Official Protocol Title:	A Single-Dose Clinical Trial to Study the Safety, Tolerability, Pharmacokinetics, and Anti- Retroviral Activity of MK-8591 Monotherapy in Anti-Retroviral Therapy (ART)-Naïve, HIV-1 Infected Patients
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TITLE:

A Single-Dose Clinical Trial to Study the Safety, Tolerability, Pharmacokinetics, and Anti-Retroviral Activity of MK-8591 Monotherapy in Anti-Retroviral Therapy (ART)-Naïve, HIV-1 Infected Patients

IND NUMBER: 128,595
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SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
1.0, 2.0 4.2.2	Trial Summary, Trial Design; Rationale for Dose Selection/Regimen	Addition of 3 Panels (E, F, and G). In Panel E, subjects will be given 0.5mg MK-8591 and in Panel F, subjects will be given 0.25mg after review of safety, tolerability, pharmacokinetics, and antiretroviral pharmacodynamics of MK-8591 from Panel E. In Panel G, subjects will be given 30 mg MK-8591 and initiated on ART at the end of monotherapy time point of 21 days or when viral load becomes detectable after having fallen below the limit of detection.	A lower dose of MK-8591 will be assessed in Panels E and F to further refine the dose response curve for MK-8591. In Panel G, 30 mg MK-8591 will be assessed to evaluate the duration of antiretroviral suppression after a single dose of 30 mg MK-8591.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
3.1	Primary Objectives	Addition of Panels E, F and G to primary objectives	See rationale above in "primary reason for this amendment"
3.2, 8.2.2, 8.2.4	Exploratory Objectives; Analysis Endpoints; Statistical Methods	Modification of exploratory objective for Panel G, 30mg	To determine whether the duration of antiretroviral suppression after a single dose of 30 mg MK-8591 can extend to at least three weeks postdose.
4.2.2	Rationale for Dose Selection/Regimen	Addition of food effect data from MK-8591 P001	Food effect data from MK-8591 P001 has been provided since this section previously stated that the effect of food on MK-8591 was not known.
		Results provided from Panel D, 1 mg MK-8591	Data from Panel D, 1 mg MK-8591, has been provided to help inform the decision to administer lower doses in Panels E and F

		Criteria added for the initiation of ART in Panel G	Criteria for the initiation of ART has been added for Panel G, based on a subject's VL starting at 10 days post-dose.
		For HIV-1 RNA blood samples taken at 336, 408, 456, and 504 (post-trial visit) hours post dose, two samples will be taken per timepoint.	To reduce the likelihood that ART initiation would occur because of random fluctuations in VL, two samples will be obtained at every timepoint starting after 10 days post-dose.
		For subjects that have VL below the LLOD at 21 days, semiweekly assessment of VL will occur after the post-trial visit.	Subjects that have not initiated ART at the post-trial visit will need to be closely monitored.
5.1.2	Subject Inclusion Criteria	Criteria added for screening plasma HIV-1 RNA for inclusion in Panel G, 30mg	For inclusion in Panel G, subjects must also have a screening plasma HIV-1 RNA ≤ 25,000 copies/mL within 30 days prior to the treatment phase. Additional rationale for this inclusion criteria is provided in 4.2.1.
6.0	Trial Flow Chart	Panels E and F added to trial flow chart and a second flow chart added for Panel G only	Additional panels included in trial flow chart and a separate flow chart added for Panel G since additional sampling for viral load and PBMCs will be collected

9.1	Investigational Product	Addition of MK-8591 0.25 mg, Capsule Clarification added for the sourcing of ART	Addition of MK-8591 0.25 mg for Panels E and F Following statement inserted: "Additionally, ART that is initiated during the study will be sourced locally by the clinical site."
Appendix 12.4	Approximate Blood Volumes Collected by Trial Visit and by Sample Types	Addition of Panels E and F to existing blood volume chart and a separate blood volume chart added for Panel G	Additional samples will be taken in Panel G for PBMC and HIV-1 viral RNA and viral resistance during the treatment period

