biomedical Research

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

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject's personal information and their specimens. In this situation, the request for specimen destruction cannot be processed.

7.1.4.2 Blinding/Unblinding

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

7.1.4.3 Calibration of Critical Equipment

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

Critical Equipment for this trial includes:

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

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

7.1.5 Visit Requirements

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

7.1.5.1 Screening

Written informed consent/assent must be obtained from the subject prior to performing any study-specific procedures. Potential subjects will be evaluated to determine if they fulfill the Inclusion/Exclusion entry requirements as set forth in Section 5.1. The investigator will discuss with each potential subject the study, its requirements, and its restrictions. The study screening period is 30 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 Study Day 1.
- Blood will be collected for safety laboratory evaluations, HIV-1 RNA quantification, hemostatic function test and hepatitis screening. 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 (Visit 2 to Visit 20)

Randomization - Study Day 1 (Visit 2)

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

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

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

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

- Subjects randomized to the Delayed Switch Group **will not** receive study medication on Day 1. They will continue their ongoing baseline regimen and will receive study drug at Study Week 24.

- The investigator/study coordinator will give a study medication diary to all subjects in both treatment groups. Subjects will start completion of the diary on Day 1 and continue throughout the treatment period. The subjects in the Delayed Switch group will also complete a study medication diary to include their ongoing baseline regimen. The site must ensure that the subject is properly trained and comfortable with completing the medication diary prior to leaving the clinic.

Drug Administration

Only subjects in the Immediate Switch Group will be dispensed study drug, MK-1439A at this visit.

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

Subjects randomized to the Immediate Switch Group will be instructed to take one tablet from the study medication (MK-1439A) bottle once a day (q.d.) orally, with or without food at approximately the same time each day. Tablets must be kept in the bottle prior to taking study medication since the formulation being used in this study is moisture sensitive.

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

Subjects randomized to the Delayed Switch Group will continue their baseline regimen as usual.

Week 4 (Visit 3) and Week 12 (Visit 4)

- All procedures for Study Week 4 (Visit 3) and Study Week 12 (Visit 4) listed on the Study Flow Chart (Section 6.0) should be performed.

- Blood will be collected for safety laboratory evaluations, HIV-1 RNA quantification, HIV viral resistance and CD4 cell counts (only at Study Week 12 visit) at the time points specified on the Study Flow Chart. These samples will be sent to the appropriate central laboratory(ies) following the procedure(s) set forth in the manual(s).

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

- For subjects in the Immediate Switch Group a blood sample for PK measurement will also be collected.

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

- Site staff will access the IVRS/IWRS for assignment of the drug to be administered and for registration of visits. Subjects randomized to the Immediate Switch Group will receive a 8-week supply of study drug at Study Week 4 (Visit 3); and a 12-week supply at Study Week 12 (Visit 4).

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

Week 24 (Visit 5):

Subjects in the Delayed Switch Group, who have been on the ongoing baseline regimen, will be switched to MK-1439A at this visit.

- All procedures for Study Week 24 (Visit 5) listed on the Study Flow Chart (Section 6.0) should be performed.

- Blood will be collected for safety laboratory evaluations, HIV-1 RNA quantification, HIV viral resistance and CD4 cell counts at the time points specified on the Study Flow Chart. Subjects will be required to fast for at least 8 hours prior to the study visit. These samples will be sent to the appropriate central laboratory(ies) following the procedure(s) set forth in the manual(s).

- A plasma sample for future biomedical research will be also collected from all subjects.

- For subjects in the Immediate Switch Group a blood sample for PK measurement will also be collected.

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

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

- Site staff will access the IVRS/IWRS for assignment of the drug to be administered and for registration of visits.

  Subjects randomized to both treatment groups will receive a 4 week supply of study medication (MK-1439A) at this visit. Subjects in the Delayed Switch Group will be instructed to take one tablet from the study medication bottle once a day (q.d.) orally, with or without food at approximately the same time each day. Tablets must be kept in the bottle prior to taking study medication since the formulation being used in this study is moisture sensitive.

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

- Study coordinator and subject will review the study medication diary information.

Week 28 (Visit 6), Week 36 (Visit 7) and Week 48 (Visit 8)

- All procedures for Study Week 28 (Visit 6), Week 36 (Visit 7) and Week 48 (Visit 8) listed on the Study Flow Chart (Section 6.0) should be performed.
- Blood will be collected for safety laboratory evaluations, HIV-1 RNA quantification and HIV viral resistance at the time points specified on the Study Flow Chart. Sample for CD4 counts will also be collected at Study Weeks 36 and 48 visits. Subjects will be required to fast for at least 8 hours prior to Study Week 48 study visit. These samples will be sent to the appropriate central laboratory(ies) following the procedure(s) set forth in the manual(s).
- For a female subject who is of childbearing potential, a urine pregnancy test will be performed at all study visits. If the urine pregnancy test result is positive, the subject must be discontinued.
- For all subjects (in both treatment groups) blood samples for PK measurements will be collected on Study Week 48 visit (see section 7.1.3.7 for details).
- All bottles of study drug will be returned to the study coordinator at each visit, at which time the drug supplies for the following time period will be dispensed. The number of tablets remaining in the bottle will be counted and recorded in the source documentation. The primary source of adherence data, however, will be the subjects study medication diary.
- Site staff will access the IVRS/IWRS for assignment of the drug to be administered and for registration of visits. Subjects will receive an 8-week supply of study drug at Study Week 28 (Visit 6), a 12-week supply at Study Week 36 (Visit 7) and, for subjects who are considered eligible and elect to enter study extension 1, a 16-week supply at Study Week 48 (Visit 8).
- At each study visit the study coordinator and subject will review the study medication diary information.

Week 64 (Visit 9) Through Week 144 (Visit 14)

- All procedures for Study Week 64 (Visit 9), Week 80 (Visit 10), Week 96 (Visit 11), Week 112 (Visit 12), Week 128 (Visit 13), and Week 144 (Visit 14) listed on the Study Flow Chart (Section 6.0) should be performed.
- Blood will be collected for safety laboratory evaluations and HIV-1 RNA quantification at the time points specified in the Study Flow Chart. Samples for CD4 counts will also be collected at the Study Week 96 and 144 visits. Subjects will be required to fast for at least 8 hours prior to the Study Week 96 and 144 visits. Samples for HIV viral resistance will be collected only at the virologic failure confirmation visit or, for subjects who discontinue due to any other reason, at the discontinuation visit. These samples will be sent to the appropriate central laboratory(ies) following the procedure(s) set forth in the manual(s).

- For a female subject who is of childbearing potential, a urine pregnancy test will be performed at all study visits. If the urine pregnancy test result is positive, the subject must be discontinued.
- All bottles of study drug will be returned to the study coordinator at each visit, at which time the drug supplies for the following time period will be dispensed. The number of tablets remaining in the bottle will be counted and recorded in the source documentation. The primary source of adherence data, however, will be the subject's study medication diary.
- Site staff will access the IVRS/IWRS for registration of visits. Subjects will receive a 16-week supply of study drug at each study visit through Week 128.
- At each study visit the study coordinator and subject will review the study medication diary information.

Week 160 (Visit 15) Through Week 240 (Visit 20)

- All procedures for Study Week 160 (Visit 15), Week 176 (Visit 16), Week 192 (Visit 17), Week 208 (Visit 18), Week 224 (Visit 19), and Week 240 (Visit 20) listed on the Study Flow Chart (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 224.

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

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

Protocol-defined virologic failure (PDVF) is defined as subjects who have two consecutive measurements of HIV-1 RNA ≥ 50 copies/mL at least one week apart.

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

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

Early Discontinuation Visit (Baseline Study, Study Extension 1, and Study Extension 2)

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

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

  - The reason the subject discontinued
  - The date of the last dose of study medications from the trial
  - The date of the last assessment and/or contact
  - All adverse events (including serious adverse events) in the base study and study extension 1
  - Only serious adverse events in study extension 2

- Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events.

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

7.1.5.3 Post-Trial

- Following the completion of study therapy (in the base study or study extensions) or in the event of early discontinuation, subjects will be required to return to the clinic approximately 14 days after the last dose of study drug for the post-study visit as outlined in the Study Flow Chart (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, 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 of study medication higher than two times the recommended daily dose in a calendar day.

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

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

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor either by electronic media or paper. Sponsor Contact information can be found in the Investigator Trial File Binder (or equivalent).

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

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

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. Pregnancies and lactations that occur from the time of treatment allocation/randomization through 14 days following cessation of Sponsor's product must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

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

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

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

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

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

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

Refer to Table 6 for additional details regarding each of the above criteria.

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

For the time period beginning at treatment allocation/randomization through 14 days following cessation of treatment, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

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

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

7.2.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported to the Sponsor.

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

For the time period beginning at treatment allocation/randomization through 14 days following cessation of treatment, any ECI, or follow up to an ECI, whether or not related to the Sponsor’s product, must be reported within 24 hours to the Sponsor, either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Events of clinical interest for this trial include:

1. an overdose of Sponsor's product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.

2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

   *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

7.2.4 Evaluating Adverse Events

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

Table 6 Evaluating Adverse Events

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

Relationship to Sponsor's Product (continued)	**The following components are to be used to assess the relationship between the Sponsor's product and the AE: (continued)**	
	Dechallenge	Was the Sponsor's product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the Sponsor's product in this trial? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time.) NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AND IF REQUIRED, BY THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE. IF ADVANCED APPROVAL OF RECHALLENGE IS NOT REQUIRED BY LOCAL REGULATIONS, THE IRB/IEC WILL RECEIVE NOTIFICATION OF INFORMATION ONLY.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following:	**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).**	
Yes, there is a reasonable possibility of Sponsor's product relationship.	There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.	
No, there is not a reasonable possibility of Sponsor's product relationship	Subject did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a subject with overdose without an associated AE.)	

7.2.5 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, i.e., per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.

7.3 TRIAL GOVERNANCE AND OVERSIGHT

7.3.1 Scientific Advisory Committee

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

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 the database lock, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to the database lock, will be documented in a supplemental Statistical Analysis Plan (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Separate analysis plans (i.e., separate documents from the sSAP) will be developed to detail other planned analyses (analysis of PK data, patient-reported outcomes, and future biomedical research). Post hoc exploratory analyses will be clearly identified in the CSR.

8.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan (SAP) are summarized below; the comprehensive plan is provided in Sections 8.2 through 8.12. Analysis of data from the study extensions does not require changes to the SAP. All data from study extension 1 will be summarized descriptively only and will be described in the sSAP. These data will be summarized separately from data generated from the base study. Serious adverse event data from study extension 2 will be summarized separately.

Study Design Overview	A Phase 3 Multicenter, Open-Label, Randomized Study to Evaluate a Switch to MK-1439A in HIV-1-Infected Subjects who are Virologically Suppressed on a Regimen of a Ritonavir-boosted Protease Inhibitor and 2 Nucleoside Reverse Transcriptase Inhibitors (NRTIs); Amendment to Include Switches From Additional Antiretroviral Regimens
Treatment Assignment	Approximately 660 subjects will be stratified by the ART class used in their regimen at screening (a ritonavir-boosted PI, specifically atazanavir, darunavir, or lopinavir vs. a cobicistat-boosted PI vs. cobicistat-boosted elvitegravir or an NNRTI, specifically, efavirenz, nevirapine, or rilpivirine) and, for subjects whose regimen at screening includes a ritonavir-boosted PI, by use of lipid lowering therapy at Study Day 1. The 4 strata are: ritonavir-boosted PI **with** lipid-lowering therapy at Day 1, ritonavir-boosted PI **without** lipid-lowering therapy at Day 1, cobicistat-boosted PI, and cobicistat-boosted elvitegravir or an NNRTI. Subjects will be randomized in a 2:1 ratio to an immediate switch to MK-1439A on Study Day 1 (Immediate Switch Group) or delayed switch to MK-1439A at Study Week 24 (Delayed Switch Group). The Delayed Switch group will continue their baseline regimen until the time of switch to MK-1439A at Study Week 24. The total duration of treatment for a given subject who does not continue into study extension 1 is 48 weeks, for subjects who continue into study extension 1, 144 weeks, and for subjects who continue into study extension 2, a maximum of 240 weeks.
Analysis Populations	Efficacy: Treatment Full Analysis Set (FAS) Safety: All Subjects as Treated (ASaT)
Primary Endpoint(s)	Proportion of subjects maintaining HIV-1 RNA <50 copies/mL by the Abbott RealTime HIV-1 Assay at Study Week 48 in the Immediate Switch Group and at Study Week 24 in the Delayed Switch Group
Key Secondary Endpoints	• For subjects with a regimen at screening of a ritonavir-boosted PI:Change from baseline in fasting LDL-C at Study Week 24 • Change from baseline in fasting non-HDL-C at Study Week 24 • For all subjects: Proportion of subjects maintaining HIV-1 RNA <50 copies/mL by the Abbott RealTime HIV-1 Assay at Study Week 24 in both treatment groups • Proportion of subjects maintaining HIV-1 RNA BLoQ by the Abbott RealTime HIV-1 Assay (<40 copies/mL) at Study Week 48 in the Immediate Switch Group vs Study Week 24 in the Delayed Switch Group and at Study Week 24 in both treatment groups • Change from baseline in CD4 cell counts at Study Week 48 in the Immediate Switch Group and at Study Week 24 in the Delayed Switch Group • Change from baseline in CD4 cell counts at Study Week 24 in both treatment groups • General safety and tolerability by Study Week 24 • PK of MK-1439 and the PK/PD association • Proportion of subjects with HIV-1 RNA ≥50 copies/mL by the Abbott RealTime HIV-1 Assay at Study Week 48 in the Immediate Switch Group and at Study Week 24 in the Delayed Switch Group