1.0 TRIAL SUMMARY

Abbreviated Title	MK-8591 Phase IB Study
Sponsor Product Identifiers	
Trial Phase	Phase IB
Clinical Indication	Treatment of HIV-1 Infection
Trial Type	Interventional
Type of control	No treatment control
Route of administration	Oral
Trial Blinding	Unblinded Open-label
Treatment Groups	Seven panels (Panel A, B, C, D, E, F and G) of 6 subjects each will receive a single dose of MK-8591.
Number of trial subjects	Approximately up to 42 subjects will be enrolled.
Estimated duration of trial	The sponsor estimates that the trial will require approximately 24 months from the time the first subject signs the informed consent until the last subject's last visit.
Duration of Participation	Each subject will participate in the trial for approximately 7 weeks from the time the subject signs the Informed Consent Form (ICF) through the final contact. After a screening phase of ~4 weeks, each subject will be receiving assigned treatment for 1 day. After the end of treatment each subject will be followed for 21 days, or longer, if ART is not initiated.

2.0 TRIAL DESIGN

2.1 Trial Design

This is an open-label, single dose, multiple panel trial to evaluate the safety, tolerability, pharmacokinetics, and anti-retroviral therapy (ART) activity of MK-8591 monotherapy in ART-naïve, HIV-1 infected subjects. The primary study endpoints are the safety and tolerability of MK-8591 and the change in plasma HIV-1 RNA (log_{10} copies/mL) compared with historical placebo data. This study will be conducted in conformance with Good Clinical Practices.

Seven panels of 6 subjects each will be enrolled in a sequential manner. In each panel, subjects will receive a single dose of MK-8591 between 0.25 mg and 30 mg. The exact dose administered will be selected following review of the safety, pharmacokinetic, and viral dynamic data from prior panels. All doses of study drug will be administered following at least an 8-hour fast.

Subjects will be encouraged to initiate a tenofovir containing ART regimen at a prespecified time following administration of study drug. Follow-on ART should be administered for ~30 days to account for the long half-life of MK-8591 triphosphate. The initiation of follow-on ART is not a requirement for participation in the study and is ultimately a decision of the patient in consultation with the PI/physician.

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.

Because this is a Phase I assessment of MK-8591 in humans, the pharmacokinetic, pharmacodynamic and safety profiles of the compound are still being elucidated. This protocol is therefore written with some flexibility to accommodate the inherent dynamic nature of Phase I clinical trials. Please refer to Section 7.1.5 – Visit Requirements for examples of modifications permitted within the protocol parameters.

2.2 Trial Diagram

The trial design is depicted in Table 1.

Table 1 MK-8591 Dosing Scheme

Panel	Dose
A	10 mg MK-8591
B	2 mg MK-8591
C	30 mg MK-8591
D	1 mg MK-8591
E	0.5 mg MK-8591
F	0.25 mg MK-8591
G	30 mg MK-8591

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

1) **Objective (Panels A, B, C, D, E, F, and G):** To evaluate the antiretroviral activity of MK-8591 in HIV-1 infected subjects relative to historical subjects receiving placebo.

Hypothesis (Panels A, B, C, D, E, F, and G): At a dose that is sufficiently safe and generally well tolerated, MK-8591 has superior antiretroviral activity compared to placebo, as measured by change from baseline in plasma HIV-1 RNA (log_{10} copies/mL) at 168 hours postdose. That is, the true mean difference in the plasma HIV-1 RNA reduction from baseline between MK-8591 and placebo is at least 0.5 log_{10} copies/mL.

2) **Objective:** To evaluate the safety and tolerability of MK-8591 in HIV-1 infected subjects.

3.2 Secondary Objective(s) & Hypothesis(es)

1) **Objective**: To evaluate the intracellular PK profile of MK-8591 triphosphate and to determine PK parameter values (including AUC0-168, Tmax, Cmax, C168hr, and apparent terminal t1/2) in peripheral blood mononuclear cells (PBMC) after administration of single oral doses to HIV-1 infected subjects.

2) **Objective**: To evaluate plasma PK profile of MK-8591 and to determine PK parameter values (including AUC0-168, Tmax, Cmax, C168hr, and apparent terminal t1/2) after administration of single oral doses to HIV-1 infected subjects.

3) **Objective**: To evaluate the pharmacokinetic-pharmacodynamic association of MK-8591 and MK-8591 triphosphate with viral load reduction to refine the clinical dose range.

3.3 Exploratory Objectives

1) To evaluate the relationship between dose and antiretroviral activity of MK-8591

2) To determine whether the duration of antiretroviral suppression after a single dose of 30 mg MK-8591 can extend to at least three weeks postdose.

4.0 BACKGROUND & RATIONALE

4.1 Background

Refer to the Investigator's Brochure (IB) for detailed background information on MK-8591.

- Physical, Chemical, and Pharmaceutical Properties and Formulation
- Nonclinical Pharmacology
- Safety Pharmacology and Supplemental Safety Pharmacology Studies
- Pharmacokinetics and Product Metabolism in Animals
- Toxicology (Preclinical Safety Assessment)
- Effects in Humans

4.1.1 Pharmaceutical and Therapeutic Background

MK-8591 is a novel, potent human immunodeficiency virus type 1 (HIV-1) nucleoside reverse transcriptase inhibitor (NRTI). MK-8591 is an inactive nucleoside prodrug that is converted to the pharmacologically active triphosphate form via endogenous intracellular kinases. MK-8591-triphosphate is a potent and specific inhibitor of HIV-1 reverse transcriptase activity in vitro. Currently marketed NRTIs include tenofovir disproxil fumarate, lamivudine, emtricitabine, abacavir, didanosine, stavudine, and zidovudine. The currently preferred recommendation for first-line treatment of HIV infection in naïve subjects calls for 3 agents and always includes 2 NRTIs in combination with either an integrase strand

transfer inhibitor, a protease inhibitor, or a non -nucleoside reverse transcriptase inhibitor. While the currently approved NRTIs represent a cornerstone of modern anti–retroviral therapy there are significant class associated toxicities including loss of bone mineral density, new or worsening renal impairment, severe lactic acidosis, and serious hypersensitivity reactions. Because tolerability issues are one of the most common reasons for lack of adherence and subsequent viral failure, a need exists for new NRTIs like MK-8591 that possess a high barrier to resistance with an improved safety and tolerability profile.

4.1.2 Completed Clinical Trials

Protocol 001

MK-8591 Protocol 001 was a randomized, placebo-controlled, single-site, double-blind trial evaluating the safety and pharmacokinetics of single doses of MK-8591 in healthy adult subjects. Overall, single doses of MK-8591 up to 400 mg were generally safe and well-tolerated by the subjects. No serious adverse experiences were reported and no subject was discontinued. The most common adverse experiences reported (seen in $\geq$ 2 subjects) were headache, nasopharyngitis, and oral herpes. Adverse experiences were mild to moderate in intensity and transient in duration.

Protocol 002

MK-8591 Protocol 002 was a randomized, placebo-controlled, single-site, double-blind trial evaluating the safety and pharmacokinetics of multiple doses of MK-8591 in healthy adult subjects. Three serial panels consisting of 8 subjects each were administered three once weekly doses of MK-8591 (n=6) or placebo (n=2). Overall, multiple doses of MK-8591 up to 100 mg were generally well tolerated by the subjects. No serious adverse experiences were reported and no subject was discontinued. The most common adverse experiences reported (seen in $\geq$ 2 subjects) were headache and nasopharyngitis. Adverse experiences were mild to moderate in intensity and transient in duration.

Detailed safety and pharmacokinetic data on Protocol 001 and 002 can be found in the Investigator Brochure.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

The primary objective of this study is to assess the single dose activity of MK-8591 in ART-naïve HIV-1 infected subjects. This study will assess the short-term antiretroviral activity of MK-8591 monotherapy, and data from this study will aid dose selection in future HIV-1 patient studies. The goals of this study will be achieved by enrolling a minimum number of subjects using the shortest treatment duration possible. The study objectives conform to the EMA guideline describing appropriate clinical development for antitretroviral agents as monotherapy and in combination with established therapy (Guideline on the Clinical Development of Medicinal Products for the Treatment of HIV Infection). In Panels A through G, the single dose safety, tolerability, pharmacokinetics, and antiretroviral

pharmacodynamics of MK-8591 will be explored at doses projected to be within, below and on the plateau of the efficacious range.