Statistical Methods for Key Efficacy Analyses	The primary hypothesis will be assessed based on the proportion of subjects maintaining HIV-1 RNA <50 copies/mL by the Abbott RealTime HIV-1 Assay at Study Week 48 in the Immediate Switch Group and at Study Week 24 in the Delayed Switch Group. The Non-Completer=Failure approach (NC=F) as defined by the FDA "snapshot" approach will be used as the primary approach for handling missing data. All missing data will be treated as failures regardless of the reason. The difference in proportions 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.. Only 2 strata will be used for this analysis: ritonavir-boosted or cobicistat-boosted PI vs. cobicistat-boosted elvitegravir or NNRTI as a component of the baseline regimen. The use of lipid-lowering therapy is not expected to be associated with virologic response; therefore, stratification by use of lipid lowering therapy will not be included in the analyses of virologic response. For the primary hypothesis, an immediate switch to MK-1439A on Study Day 1 will be concluded non-inferior to continuation of the baseline regimen, if the lower bound of the two-sided 95% CI for the difference in the proportion of subjects maintaining HIV-1 RNA <50 copies/mL by the Abbott RealTime HIV-1 Assay (Immediate Switch Group minus Delayed Switch Group) is greater than -8 percentage points. It can be further concluded that an immediate switch to MK-1439A is superior to continuation of the baseline regimen if the lower bound of the two-sided 95% CI for the difference in response rates (Immediate Switch Group minus Delayed Switch Group) is greater than zero contingent upon satisfying the multiplicity criteria. A similar approach will be used for the supportive secondary efficacy hypotheses for non-inferiority and superiority at Study Week 24 for both treatment groups.
Statistical Methods for Key Safety Analyses	Tier I: Lipids (secondary safety hypothesis): For subjects on a stable antiretroviral regimen of a ritonavir-boosted PI + 2 NRTIs at screening, the change from baseline in fasting lipids (total cholesterol, LDL-C, non-HDL-C, and triglycerides) at Study Week 24 will be analyzed using ANCOVA models adjusted by baseline lipid level, use of lipid-lowering therapy at Study Day 1 and treatment group. The treatment differences (95% confidence intervals) will be provided for all lipid parameters, and p-values for between treatment comparisons will be provided for LDL-C and non-HDL-C. Tier II The treatment differences and the associated 95% confidence intervals will be provided for the percentage of subjects with the following events based on specific AE categories (i.e., Tier-2 events) by Study Week 24: (1) at least one adverse experience; (2) at least one drug related adverse experience; (3) at least one serious adverse experience; (4) at least one serious and drug related adverse experience; (5) discontinued study therapy due to an adverse experience. Other Tier-2 events require a minimum of 1% of subjects in at least one treatment group. These analyses will be performed using the Miettinen and Nurminen method [9], an unconditional, asymptotic method.
Interim Analyses	No interim analyses are planned for this study.

Multiplicity	The following hypotheses will be tested sequentially at the one-sided Type 1 error rate of 2.5% in the following order: 1) Primary efficacy hypothesis testing non-inferiority at Study Week 48 for the Immediate Switch Group vs Study Week 24 for the Delayed Switch Group 2) Secondary safety hypothesis for LDL-C 3) Secondary safety hypothesis for non-HDL-C 4) Secondary efficacy hypothesis testing superiority at Study Week 48 for the Immediate Switch Group vs Study Week 24 for the Delayed Switch Group. Testing will stop with the first of these tests failing to reach statistical significance and all subsequent tests would not be considered for statistical significance. In this way, the overall one-sided Type 1 error rate in testing these hypotheses is strongly controlled at a 2.5% level. Note the secondary efficacy hypotheses testing non-inferiority and superiority at Study Week 24 for both treatment groups are only supportive to the primary and secondary efficacy hypotheses at Study Week 48 for the Immediate Switch Group and Study Week 24 for the Delayed Switch Group and are not considered in the strong control strategy for the Type 1 error for this study. There are no other hypotheses that will be tested and analyses associated with objectives without hypotheses will be considered supportive and/or explanatory.
Sample Size and Power	The planned sample size is 660 subjects to be randomized in a 2:1 ratio to either an immediately switch to MK-1439A (Immediate Switch Group) or a delayed switch to MK-1439A after continuation of a ritonavir- or cobicistat-boosted PI-based or cobicistat-boosted elvitegravir-based or NNRTI-based regimen for 24 weeks (Delayed Switch Group). The primary hypothesis will be assessed based on the proportion of subjects maintaining HIV-1 RNA <50 copies/mL by the Abbott RealTime HIV-1 Assay at Study Week 48 in the Immediate Switch Group and at Study Week 24 in the Delayed Switch Group. A margin of 8 percentage points is used to define the non-inferiority of an immediate switch to MK-1439A relative to continuation of the baseline regimen for 24 weeks. The study will have 80% power to demonstrate that an immediate switch to MK-1439A is non-inferior to continuation of the baseline regimen for 24 weeks, at an overall one-sided 2.5% alpha level, as measured by the proportion of subjects maintaining HIV-1 RNA <50 copies/mL by the Abbott RealTime HIV-1 Assay at Study Week 48 in the Immediate Switch Group and at Study Week 24 in the Delayed Switch Group. The power calculation assumes a true response rate of 85% for both arms using the NC=F approach, as defined by the FDA “snapshot” approach.

8.2 Responsibility for Analyses/In-House Blinding

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

This trial is being conducted as an open-label study, i.e., subjects, investigators, and SPONSOR personnel will be aware of subject treatment assignments after each subject is enrolled and treatment is assigned.

The 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/IWRS).

8.3 Hypotheses/Estimation

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

8.4 Analysis Endpoints

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

8.4.1 Efficacy/Pharmacokinetics Endpoints

8.4.1.1 Efficacy Endpoints

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

Proportions of Subjects Maintaining HIV-1 RNA <50 copies/mL or <40 copies/mL

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

The primary hypothesis will be assessed based upon the proportion of subjects maintaining HIV-1 RNA <50 copies/mL by the Abbott RealTime HIV-1 Assay at Study Week 48 in the Immediate Switch Group and at Study Week 24 in the Delayed Switch Group. In the Immediate Switch Group, subjects will have received MK-1439A for 48 weeks; in the Delayed Switch Group, subjects will have received their baseline regimen for 24 weeks on-study (though they will have received the same regimen for at least 6 months prior to the study [note that the primary endpoint will be assessed before the Delayed Switch Group switches to MK-1439A]). Because there will be different lengths of study follow-up in the 2 treatment groups at the time of the primary efficacy assessment, there is potentially a bias in favor of the Delayed Switch Group as the likelihood to discontinue is greater in the Immediate Switch Group simply due to the longer duration (48 weeks) on study as compared to the Delayed Switch Group (24 weeks).

Proportions of Subjects With HIV-1 RNA ≥50 copies/mL Based on the FDA Snapshot Approach

The proportion of subjects with HIV-1 RNA ≥50 copies/mL based on the FDA snapshot approach (the second category of the virologic outcome; details in Section 8.6.1) at study Week 48 in the Immediate Switch Group and at Study Week 24 in the Delayed Switch Group will be analyzed.

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 Study Week 48 for the Immediate Switch Group and at Study Week 24 for the Delayed Switch Group.

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

Protocol Defined Virologic Failure (PDVF)

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

8.4.2 Safety Endpoints

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

Change From Baseline in Fasting Lipids

The change from baseline in fasting lipids (LDL-C, non-HDL-C, total cholesterol, HDL-C, and triglycerides) will be analyzed with primary interest in LDL-C and non-HDL-C. Primary analyses of these endpoints will be applied only to subjects whose regimen at screening is a ritonavir-boosted PI (see Table 10). The analysis is restricted to this subset of subjects (Strata 1 and 2) because:

1) Ritonavir-boosted PIs, as a class, are known to have adverse effects on lipid profiles.

2) Individuals on regimens other than a ritonavir-boosted PI are eligible to enter the study beginning only with Amendment 06, thus relatively few subjects on a cobicistat-boosted PI regimen are expected to be enrolled compared with the number of already-enrolled subjects on a ritonavir-boosted PI, such that statistical analysis of these subjects would not be feasible.

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.

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 12.7). A listing of the subjects who meet the criteria will be provided.

8.5 Analysis Populations

8.5.1 Efficacy Analysis Populations

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

- receive at least one dose of study treatment (note that for subjects who were randomized to the Delayed Switch Group, study treatment also includes their ongoing baseline regimen during Study Week 0 to Study Week 24),
- 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 populations. Details on the approach to handling missing data are provided in Section 8.6 Statistical Methods.

8.5.2 Safety Analysis Populations

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

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

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

8.6 Statistical Methods

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

Subjects in the Immediate Switch Group will receive MK-1439A throughout the treatment period in the base study. Subjects in the Delayed Switch Group will continue their baseline regimen from Study Day 1 through Study Week 24 and then receive MK-1439A from Study Week 24 through Study Week 48 in the base study. Subjects in both treatment groups who continue into the study extensions will receive MK-1439A throughout the extension periods. Between-treatment comparisons that address key efficacy and safety objectives will be limited to data from the Immediate Switch Group and data collected from the Delayed Switch Group BEFORE the switch in the base study. Efficacy and safety data from Study Week 24 through 48 for the Delayed Switch Group will be summarized separately. In addition, the safety data from Study Week 24 to 48 for the Delayed Switch Group will be combined with the Immediate Switch Group safety data for descriptive summaries.

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

8.6.1 Statistical Methods for Efficacy Analyses

Time Window

Table 7 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 7 Definition of Study Timepoint

Treatment Phase	Treatment Period	Protocol Time	Day-Range Rules	Target Day[1]	CSR Time[2]
Pre-treatment	Baseline	Day 1 (Baseline)	≤1	1	Day 1
Treatment	Treatment	Week 4	≥2 and ≤56	29	Week 4
		Week 12	≥57 and ≤126	85	Week 12
		Week 24	For DSG, ≥127 and ≤last day of baseline regimen treatment period For ISG, ≥127 and ≤reported Week 24 visit date for subject completed Week 24 visit or last day of treatment period for subject discontinued before having Week 24 visit	169	Week 24
		Week 28	For DSG, ≥first day of MK-1439A treatment and ≤224 For ISG, ≥first day after reported Week 24 visit date and ≤224	197	Week 28
		Week 36	≥225 and ≤294	253	Week 36
		Week 48	≥295 and ≤last day of base study treatment period	337	Week 48
Treatment	Extension 1	Week 64	≥first day of Extension 1 treatment period and ≤504	449	Week 64
		Week 80	≥505 and ≤616	561	Week 80
		Week 96	≥617 and ≤728	673	Week 96
		Week 112	≥729 and ≤840	785	Week 112
		Week 128	≥841 and ≤952	897	Week 128
		Week 144	≥953 and ≤last day of Extension 1 treatment period	1009	Week 144

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

Missing Values

There are 3 types of missing values:

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

Two approaches will be used to handle missing values (Table 8). The primary approach for the analysis of the proportion of subjects maintaining HIV-1 RNA <50 copies/mL is the Non-Completer=Failure (NC=F) approach as defined by the FDA "snapshot" approach [13]. Under this approach, only those subjects who 1) are on study-assigned treatment; 2) have HIV-1 RNA measurement(s) within the time window specified in Table 7; 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 maintaining HIV-1 RNA <50 copies/mL at that timepoint.

A second approach, the Observed Failure (OF) approach will be performed as a sensitivity analysis for the proportion of subjects maintaining HIV-1 RNA <50 copies/mL at Study Week 48 in the Immediate Switch Group and at Study Week 24 in the Delayed Switch Group. 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.

Table 8 Summary of the Two Approaches to Handle Missing Values

Approaches[§]	Intermittent Missing	Non-intermittent Missing Not Related to Treatment		Non-intermittent Missing Related to Treatment	
		Success at Study Therapy Discontinuation	Failure at Study Therapy Discontinuation	Study Therapy Discontinuation Due to Clinical/Lab Adverse Experience	Study Therapy Discontinuation Due to Lack of Efficacy
OF	Excluded	Excluded	Failures	Excluded	Failures
NC=F	Failure	Failures	Failures	Failures	Failures
[§] OF (Observed Failure); NC=F (Non-Completer=Failure) is the primary approach.					

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

The proportion of subjects maintaining HIV-1 RNA <50 copies/mL will be summarized by treatment group at each time point, with primary interest at Study Week 48 in the Immediate Switch Group and at Study Week 24 in the Delayed Switch Group. 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 (ART class included in baseline regimen: ritonavir- or cobicistat-boosted PI vs. cobicistat-boosted elvitegravir or NNRTI). Although the study has two stratification factors, ART class use in baseline regimen and use of lipid-lowering therapy at Study Day 1, the use of lipid-lowering therapy is not expected to be associated with virologic response; therefore, stratification by use of lipid-lowering therapy will not be included in the analyses of virologic response.

The NC=F approach as defined by FDA "snapshot" approach will be used as the primary approach to analysis with respect to the proportion of subjects maintaining virologic 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 within the time window with reasons of 1) discontinued study due to an AE, 2) discontinued study for other reasons (includes withdrawal of consent, loss to follow-up, moved, etc.), or 3) on study but missing data in window. The full categorization of virologic outcome at Study Week 24 and Study Week 48 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 and secondary timepoints only (i.e., the proportion of subjects maintaining HIV-1 RNA <50 copies/mL at Study Week 24 and Study Week 48).

For the evaluation of primary and secondary hypotheses, a margin of 8 percentage points is used to define the non-inferiority of an immediate switch to MK-1439A at Day 1 to continuation of the baseline regimen for 24 weeks. An immediate switch to MK-1439A on Day 1 will be concluded non-inferior to continuation of the baseline regimen for 24 weeks, if the lower bound of the two-sided 95% CI for the difference in the proportion of subjects maintaining HIV-1 RNA <50 copies/mL (Immediate Switch Group minus Delayed Switch Group) is greater than -8 percentage points. It can be further concluded that an immediate switch to MK-1439A is superior to continuation of the baseline regimen for 24 weeks if the lower bound of the two-sided 95% CI for the difference in response rates (Immediate Switch Group minus Delayed Switch Group) is greater than zero contingent upon satisfying the multiplicity criteria.

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

Proportions of Subjects With HIV-1 RNA ≥50 copies/mL Based on the FDA Snapshot Approach

The full categorization of virologic outcome at a timepoint by the FDA snapshot approach includes 1) HIV-1 RNA <50 copies/mL, 2) HIV-1 RNA ≥50 copies/mL, and 3) having no virologic data within the time window for reasons of a) discontinued study due to an AE, b) discontinued study for other reasons (includes withdrawal of consent, loss to follow-up, moved, etc.), or c) on study but missing data in window. The proportion of subjects with HIV-1 RNA ≥50 copies/mL based on the FDA snapshot approach (the second category of the virologic outcome) at study Week 48 in the Immediate Switch Group and at Study Week 24 in the Delayed Switch Group will be analyzed. 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 (ART class used in baseline regimen: ritonavir- or cobicistat-boosted PI vs. cobicistat-boosted elvitegravir or NNRTI). A margin of 4 percentage points will be used to assess the non-inferiority of an immediate switch to MK-1439A at Day 1 to continuation of the baseline regimen for 24 weeks with respect to this endpoint as a measure of the strength of evidence for the treatment effect. (Note that the margin used to assess non-inferiority for this endpoint of HIV-1 RNA ≥50 copies/mL is 4 percentage points while the margin used for the endpoint of HIV-1 RNA <50 copies/mL is 8 percentage points.) There will not be a multiplicity adjustment for this endpoint.

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 Study Week 48 in the Immediate Switch Group and at Study Week 24 in the Delayed Switch Group.

The treatment difference in changes from baseline in CD4 cell count at each time point will be estimated between the two treatment groups. However, these estimates will not be subject to an absolute criterion for similarity. The clinical interpretation of the treatment difference is dependent upon the absolute value at baseline, and the magnitude and direction of the CD4 changes seen in each treatment arm.

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

Protocol Defined Virologic Failure (PDVF)

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

Table 9 summarizes the key efficacy analyses.

Table 9 Analysis Strategy for Key Efficacy Variables

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach[†]	Statistical Method	Analysis Population	Missing Data Approach[†]
Primary Hypothesis				
Proportion of subjects maintaining HIV-1 RNA <50 copies/mL at Study Week 48 in the Immediate Switch Group and at Study Week 24 in the Delayed Switch Group	P	Stratum-adjusted Mantel-Haenszel[‡]	FAS	NC=F approach
Proportion of subjects maintaining HIV-1 RNA <50 copies/mL at Study Week 48 in the Immediate Switch Group and at Study Week 24 in the Delayed Switch Group	S	Stratum-adjusted Mantel-Haenszel[‡]	FAS	OF approach
Secondary Objectives				
Proportion of subjects maintaining HIV-1 RNA <50 copies/mL at Study Week 24 in each treatment group	P	Stratum-adjusted Mantel-Haenszel[‡]	FAS	NC=F approach
Change from baseline in CD4 cell counts at Study Week 48 in the Immediate Switch Group and at Study Week 24 in the Delayed Switch Group	P	Two sample t-test	FAS	OF approach assuming baseline-carried-forward
Change from baseline in CD4 cell counts at Study Week 24 in each treatment group	P	Two sample t-test	FAS	OF approach assuming baseline-carried-forward
Proportion of subjects with HIV-1 RNA ≥50 copies/mL at Study Week 48 in the Immediate Switch Group and at Study Week 24 in the Delayed Switch Group	S	Stratum-adjusted Mantel-Haenszel[‡]	FAS	FDA snapshot approach

[†] P=Primary approach; S=Supportive approach; OF = Observed Failure; NC=F = Non-completer=Failure.

[‡] Stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of the sample size per arm for each stratum (ART class used in baseline regimen: ritonavir- or cobicistat-boosted PI vs. cobicistat-boosted elvitegravir or NNRTI).

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

8.6.2 Statistical Methods for Safety Analyses

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

The analysis of safety results will follow a tiered approach (Table 10). 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. 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.

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 1% of subjects in any treatment group exhibit the event; all other adverse experiences and predefined limits of change will belong to Tier 3.

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

For this protocol, the Tier 1 events are the change from baseline in fasting LDL-C and non-HDL-C at Study Week 24. Change from baseline in other fasting lipids (total cholesterol, HDL-C, and triglycerides) will be Tier 2 events. These endpoints are evaluated based only on subjects whose regimen at screening consists of a ritonavir-boosted PI + 2 NRTIs. The change from baseline in fasting lipids will be analyzed using ANCOVA models adjusted by baseline lipids level, use of lipid-lowering therapy at Study Day 1 and treatment group. The treatment differences and 95% confidence intervals will be provided for all lipid parameters, and p-values for the between treatment comparisons will be provided for LDL-C and non-HDL-C. The missing lipid data will be handled by the following principle: for subjects who have missing lipid data, the last lipid observation after randomization will be carried forward. For subjects who modify lipid-lowering therapy use during the study, the last lipid measurement before modifying the lipid-lowering therapy use will be carried forward.

The percentages of subjects who modify lipid-lowering therapy use prior to Study Week 24 will be summarized by treatment group.

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) [9], an unconditional, asymptotic method.

Table 10 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
	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 ≥1% of subjects in one of the treatment groups)		X	X
Tier 3	Specific AEs, SOCs or PDLCs‡ (incidence <1% of subjects in all of the treatment groups)			X
	Change from Baseline Results (Labs, Vital Signs)			X

† Adverse Experience references refer to both Clinical and Laboratory AEs.

* Includes only those subjects whose regimen at screening is a ritonavir-boosted PI + 2 NRTIs.

‡ Includes only those endpoints not pre-specified as Tier 1 or not already pre-specified as Tier-2 endpoints.

Note: SOC=System Organ Class; PDLC=Pre-Defined Limit of Change; X = results will be provided.

8.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

8.6.3.1 Demographic and Baseline Characteristics

The comparability of the treatment groups for each relevant characteristic will be assessed by the use of 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.

8.7 Interim Analyses

No interim analyses are planned for this study.

8.8 Multiplicity

The following hypotheses will be tested sequentially at the one-sided Type 1 error rate of 2.5% in the following order:

1) Primary efficacy hypothesis testing non-inferiority at Study Week 48 for the Immediate Switch Group vs Study Week 24 for the Delayed Switch Group

2) Secondary safety hypothesis for LDL-C

3) Secondary safety hypothesis for non-HDL-C

4) Secondary efficacy hypothesis testing superiority at Study Week 48 for the Immediate Switch Group vs Study Week 24 for the Delayed Switch Group

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

Note the secondary efficacy hypotheses testing non-inferiority and superiority at Study Week 24 for both treatment groups are considered supportive of the primary and secondary efficacy hypotheses at Study Week 48 for the Immediate Switch Group and Study Week 24 for the Delayed Switch Group and are not considered in the strong control strategy for the Type 1 error for this study.

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

8.9 Sample Size and Power Calculations

8.9.1 Sample Size and Power for Efficacy Analyses

This study will randomize 660 subjects in a 2:1 ratio to either an immediate switch to MK-1439A at Study Day 1 (Immediate Switch Group, 440 subjects) or a delayed switch to MK-1439A after continuation of a ritonavir- or cobicistat-boosted PI-based regimen or a cobicistat-boosted elvitegravir-based regimen or an NNRTI-based regimen for 24 weeks (Delayed Switch Group, 220 subjects). The study will have 80% power to demonstrate the primary hypothesis that immediately switching to MK-1439A is non-inferior to continuing the baseline regimen for 24 weeks, at an overall one-sided 2.5% alpha level, as measured by the proportion of subjects maintaining HIV-1 RNA <50 copies/mL at Study Week 48 in the Immediate Switch Group and at Study Week 24 in the Delayed Switch Group using the Abbott RealTime HIV-1 Assay. The power calculation assumes a true response rate of 85% for both arms using the NC=F approach, as defined by the FDA "snapshot" approach. The

assumed response rate for the delayed switch arm is based on the result from a similar switch study (the SPIRIT study) but takes into consideration the different assay used in this study. A margin of 8 percentage points is used to define the non-inferiority of an immediate switch to MK-1439A at Study Day 1 to continuation of the baseline regimen for 24 weeks. Given the non-inferiority margin of 8%, the assumed response rates in the Delayed Switch Group, and the chosen sample size, non-inferiority may be established when the observed difference in response rates (Immediate Switch Group minus Delayed Switch Group) is approximately -2.1% or larger; superiority may be concluded when the observed difference in response rates is approximately 5.5% or larger contingent upon satisfying the multiplicity criteria. The power calculation is based on an asymptotic method proposed by Farrington and Manning (1990) [10] and is carried out using SAS v9.3. Table 11 summarizes the power for the primary comparison under various assumptions for the control response rate and underlying difference in response rates.

Table 11 Power (%) Under Various Assumptions (With 440 Subjects Randomized in Immediate Switch Group and 220 Subjects Randomized in the Delayed Switch Group)

Response Rate (%) in Delayed Switch Group	Underlying Difference in Response Rates (%) (Immediate Switch Group – Delayed Switch Group)						
	-3	-2	-1	0	1	2	3
83	37	51	64	76	86	93	97
85	41	55	69	**80**	89	95	98
87	45	60	74	85	93	97	99
90	53	69	83	92	97	99	>99

Note: The power is calculated based on 440 subjects expected to be included in the analysis for the Immediate Switch Group and 220 subjects expected to be included in the analysis for the Delayed Switch Group.

8.9.2 Sample Size and Power for Safety Analyses

Lipids

Tier 1 events are evaluated based only on subjects whose regimen at screening is a ritonavir-boosted PI + 2 NRTIs. The change from baseline in fasting LDL-C and non-HDL-C at Study Week 24 will be analyzed using ANCOVA models adjusted by baseline lipid level, use of lipid-lowering therapy at Study Day 1 and treatment group. The primary hypothesis of non-inferior efficacy must first be established before testing the hypothesis on lipids. An immediate switch to MK-1439A on Study Day 1 will be concluded to be superior to continuation of a ritonavir-boosted, PI-based regimen if the mean change from baseline in LDL-C in the Immediate Switch Group is significantly lower than that in the Delayed Switch Group (the one-sided p-value for the between-treatment comparison is less than 0.025). If superiority for LDL-C is established, sequential testing for non-HDL-C will be conducted at the same α level.

The estimated between-treatment differences in the mean changes in fasting LDL-C and non-HDL-C, based on the results from a similar switch study (the SPIRIT study [12]), are 16 mg/dL and 21 mg/dL, respectively. It is expected that at least one half of enrolled subjects will, at screening, be on a regimen consisting of a ritonavir-boosted PI. With at least 220 subjects in the Immediate Switch Group and at least 110 subjects in the Delayed Switch Group whose regimen at screening is based on a ritonavir-boosted PI, the study has >99% power to detect a between-treatment difference of 16 mg/dL for the mean change from baseline in LDL-C assuming a common standard deviation of 20 mg/dL. The study also has >99% power to detect a between-treatment difference of 21 mg/dL for the mean change from baseline in non-HDL-C assuming a common standard deviation of 25 mg/dL.