The reduction in viral load for each dose level will be compared to historical placebo data from clinical trials previously conducted by the Sponsor. Given the overall clean safety profile of MK-8591 in preclinical and clinical testing to date the need for a placebo control to minimize investigator and patient bias with respect to adverse experiences was deemed not necessary. Additionally, the doses to be tested in this study are below the maximum dose assessed in Protocol 001 and the plasma MK-8591 AUC_{0-168} is anticipated to be below those established from preclinical toxicity studies.

This study will evaluate the efficacy and kinetics by which MK-8591 reduces HIV-1 RNA viral load over time. The doses tested in this study will evaluate the effectiveness of MK-8591 in suppressing viral replication and to assess any potential for differentiation with respect to safety, tolerability, and efficacy. The study is specifically designed with an emphasis on collecting single dose viral dynamic data. Because MK-8591 is intended for the treatment of subjects with wild-type strains of HIV-1, infected subjects who are therapy-naïve will be enrolled in this study. Although antiretroviral agents are usually administered in combination to minimize the risk for resistance, MK-8591 will be given as monotherapy in order to evaluate the effect of this agent alone on HIV-1 viral load. Since only a single dose will be administered, risk of resistant strain emergence is minimal. Prior to enrollment subjects will be screened for the presence of common NRTI resistance mutations (International AIDS Society - USA (IASUSA) [1]) to set a baseline standard for MK-8591-sensitivity to the viral variants present in each patient. Subjects identified with a common NRTI mutation (e.g., M184V or M184I) will be excluded from the study. Blood samples will be collected on Day 1 and potentially up to Day 21 or longer for HIV viral RNA quantitation and to assess the potential for resistant variants in those samples showing significant treatment-related reductions in HIV-1 viral RNA. Should unanticipated non-responders or viral breakthrough be observed despite this pre-screening process a portion of the screening blood sample will be archived for phenotyping and/or genotyping of any previously unidentified clinically meaningful resistance variants.

Subjects enrolling in Panel G will be limited to VL of $\leq$25,000 copies/mL. Starting at a relatively lower level will increase the likelihood that treatment will reduce the VL to a low enough level such that ongoing replication of HIV is minimal. This will in turn reduce the likelihood of selection for mutant strains such as M184V.

4.2.2 Rationale for Dose Selection/Regimen

A single dose of MK-8591 is thought to be sufficient to provide antiviral assessment while at the same time minimizing the development of resistance mutations. A design that includes a single dose of MK-8591, equivalent to 7 days of exposure, is based on previous clinical short term studies with other HIV antiretrovirals including NRTIs (BMS-986001, emtracitabine, lamivudine and emtracitabine, tenofovir alafenamide (TAF) and tenofovir disoproxil fumarate (TDF), and abacavir). Each of these studies employed a monotherapy arm that included 7 to 10 days of dosing for the respective investigative agent.

In preclinical monkey efficacy studies with MK-8591, M184V viral breakthrough occurred. Based on these data combined with the observation of viral resistance from the emtricitabine clinical study and that the M184V mutation has high level of resistance to lamivudine, subjects enrolled in Protocol 003 are recommended to begin treatment with a tenofovir based ART when MK-8591 triphosphate levels fall below the predicted efficacy target. Tenofovir has favorable efficacy on this particular variant. ART began 10 days after dosing in Panel A (10 mg dose), 7 days after dosing in Panel B (2 mg dose), 10 days after dosing in Panel C (30 mg), and 7 days after dosing in Panel D (1 mg dose) when intracellular levels of MK-8591 triphosphate may fall below target efficacious concentrations. The timing of ART initiation for Panels E and F will be 7 days after dosing.

Subjects recruited for Panel G would be closely monitored with semiweekly assessment started after the 10 day timepoint, consisting of two separate samples (hours 336, 408, 456, and post-trial visit). In Panel G, ART will be initiated based on the following:

1. ART will be initiated at the "end of monotherapy" timepoint (VL as determined at 456 hours postdose) for those subjects with detectable VL (i.e., >20 copies/mL). This timepoint is derived based on available data. MK-8591 concentrations following the 30 mg dose are expected to be efficacious through 21 days post dose, based on PK data from the 1 mg dose. Thus, subjects with detectable VL at 21 days will be offered ART at that time.