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 98.8% and 89.0% chance of observing at least one adverse experience among the 440 subjects in the Immediate Switch Group and the 220 subjects in the Delayed Switch Group, respectively. If no adverse experience of that type is observed among the 440 subjects in the Immediate Switch Group and 220 subjects in the Delayed Switch Group, this study will provide 95% confidence that the underlying percentage of subjects with that particular adverse experience is <0.8% for the Immediate Switch Group and <1.7% for the Delayed Switch 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 12. These calculations are based on the exact binomial method proposed by Clopper and Pearson (1934) [11].

Table 12 Estimate of Incidence of AEs and 95% Upper Confidence Bound Based on Hypothetical Numbers of Subjects with AEs Among 440 Subjects Randomized to the Immediate Switch Group and 220 Subjects Randomized to the Delayed Switch Group

Hypothetical Number of Subjects With An Adverse Event	440 Subjects in Treatment Group		220 Subjects in Treatment Group	
	Estimate of Incidence	95% Upper Confidence Bound†	Estimate of Incidence	95% Upper Confidence Bound†
0	0.0%	0.8%	0.0%	1.7%
5	1.1%	2.6%	2.3%	5.2%
10	2.3%	4.1%	4.5%	8.2%
15	3.4%	5.6%	6.8%	11.0%
20	4.5%	6.9%	9.1%	13.7%
25	5.7%	8.3%	11.4%	16.3%
30	6.8%	9.6%	13.6%	18.9%

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

Table 13 gives the difference in the incidence of adverse experience (Immediate Switch Group minus Delayed Switch Group) that can be ruled out with different power levels and 95% confidence when there are 440 subjects in the Immediate Switch Group and 220 subjects in the Delayed Switch Group. The underlying incidence of adverse experiences is assumed to be the same for the two treatment groups. For a reasonably common adverse experience which occurs in 20% of subjects either in the Immediate Switch Group or the Delayed Switch Group, the study has 90% power to declare with 95% confidence that the true difference between the treatment groups is no more than 10.7 percentage points. The calculations are based on an asymptotic method proposed by Farrington and Manning (1990) [10].

Table 13 Differences in Incidences of AEs (Immediate Switch Group minus Delayed Switch Group) That Can Be Ruled Out With 440 Subjects Randomized to the Immediate Switch Group and 220 Subjects Randomized to the Delayed Switch 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	6.9	9.3	10.6	11.3	11.6
85	7.4	9.9	11.3	12.1	12.4
90	8.0	**10.7**	12.3	13.1	13.4
95	8.9	11.9	13.6	14.6	14.9

†The upper bound of the two-sided 95% confidence interval (Farrington and Manning (1990) for the difference in AE incidences (Immediate Switch Group minus Delayed Switch Group) assuming the incidences are the same.

8.9.3 Overall Power

The key efficacy and safety hypotheses of the study will be tested sequentially at the one-sided Type 1 error rate of 2.5% in the following order:

1) Primary efficacy hypothesis testing non-inferiority at Study Week 48 for the Immediate Switch Group vs. Study Week 24 for the Delayed Switch Group

2) Secondary safety hypothesis for LDL-C

3) Secondary safety hypothesis for non-HDL-C

4) Secondary efficacy hypothesis testing superiority at Study Week 48 for the Immediate Switch Group vs. Study Week 24 for the Delayed Switch Group.

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

Based on the estimated power for each individual hypothesis, the probability of reaching steps 2 through 4 for statistical testing is approximately 80%, 79%, and 78%, respectively.

8.10 Subgroup Analyses and Effect of Baseline Factors

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

- Age category (≤ median vs. > median)
- Gender (female, male)
- Region (North America, South America, Europe, Asia, Africa, etc.)
- Race (White, Black, Asian, Other)
- Ethnicity (Hispanic/Latino, not Hispanic/Latino)
- Chronic Hepatitis B or C status (HBV/HCV-infected or HBV/HCV-uninfected)
- Baseline CD4 categories (<200 cells/mm^3, ≥200 cells/mm^3)
- ART class used in baseline regimen (ritonavir- or cobicistat-boosted PI or cobicistat-boosted elvitegravir or NNRTI)
- Duration of ART regimen (in use at screening) prior to enrollment (≥1 year, <1 year)
- For subjects whose baseline regimen includes a ritonavir- or cobicistat-boosted PI or cobicistat-boosted elvitegravir, historical documentation of selected NNRTI-class mutations that confer resistance to other NNRTIs but are considered susceptible to MK-1439 (K103N, Y181C, G190A and K103N + Y181C).

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

8.11 Compliance (Medication Adherence)

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

For the main analysis of compliance in this study, a day within the study will be considered an "On-Therapy" day if the subject takes at least one tablet from any bottle provided for this study.

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

the "Number of Days Should be on Therapy" is the total number of days from Day 1 to the date of the last dose of study medication.

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

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

Summary statistics will be provided on percent compliance by treatment group for the FAS population.

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.

8.12 Extent of Exposure

The extent of exposure to study therapy for all randomized and treated subjects will be evaluated by treatment group. 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 14.

Table 14 Product Descriptions

Product Name & Potency	Dosage Form
MK-1439A 100 mg/ 300 mg/ 300 mg	Tablet

9.2 Packaging and Labeling Information

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

Subjects will receive open label monthly bottles. No kitting is required.

9.3 Clinical Supplies Disclosure

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

9.4 Storage and Handling Requirements

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

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

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

9.5 Returns and Reconciliation

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

9.6 Standard Policies

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

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

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

10.1.2 Confidentiality of Subject Records

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

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

10.1.3 Confidentiality of Investigator Information

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

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

2. hospital or clinic address and telephone number;

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

4. other professional documentation.

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

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

10.1.4 Confidentiality of IRB/IEC Information

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

10.2 Compliance with Financial Disclosure Requirements

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

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

10.3 Compliance with Law, Audit and Debarment

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

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

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

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

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

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

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

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

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

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

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

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

10.4 Compliance with Trial Registration and Results Posting Requirements

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

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

10.5 Quality Management System

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

10.6 Data Management

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

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

10.7 Publications

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

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

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

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

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

11.0 LIST OF REFERENCES

1. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. 28 January 2016; 1-139. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.

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12.0 APPENDICES

12.1 Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

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

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

III. Subject Protection

A. IRB/ERC review

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

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

12.2 Collection and Management of Specimens for Future Biomedical Research

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens collected in this trial as outlined in Section 7.1.3.8 – Future Biomedical Research will be used to study various causes for how subjects may respond to a drug/vaccine. Future biomedical research specimen(s) will be stored to provide a resource for future trials conducted by Merck focused on the study of biomarkers responsible for how a drug/vaccine enters and is removed by the body, how a drug/vaccine works, other pathways a drug/vaccine may interact with, or other aspects of disease. The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by Merck or designees and research will be monitored and reviewed by a committee of our scientists and clinicians.

3. Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

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

- Informed Consent

Informed consent for specimens (i.e., DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all subjects or legal guardians, at a trial visit by the investigator or his or her designate. Informed consent for Future Biomedical Research should be presented to the subjects on Visit 1. If delayed, present consent at next possible Subject Visit. Informed consent must be obtained prior to collection of all Future Biomedical Research specimens. Consent forms signed by the subject will be kept at the clinical trial site under secure storage for

regulatory reasons. Information contained on the consent form alone cannot be traced to any specimens, test results, or medical information once the specimens have been rendered de-identified

A template of each trial site's approved informed consent will be stored in the Sponsor's clinical document repository. Each consent will be assessed for appropriate specimen permissions.

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

c. eCRF Documentation for Future Biomedical Research Specimens

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

d. Future Biomedical Research Specimen Collections

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

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

If specimens are collected for a specific genotype or expression analysis as an objective to the main trial, this analysis is detailed in the main body of this protocol (**Section 8.0 – Statistical Analysis Plan**). These specimens will be processed, analyzed, and the remainder of the specimen will be destroyed. The results of these analyses will be reported along with the other trial results. A separate specimen will be obtained from properly-consented subjects in this protocol for storage in the biorepository for Future Biomedical Research.

4. Confidential Subject Information for Future Biomedical Research

In order to optimize the research that can be conducted with Future Biomedical Research specimens, it is critical to link subject' clinical information with future test results. In fact little or no research can be conducted without connecting the clinical trial data to the specimen. The clinical data allow specific analyses to be conducted. Knowing subject characteristics like gender, age, medical history and treatment outcomes are critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for Future Biomedical Research, Merck has developed secure policies and procedures. All specimens will be de-identified as described below.

At the clinical trial site, unique codes will be placed on the Future Biomedical Research specimens for transfer to the storage facility. This first code is a random number which does not contain any personally identifying information embedded within it. The link (or key) between subject identifiers and this first unique code will be held at the trial site. No personal identifiers will appear on the specimen tube.

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

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

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

5. Biorepository Specimen Usage

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

Analyses utilizing the Future Biomedical Research specimens may be performed by Merck, or an additional third party (e.g., a university investigator) designated by Merck. The investigator conducting the analysis will be provided with double coded specimens.

Re-association of analysis results with corresponding clinical data will only be conducted by the Merck Entrusted Keyholder. Any contracted third party analyses will conform to the specific scope of analysis outlined in this sub-trial. Future Biomedical Research specimens remaining with the third party after the specific analysis is performed will be returned to the sponsor or destroyed and documentation of destruction will be reported to Merck.

6. Withdrawal From Future Biomedical Research

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

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject’s personal information and their specimens. In this situation, the request for specimen destruction can not be processed.

7. Retention of Specimens

Future Biomedical Research specimens will be stored in the biorepository for potential analysis for up to 20 years from acquisition. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the trial site will be shipped to a central laboratory and then shipped to the Merck designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according to Merck policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

Separate databases for specimen information and for results from the Future Biomedical Research sub-trial will be maintained by Merck. This is done to separate the future exploratory test results (which include genetic data) from the clinical trial database thereby maintaining a separation of subject number and these results. The separate databases are accessible only to the authorized Sponsor and the designated trial

administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based in international standards (e.g., ISO17799) to protect against unauthorized access. The Merck Entrusted Keyholder maintains control over access to all specimen data. These data are collected for future biomedical research purposes only as specified in this sub-trial will not be used for any other purpose.

9. Reporting of Future Biomedical Research Data to Subjects

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

If any exploratory results are definitively associated with clinical significance for subjects while the clinical trial is still ongoing, investigators will be contacted with information as to how to offer clinical diagnostic testing (paid for by Merck) to subjects enrolled and will be advised that counseling should be made available for all who choose to participate in this diagnostic testing.

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

10. Gender, Ethnicity and Minorities

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

11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the subject have been minimized. Risks include those associated with venipuncture to obtain the whole blood specimen. This specimen will be obtained at the time of routine blood specimens drawn in the main trial.

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

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

12. Self-Reported Ethnicity

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

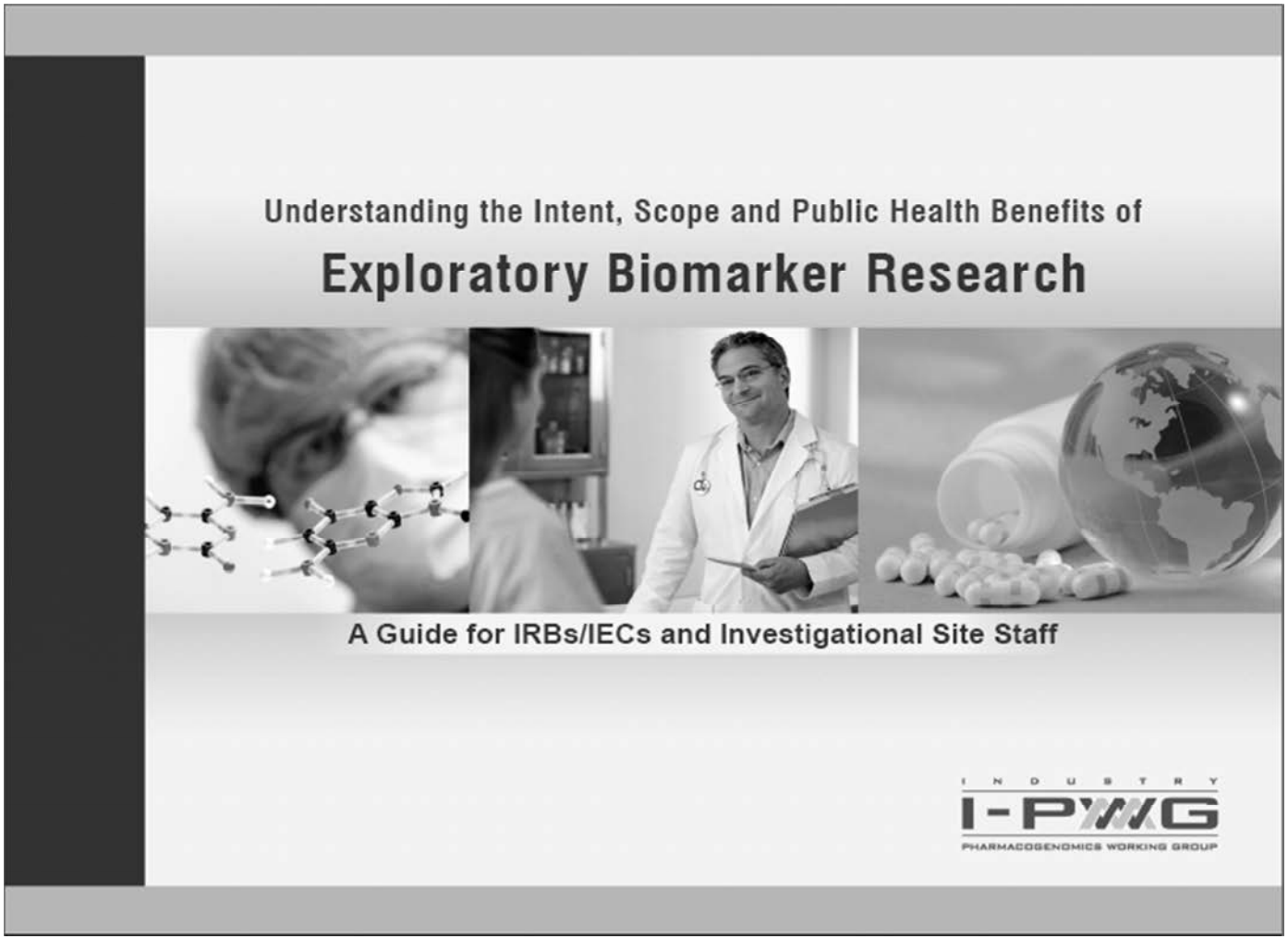
13. Questions

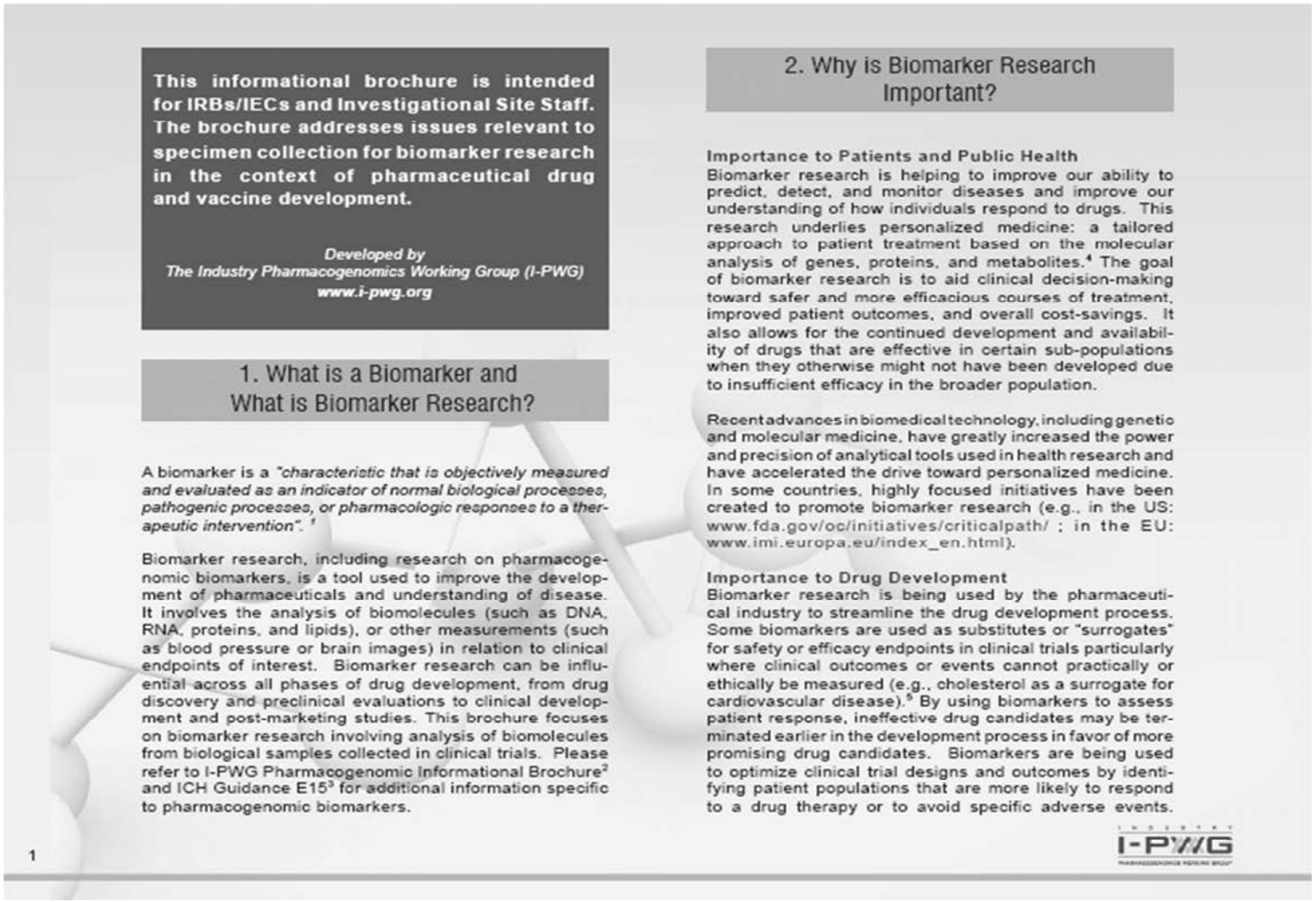
Any questions related to the future biomedical research should be e-mailed directly to clinical.specimen.management@merck.com.

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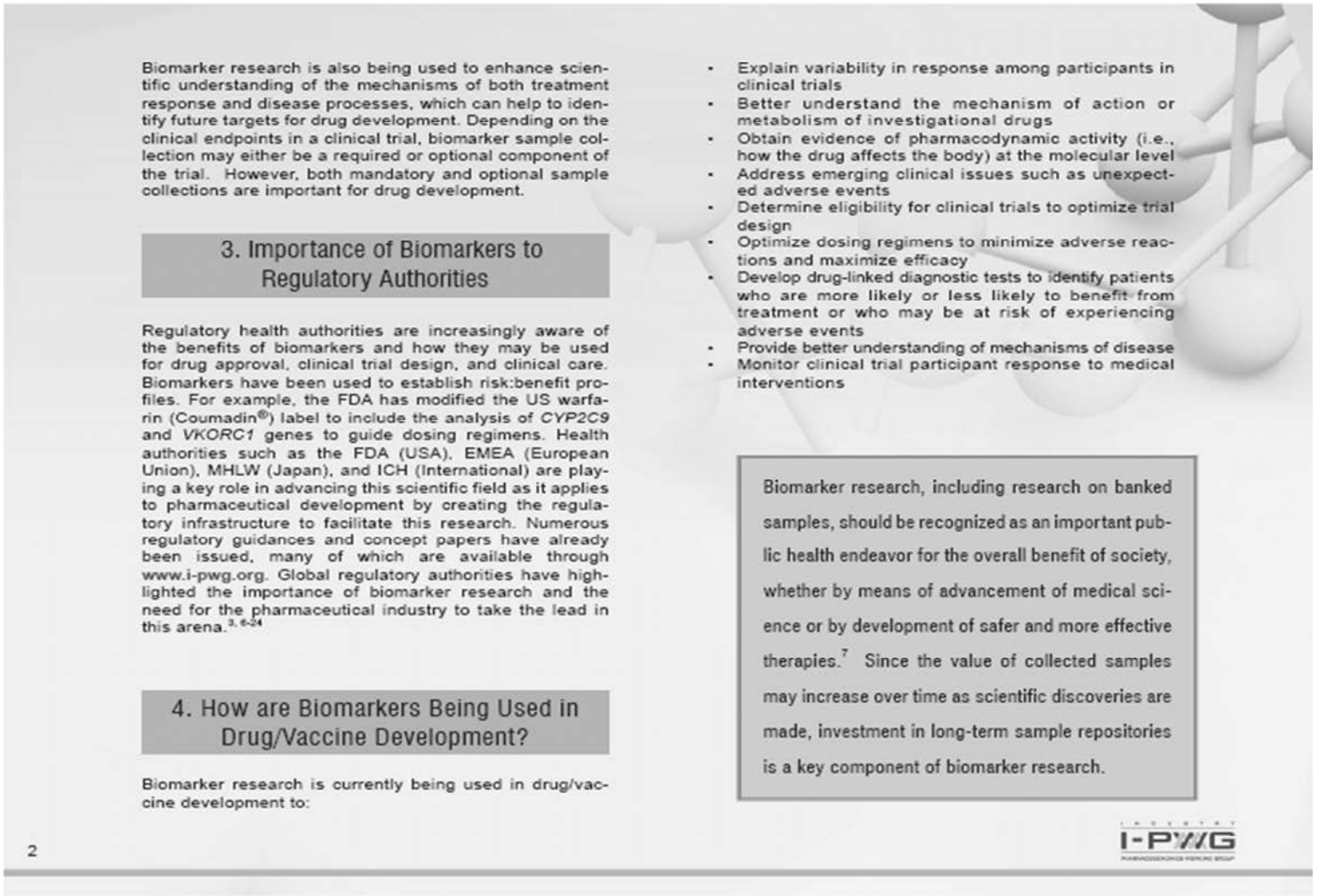
Biomarker research is also being used to enhance scientific understanding of the mechanisms of both treatment response and disease processes, which can help to identify future targets for drug development. Depending on the clinical endpoints in a clinical trial, biomarker sample collection may either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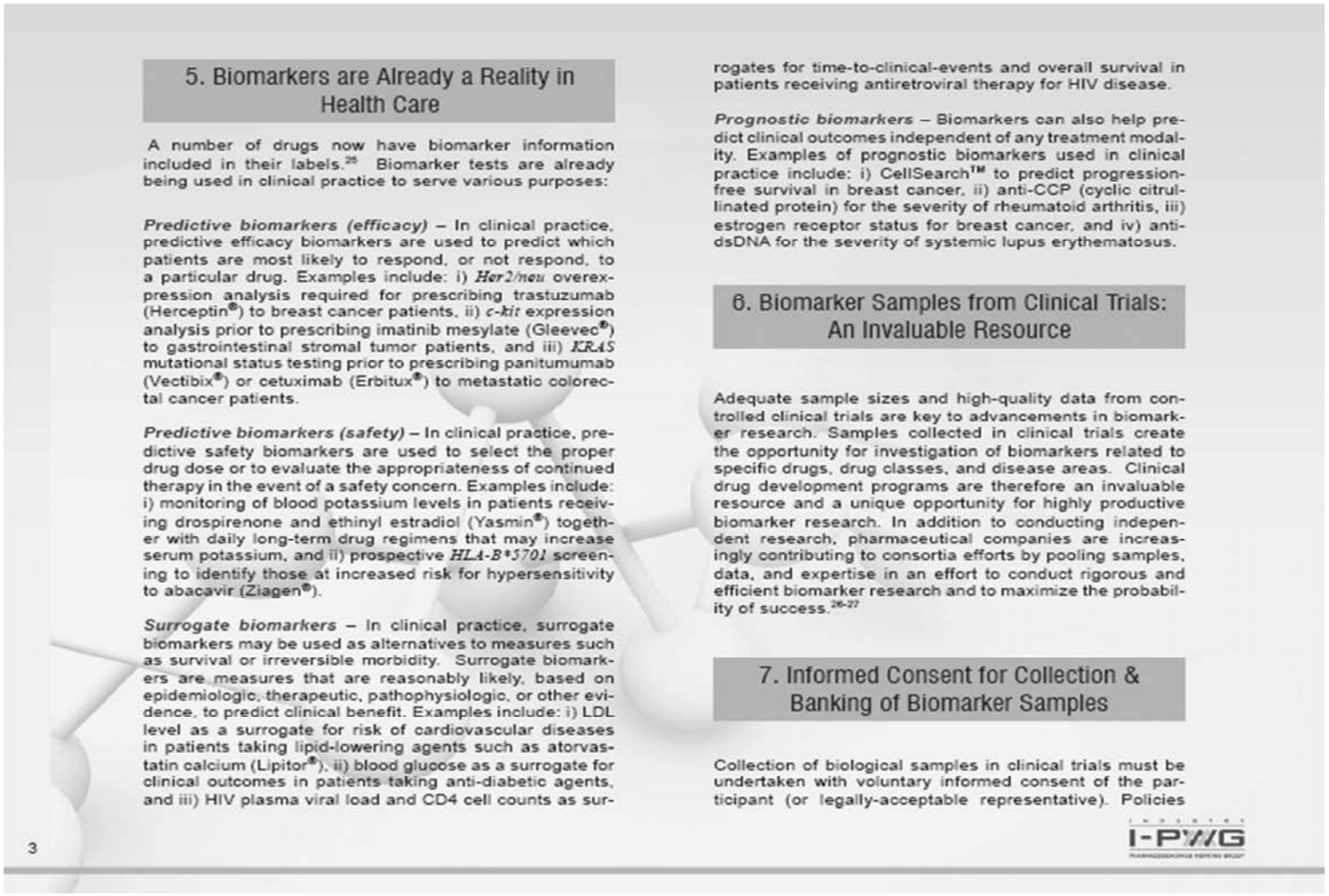

5. Biomarkers are Already a Reality in Health Care

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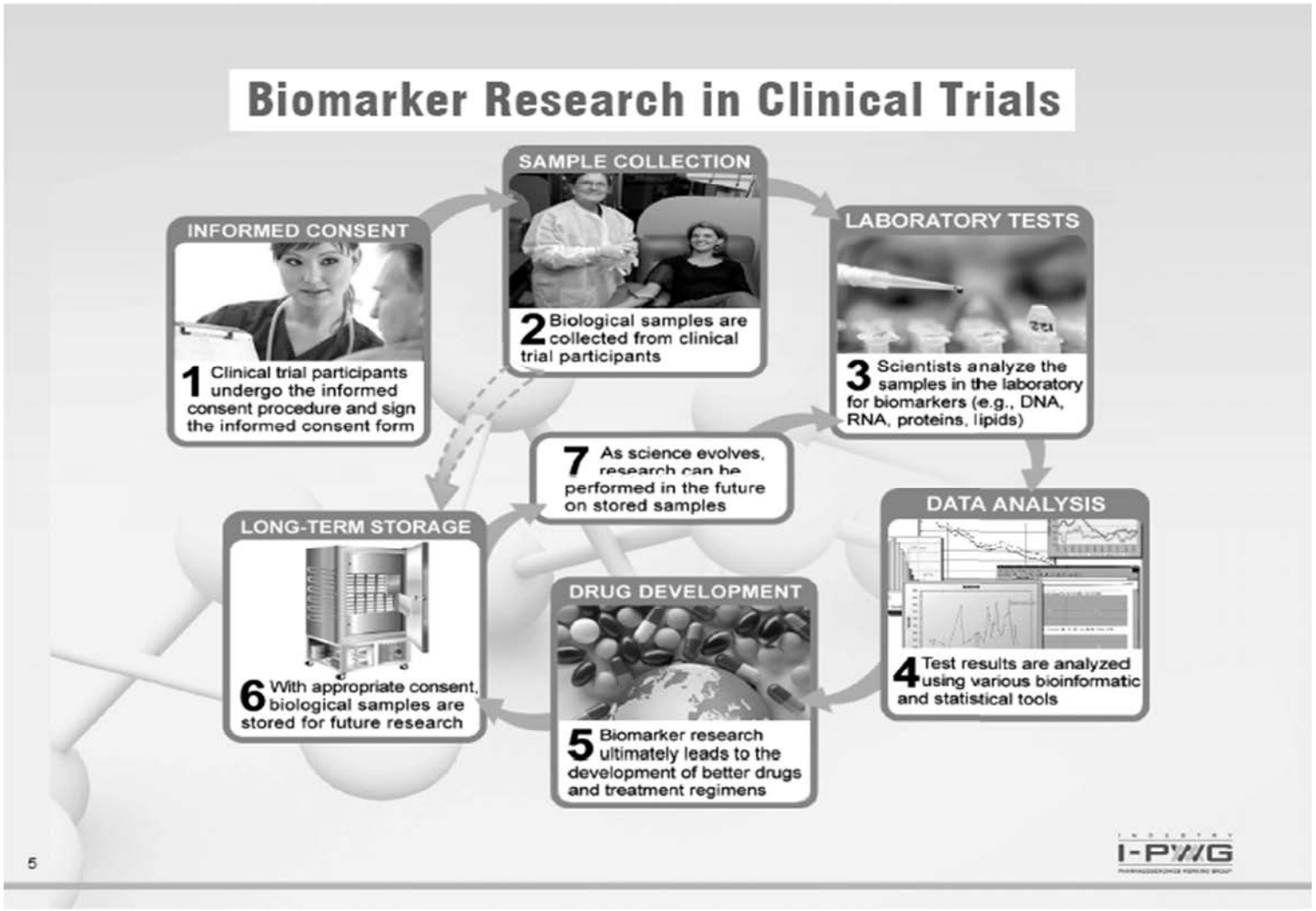
Biomarker Research in Clinical Trials
SAMPLE COLLECTION
2 Biological samples are collected from clinical trial participants
INFORMED CONSENT
1 Clinical trial participants undergo the informed consent procedure and sign the informed consent form
LABORATORY TESTS
3 Scientists analyze the samples in the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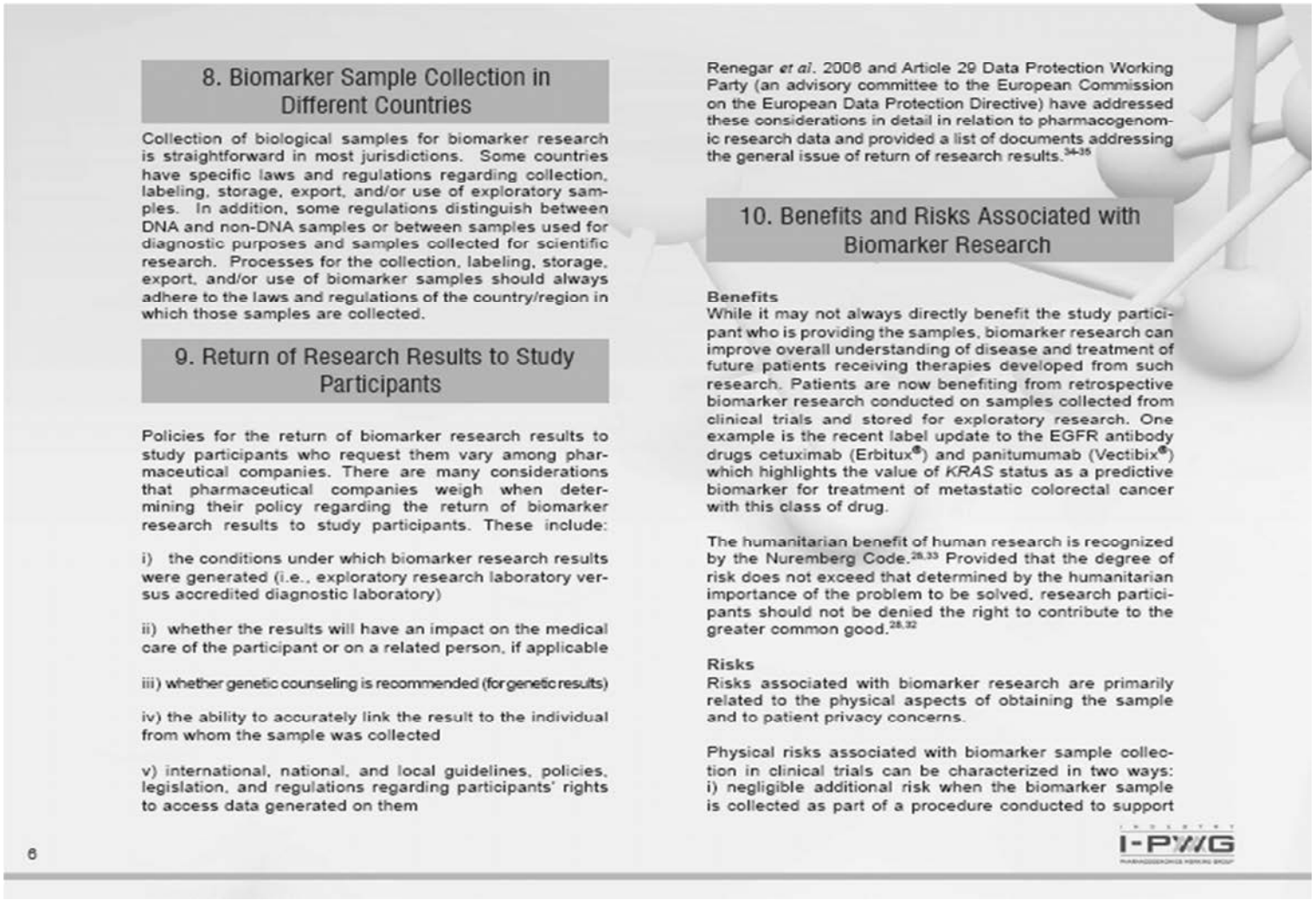

8. Biomarker Sample Collection in Different Countries

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).[35-37]

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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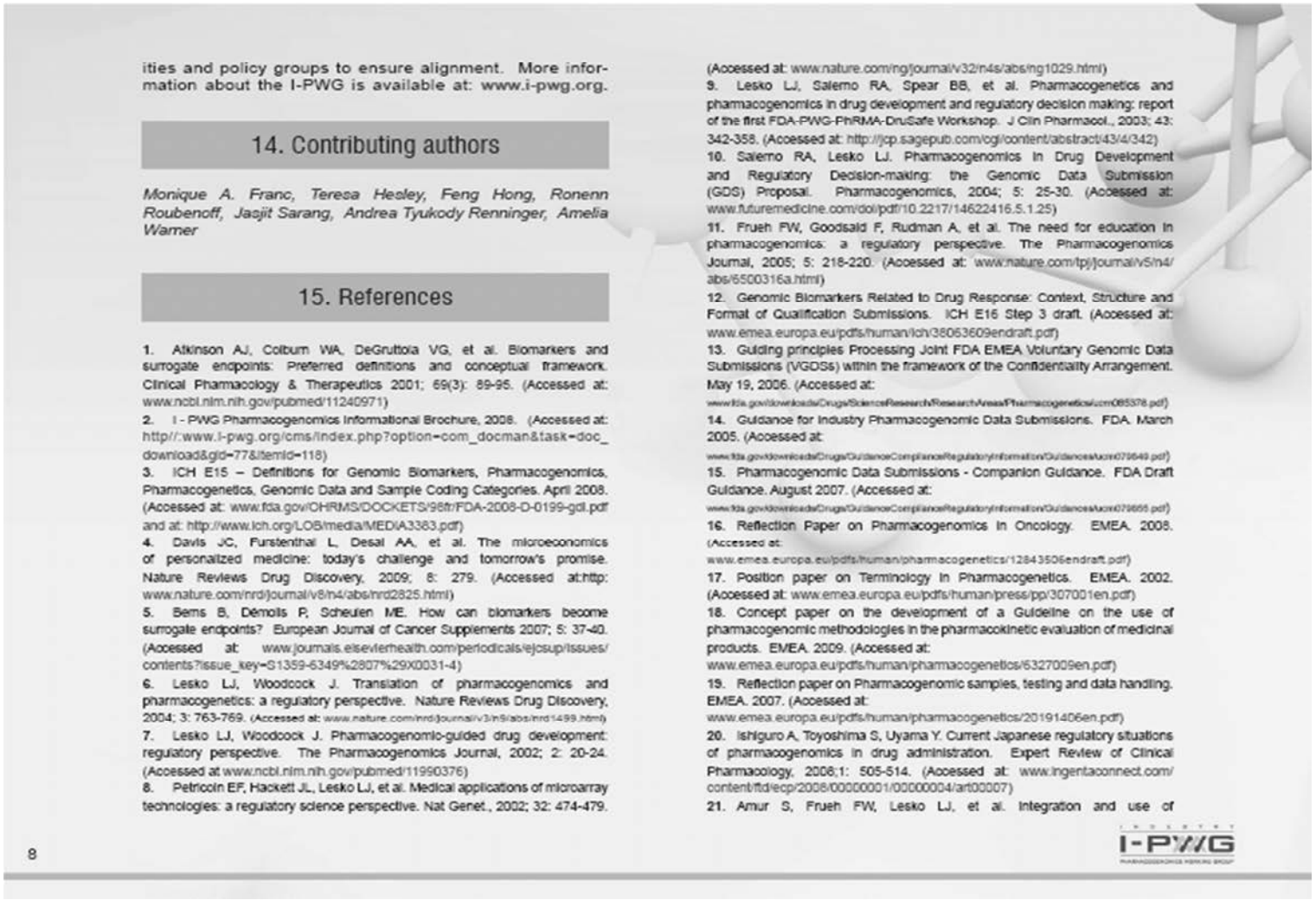

ities and policy groups to ensure alignment. More information about the I-PWG is available at: www.i-pwg.org.

14. Contributing authors

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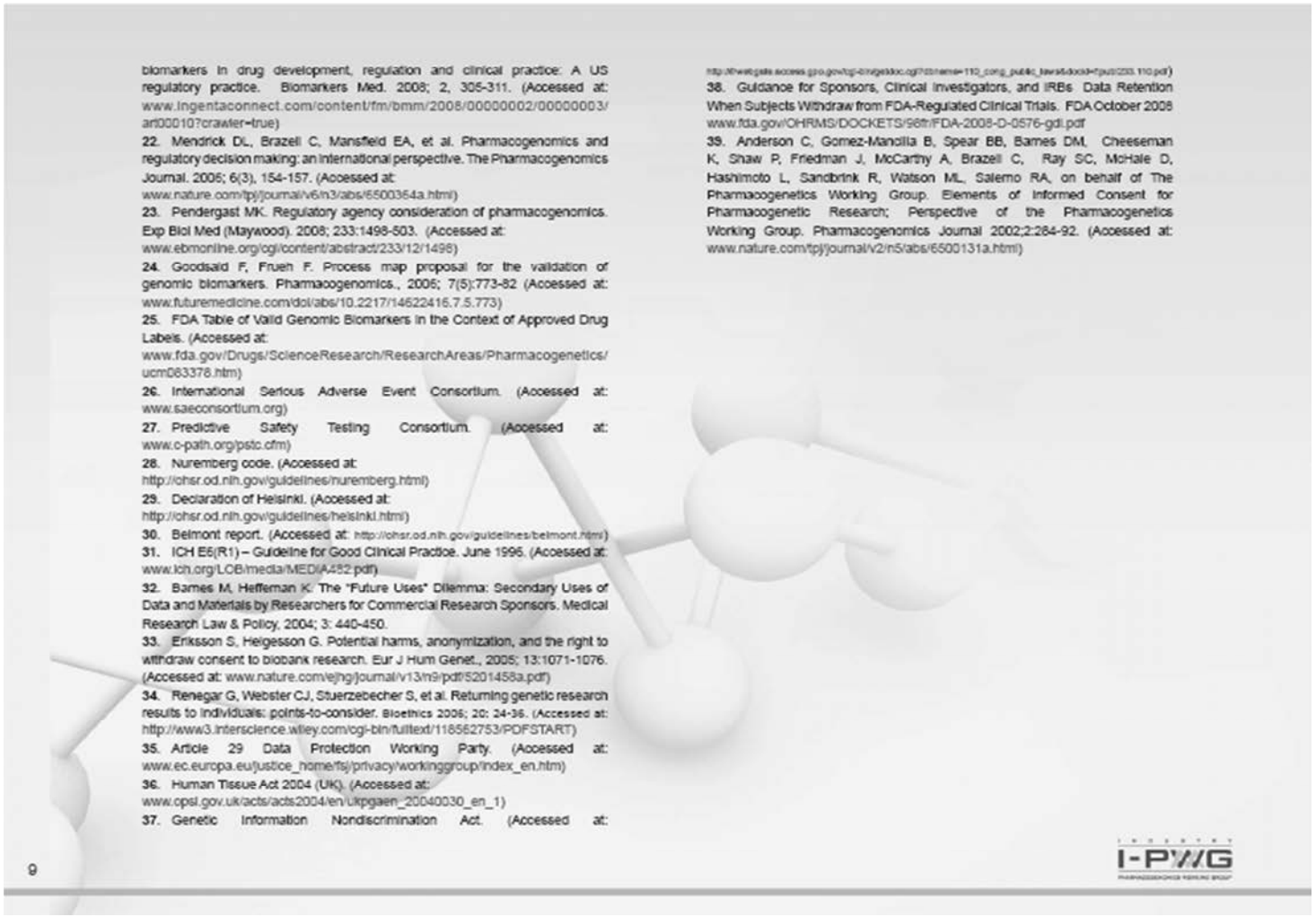

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12.4 Approximate Blood Volumes Drawn/Collected by Trial Visit and by Sample Types

Table A: Approximate Blood Volume Drawn From Screening Through Week 48 Plus 14 Days Follow-up (Base Study)

Week (Visit)	Screen (V1)	Randomization Day 1 (V2)	WK 4 (V3)	WK 12 (V4)	WK 24 (V5)	WK 28 (V6)	WK 36 (V7)	WK 48 (V8)	Virologic Failure Confirmation (U)	Early Discontinuation (U)	14 Day Follow-up (Post Treatment) (99)	Total Volume
Hematology	2	2	2	2	2	2	2	2	2	2	2	**22**
Chemistry	29	7 [a]	7	7	7 [a]	7	7	7 [a]	7	7	7	**99**
HIV/Hepatitis Screen [b]												
Serum Pregnancy Test [c]												
Hemostatic Function Test [d]	4.5											**4.5**
Plasma for HIV Viral RNA	10	10	10	10	10	10	10	10	10	10	10	**110**
CD4 Cell Count		2		2	2		2	2				**10**
Plasma for Viral Resistance		14	14	14	14	14	14	14	14	14[g]		**126**
Blood for MK1439 PK [e]		4	4	4	8			8				**28**
Blood for Genetics		8.5										**8.5**
Plasma for Future Biomedical Research		10			10			10				30
TOTAL (mL)	**45.5**	**57.5**	**37**	**39**	**53**	**33**	**35**	**53**	**33**	**33**	**19**	**438**
Total (tablespoons) [f]	**3**	**3.8**	**2.5**	**2.6**	**3.5**	**2.2**	**2.3**	**3.5**	**2.2**	**2.2**	**1.3**	**~29.1**

a. Fasting is required at these visits for lipids measurement.
b. Includes Enzyme Immunoassay HIV Antibody Screen, Serum Hepatitis B Surface Antigen, Serum Hepatitis B Surface Antibody, Serum Hepatitis B e-Antigen and Serum Hepatitis C Antibody. A plasma Hepatitis C virus PCR quantitative test (an additional ~6 ml= 0.4 tablespoon of blood) will be performed if the Hepatitis C antibody test is positive.
c. For women of childbearing potential.
d. Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT) and International Normalized Ratio (INR).
e. At Study Day 1 and Study Week 4, sample must be collected predose. At Study Week 12, the sample may be collected irrespective of time of dose. At Study Weeks 24 and 48, samples must be collected predose, and within 0.5 to 2 hours postdose (subjects should remain fasting until postdose PK sample is collected).
f. One Tablespoon = 15 mL.
g. If viral failure or relapse is confirmed (with a confirmatory HIV-1 RNA at least one week later), and the decision is made to discontinue the subject, plasma for resistance need not be collected again at the discontinuation visit.

Table B: Approximate Blood Volume Drawn From Week 64 Through Week 144 Plus 14 Days Follow-up (Study Extension 1)

Week (Visit)	WK 64 (V 9)	WK 80 (V 10)	WK 96 (V 11)	WK 112 (V 12)	WK 128 (V 13)	WK 144 (V 14)	Virologic Failure Confirmation (U)	Extension Early Discontinuation (U)	14 Day Follow-up (Post Treatment) (99)	Total Volume
Hematology	2	2	2	2	2	2	2	2	2	**18**
Chemistry	7	7	7 [a]	7	7	7 [a]	7	7	7	**63**
Plasma for HIV Viral RNA	10	10	10	10	10	10	10	10	10	**90**
CD4 Cell Count			2			2				**4**
Plasma for Viral Resistance							14	14 [b]		**28**
TOTAL (mL)	**19**	**19**	**21**	**19**	**19**	**21**	**33**	**33**	**19**	**203**
Total (tablespoons) [c]	**1.3**	**1.3**	**1.4**	**1.3**	**1.3**	**1.4**	**2.2**	**2.2**	**1.3**	**~13.5**

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

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

See Laboratory Manual.

12.6 List of Abbreviations and Acronyms

3TC	Lamivudine
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ALT	Serum Alanine Aminotransferase
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
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
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
HIV-SI	Human Immunodeficiency Virus - Symptom Index
IB	Investigator's Brochure
IBS-QoL	Irritable Bowel Syndrome - Quality Of Life
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
NHS	Normal Human Serum
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
OF	Observed Failure
PCR	Polymerase Chain Reaction
PDLC	Pre-Defined Limit of Change
PDVF	Protocol Defined Virologic Failure
PGt	Pharmacogenetic
PI	Protease Inhibitors
PK	Pharmacokinetics
PK/PD	Pharmacokinetic/Pharmacodynamic
PO	Per os
PT	Prothrombin Time
QD	Once Daily
(v)RNA	(viral) Ribonucleic Acid
SAC	Scientific Advisory Committee
SOC	System Organ Class
(s)SAP	(supplemental) Statistical Analysis Plan
TDF	Tenofovir Disoproxil Fumarate
TDF/FTC	Tenofovir Disoproxil Fumarate/ Emtricitabine (TRUVADA™)
TLOVR	Time to Loss of Virologic Response
ULN	Upper Limit of Normal
US	United States
WPAI	Work Productivity and Activity Impairment Questionnaire

12.7 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 10^9 – 0.650 x 10^9/L*	500 – 599/mm3 *0.500 x 10^9 – 0.599 x 10^9/L*	350 – 499/mm3 *0.350 x 10^9 – 0.499 x 10^9/L*	< 350/mm3 < *0.350 x 10^9/L*
Comment: Values in children ≤ 13 years are not given for the two parameters above because the absolute counts are variable.				
Absolute neutrophil count (ANC)				
Adult and Pediatric, > 7 days	1,000 – 1,300/mm3 *1.000 x 10^9 – 1.300 x 10^9/L*	750 – 999/mm3 *0.750 x 10^9 – 0.999 x 10^9/L*	500 – 749/mm3 *0.500 x 10^9 – 0.749 x 10^9/L*	<500/mm3 < *0.500 x 10^9/L*
Fibrinogen, decreased	100 – 200 mg/dL *1.00 – 2.00 g/L* OR 0.75 – 0.99 x LLN	75 – 99 mg/dL *0.75 – 0.99 g/L* OR 0.50 – 0.74 x LLN	50 – 74 mg/dL *0.50 – 0.74 g/L* OR 0.25 – 0.49 x LLN	<50 mg/dL < *0.50 g/L* OR < 0.25 x LLN OR Associated with gross bleeding
† Use age and sex appropriate values (e.g., bilirubin).				

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Hemoglobin (Hgb)				
Comment: The Hgb values in mmol/L have changed because the conversion factor used to convert g/dL to mmol/L has been changed from 0.155 to 0.6206 (the most commonly used conversion factor). For grading Hgb results obtained by an analytic method with a conversion factor other than 0.6206, the result must be converted to g/dL using the appropriate conversion factor for that lab.				
Adult and Pediatric ≥ 57 days (HIV POSITIVE ONLY)	8.5 – 10.0 g/dL *5.24 – 6.23 mmol/L*	7.5 – 8.4 g/dL *4.62–5.23 mmol/L*	6.50 – 7.4 g/dL *4.03–4.61 mmol/L*	< 6.5 g/dL < *4.03 mmol/L*
Adult and Pediatric ≥ 57 days (HIV NEGATIVE ONLY)	10.0 – 10.9 g/dL *6.18* – 6.79 *mmol/L* OR Any decrease 2.5 – 3.4 g/dL *1.58 – 2.13 mmol/L*	9.0 – 9.9 g/dL *5.55 - 6.17 mmol/L* OR Any decrease 3.5 – 4.4 g/dL *2.14 – 2.78 mmol/L*	7.0 – 8.9 g/dL *4.34 - 5.54 mmol/L* OR Any decrease ≥ 4.5 g/dL > *2.79 mmol/L*	< 7.0 g/dL < *4.34 mmol/L*
Comment: The decrease is a decrease from baseline				
International Normalized Ratio of prothrombin time (INR)	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 3.0 x ULN	> 3.0 x ULN
Methemoglobin	5.0 – 10.0%	10.1 – 15.0%	15.1 – 20.0%	> 20.0%
Prothrombin Time (PT)	1.1 – 1.25 x ULN	1.26 – 1.50 x ULN	1.51 – 3.00 x ULN	> 3.00 x ULN
Partial Thromboplastin Time (PTT)	1.1 – 1.66 x ULN	1.67 – 2.33 x ULN	2.34 – 3.00 x ULN	> 3.00 x ULN
Platelets, decreased	100,000 – 124,999/mm3 *100.000 x 10^9 – 124.999 x 10^9/L*	50,000 – 99,999/mm3 *50.000 x 10^9 – 99.999 x 10^9/L*	25,000 – 49,999/mm3 *25.000 x 10^9 – 49.999 x 10^9/L*	< 25,000/mm3 < *25.000 x 10^9/L*
WBC, decreased	2,000 – 2,500/mm3 *2.000 x 10^9 – 2.500 x 10^9/L*	1,500 – 1,999/mm3 *1.500 x 10^9 – 1.999 x 10^9/L*	1,000 – 1,499/mm3 *1.000 x 10^9 – 1.499 x 10^9/L*	< 1,000/mm3 < *1.000 x 10^9/L*

∗ Values are for term infants. Preterm infants should be assessed using local normal ranges.

† Use age and sex appropriate values (e.g., bilirubin).

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

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

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

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Phosphate, serum, low				
Adult and Pediatric > 14 years	2.5 mg/dL – < LLN *0.81 mmol/L – < LLN*	2.0 – 2.4 mg/dL *0.65 – 0.80 mmol/L*	1.0 – 1.9 mg/dL *0.32 – 0.64 mmol/L*	< 1.00 mg/dL < *0.32 mmol/L*
Pediatric 1 year – 14 years	3.0 – 3.5 mg/dL *0.97 – 1.13 mmol/L*	2.5 – 2.9 mg/dL *0.81 – 0.96 mmol/L*	1.5 – 2.4 mg/dL *0.48 – 0.80 mmol/L*	< 1.50 mg/dL < *0.48 mmol/L*
Pediatric < 1 year	3.5 – 4.5 mg/dL *1.13 – 1.45 mmol/L*	2.5 – 3.4 mg/dL *0.81 – 1.12 mmol/L*	1.5 – 2.4 mg/dL *0.48 – 0.80 mmol/L*	< 1.50 mg/dL < *0.48 mmol/L*
Potassium, serum, high	5.6 – 6.0 mEq/L *5.6 – 6.0 mmol/L*	6.1 – 6.5 mEq/L *6.1 – 6.5 mmol/L*	6.6 – 7.0 mEq/L *6.6 – 7.0 mmol/L*	> 7.0 mEq/L > *7.0 mmol/L*
Potassium, serum, low	3.0 – 3.4 mEq/L *3.0 – 3.4 mmol/L*	2.5 – 2.9 mEq/L *2.5 – 2.9 mmol/L*	2.0 – 2.4 mEq/L *2.0 – 2.4 mmol/L*	< 2.0 mEq/L < *2.0 mmol/L*
Sodium, serum, high	146 – 150 mEq/L *146 – 150 mmol/L*	151 – 154 mEq/L *151 – 154 mmol/L*	155 – 159 mEq/L *155 – 159 mmol/L*	≥ 160 mEq/L ≥ *160 mmol/L*
Sodium, serum, low	130 – 135 mEq/L *130 – 135 mmol/L*	125 – 129 mEq/L *125 – 129 mmol/L*	121 – 124 mEq/L *121 – 124 mmol/L*	≤ 120 mEq/L ≤ *120 mmol/L*
Triglycerides (fasting)	NA	500 – 750 mg/dL *5.65 – 8.48 mmol/L*	751 – 1,200 mg/dL *8.49 – 13.56 mmol/L*	> 1,200 mg/dL > *13.56 mmol/L*
† Use age and sex appropriate values (e.g., bilirubin).				

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

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

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

13.2 Investigator

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

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

Exclusion Criteria: Resistance to Study Drugs

- Resistance to doravirine was considered to include the following NNRTI resistance mutations (as single mutations or components of double or triple mutations): L100I, K101E, K101P, K103S, V106A, V106I, V106M, V108I, E138A, E138G, E138K, E138Q, E138R, V179L, Y181I, Y181V, Y188C, Y188H, Y188L, G190S, H221Y, L234I, P225H, F227C, F227L, F227V, M230L, M230I.
- RT mutations that confer resistance to other NNRTIs but are considered to retain susceptibility to doravirine (K103N, Y181C, G190A) were not excluded.
- Resistance to lamivudine and tenofovir included the following RT mutations: K65R, M41L, T69S (insertion complex), Q151M, M184I, M184V, L210W, T215F, T215Y, K219E, K219Q, D67N, K70R and K70E.

Switching to Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate (DOR/3TC/TDF) Maintains HIV-1 Virologic Suppression Through 48 Weeks: Results of the DRIVE-SHIFT Trial

Virologic Outcomes, FDA Snapshot Approach

	Study Week 24		Study Week 48	
	DOR/3TC/TDF ISG N=447	Baseline Regimen N=223	DOR/3TC/TDF ISG N=447	DOR/3TC/TDF DSG N=209
Outcome	n (%)	n (%)	n (%)	n (%)
HIV-1 RNA <50 copies/mL	419 (93.7)	211 (94.6)	406 (90.8)	198 (94.7)
HIV-1 RNA ≥50 copies/mL[†]	8 (1.8)	4 (1.8)	7 (1.6)	6 (2.9)
No virologic data in time window	20 (4.5)	8 (3.6)	34 (7.6)	5 (2.4)
Discontinued study due to AE or death[‡]	6 (1.3)	0 (0.0)	14 (3.1)	2 (1.0)
Discontinued study for other reasons[§]	12 (2.7)	8 (3.6)	20 (4.5)	3 (1.4)
On study but missing data	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)

[†] Includes subjects who changed (a) any component of background therapy to a new drug class or (b) background components that were not permitted per protocol or (c) any background drug in the regimen because of lack of efficacy (perceived or documented) before Study Week 24; subjects who discontinued study drug or study before Study Week 48 for lack or loss of efficacy; and subjects with HIV-1 RNA ≥50 copies/mL in the time window.

[‡] Includes subjects who discontinued because of adverse event (AE) or death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.

[§] Other Reasons include: lost to follow-up, non-compliance with study drug, physician decision, protocol deviation, withdrawal by subject.

Baseline Regimen = ritonavir or cobicistat-boosted PI, or cobicistat-boosted elvitegravir, or NNRTI, each administered with two NRTIs.

ISG = Immediate Switch Group; DSG = Delayed Switch Group.

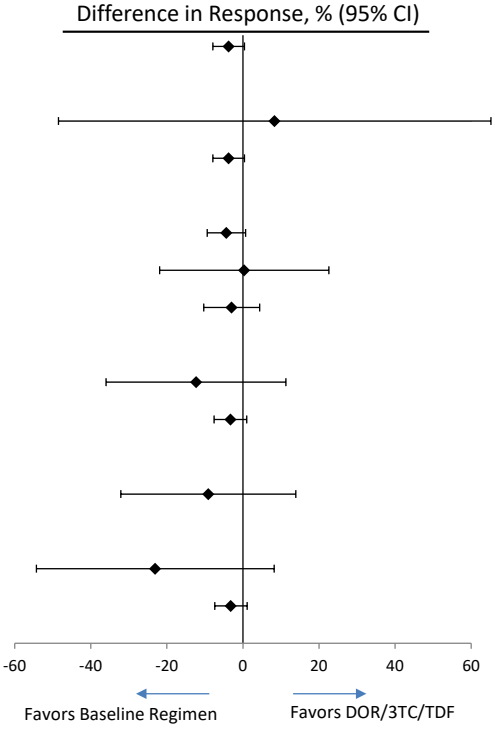
Note: The DSG continued their baseline regimen until Study Week 24, when they switched to DOR/3TC/TDF.

Switching to Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate (DOR/3TC/TDF) Maintains HIV-1 Virologic Suppression Through 48 Weeks: Results of the DRIVE-SHIFT Trial

HIV-1 RNA <50 copies/mL by Prognostic Factors

DOR/3TC/TDF Week 48 vs Baseline Regimen Week 24, FDA Snapshot Approach

	DOR/3TC/TDF		Baseline Regimen	
	n/N	%	n/N	%
All participants	406/447	90.8	211/223	94.6
Baseline CD4+ T-cell count				
< 200 cells/mm^3	11/13	84.6	3/4	75.0
≥ 200 cells/mm^3	388/426	91.1	205/216	94.9
Baseline ART regimen				
Boosted PI	284/316	89.9	147/156	94.2
Boosted elvitegravir	23/25	92.0	11/12	91.7
NNRTI	99/106	93.4	53/55	96.4
Duration of prior regimen				
< 12 months	23/26	88.5	12/12	100
≥ 12 months	383/421	91.0	199/211	94.3
History of NNRTI mutations				
K103N, Y181C, or G190A	10/11	90.9	13/13	100
HBV or HCV Co-infection				
Positive	11/14	78.6	9/9	100
Negative	395/433	91.2	202/214	94.4

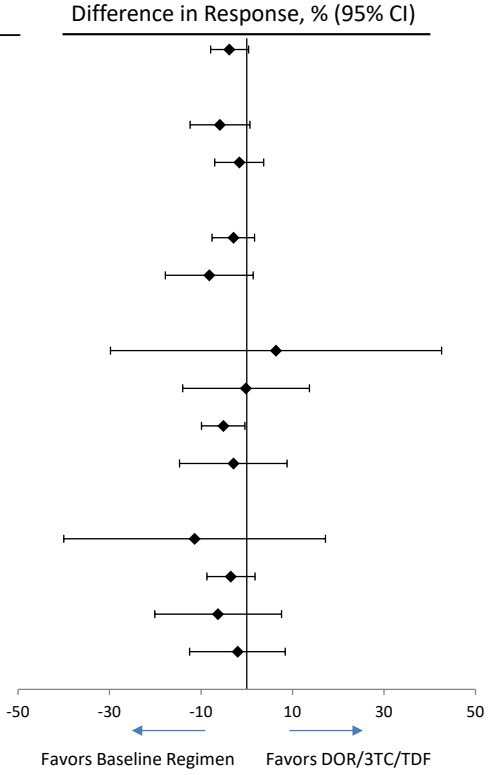


Switching to Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate (DOR/3TC/TDF) Maintains HIV-1 Virologic Suppression Through 48 Weeks: Results of the DRIVE-SHIFT Trial

HIV-1 RNA <50 copies/mL by Demographic Factors

DOR/3TC/TDF Week 48 vs Baseline Regimen Week 24, FDA Snapshot Approach

	DOR/3TC/TDF		Baseline Regimen	
	n/N	%	n/N	%
All participants	406/447	90.8	211/223	94.6
Age				
≤ Median (43y)	201/230	87.4	110/118	93.2
> Median (43y)	205/217	94.5	101/105	96.2
Gender				
Male	338/372	90.9	182/194	93.8
Female	68/75	90.7	29/29	100
Race/Ethnicity				
Asian	16/17	94.1	7/8	87.5
Black	51/56	91.1	31/34	91.2
White	310/344	90.1	160/168	95.2
Hispanic/Latino	87/99	87.9	41/45	91.1
Region				
Asia/Pacific	17/19	89.5	12/12	100
Europe	245/268	91.4	130/137	94.9
Latin America	44/49	89.8	23/24	95.8
North America	100/111	90.1	46/50	92.0



Switching to Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate (DOR/3TC/TDF) Maintains HIV-1 Virologic Suppression Through 48 Weeks: Results of the DRIVE-SHIFT Trial

Adverse Events Resulting in Discontinuation of DOR/3TC/TDF

ID	Adverse Event	Serious	Treatment Group	Day of Onset†	Intensity	Outcome
EVENTS CONSIDERED RELATED TO TREATMENT‡						
1	Depression	Yes	ISG	6	Severe	Resolved
2	Lipase increased	Yes	ISG	31	Mild	Resolving
3	Amylase increased	Yes	ISG	334	Severe	Resolved
	Lipase increased	Yes		334	Severe	Not resolved
4	Renal failure§	Yes	DSG	261	Severe	Resolved
5*	Memory impairment	No	ISG	1	Mild	Not resolved
	Memory impairment	No		189	Moderate	Not resolved
6	Fatigue	No	ISG	2	Moderate	Resolved
	Sleep disorder	No		2	Moderate	Resolved
7	Decreased appetite	No	ISG	11	Mild	Resolved
8	ALT increased	No	ISG	29	Moderate	Resolving
9*	Generalized edema	No	ISG	167	Moderate	Not resolved
	Myalgia	No		167	Moderate	Resolved
	Rash, macular	No		167	Moderate	Resolved
	Renal pain	No		196	Mild	Resolving
10	AST increased	No	ISG	176	Moderate	Resolved
11	ALT increased	No	DSG	197	Moderate	Resolved
	AST increased	No		197	Moderate	Resolved
12	Memory impairment	No	DSG	243	Mild	Not resolved
13	Hepatitis	No	DSG	337	Moderate	Not resolved
EVENTS CONSIDERED NOT RELATED TO TREATMENT						
14	Rash, maculopapular	Yes	ISG	86	Mild	Resolved
15	ALT increased	Yes	ISG	150	Severe	Resolved
	AST increased	Yes		150	Severe	Resolved
16	Endocarditis	Yes	ISG	176	Severe	Resolved
17	Renal impairment	No	ISG	88	Moderate	Not resolved
18	Ascites	No	ISG	96	Moderate	Not resolved
	Hepatitis, alcoholic	No		120	Moderate	Not resolved
19	Amylase increased	No	ISG	192	Mild	Not resolved
	Lipase increased	No		192	Severe	Not resolved

† For participants in the DSG, the day of onset is calculated from Day 1 of the study and includes 24 weeks (approximately 168 days) on the Baseline Regimen.

‡ These events were determined by the investigator to be related to study therapy.

§ This participant had a history of hypertension, coronary artery disease, and renal insufficiency.

* These participants discontinued due to AEs that occurred during both time periods (wk 0-24 and wk 24-48).