2. If VL is below the lower limit of detection (LLOD; see 4.2.3.1) at the end of monotherapy timepoint (VL as determined at 456 hours postdose), subjects will not immediately initiate ART. Subjects will be followed closely after the post-trial visit, with semiweekly assessment of two measurements of VL/timepoint. ART will be initiated when VL increases above LLOD in both samples. However, subjects may request ART at any time during the study.

3. Subjects will initiate ART no earlier than 10 days post-dose. For those subjects who achieve a VL nadir prior to the end of monotherapy timepoint (Day 21), an increase in VL in both samples will result in initiation of ART, even if occurring prior to the end of monotherapy timepoint defined in (1) above, at the discretion of the investigator and in consultation with the sponsor.

As detailed below, final VL samples prior to initiation of ART will be submitted for Sanger mutation analysis.

The duration of suppressive ART should be ~30 days, or 5 half-lives. The Sponsor will provide this therapy, but it will not be mandated for participation in the study. After completion of the treatment phase of this study, subjects will be encouraged to initiate a non-NRTI containing ART regimen according to local guidelines.

The effect of food on MK-8591 PK has been studied at 30 mg. Plasma PK had a reduction in Cmax of 49% and a 10% increase in AUC0-inf. Intracellular MK-8591 PK was largely unaffected. All doses will be administered following an overnight fast to reduce potential pharmacokinetic variability that could occur with food.

This study will assess a solid capsule formulation of MK-8591. Dose potencies of 0.25, 1, 10 and 100 mg are currently available. Please refer to Section 9.0 for more details.

Panel A and Panel B Dose Selection

The originally proposed doses for Panels A and B were 10 mg and 100 mg, respectively, and were selected for pharmacokinetic, safety, and expected viral pharmacodynamic considerations. Furthermore, these doses are anticipated to bracket the projected doses used in future clinical studies. Because MK-8591 plasma and intracellular triphosphate pharmacokinetic data from healthy volunteers are expected to be similar to that of HIV-1 infected subjects, data from Protocol 001 were used to aid in the selection of doses for the present study.

Available pharmacokinetic data from Protocol 001 indicate that MK-8591 plasma and intracellular triphosphate pharmacokinetics are approximately and slightly less than dose proportional across the explored range of 2-400 mg, respectively. However, the nonlinearity observed with the triphosphate is somewhat confounded by issues with the sample preparation at the 15, 30, and 100 mg doses. Corrective action was employed for all subsequent doses in Protocol 001. The C168hr intracellular triphosphate target of 0.53 pmol/10^6 cells was achieved in all subjects at the 15 mg dose. This intracellular trough concentration is predicted to correspond to clinical efficacy. The geometric mean C168hr following a 15 mg dose was 1.24 pmol/10^6 cells, which is ~2.3-fold higher than the current 0.53 pmol/10^6 cells target (see Section 4.2.3.3.). Using the data from Protocol 001, a 10-mg dose is predicted to result in a mean intracellular triphosphate C168hr of ~1.1 pmol/10^6 cells. This value is ~2.0-fold higher than the PK target. While 10 mg is considered to be on the lower end of the efficacious range, all subjects are expected to exceed the target 0.53 pmol/10^6 cells target.

A 100 mg dose will explore the safety, tolerability, pharmacokinetics, and the potential for viral pharmacodynamic differentiation at higher exposures. Inclusion of this dose will also help to assess MK-8591's viral reduction durability along with its ability to remain above the 0.53 pmol/10^6 cells target for an extended period of time (e.g., 14 days). If the MK-8591 plasma and triphosphate pharmacokinetics remain proportional across formulations, a 100-mg dose is projected to result in a mean MK-8591 triphosphate C168hr of 4.80 pmol/10^6 cells which is ~9-fold higher than the target concentration and is intended to cover the shift in MK-8591 potency due to the M184V variant. The predicted mean MK-8591 triphosphate C336 hr concentration will be ~2.1 pmol/10^6 cells, and is ~4-fold above the PK target. Collection of viral load data through 21 days in Panel B is supported by the prediction that MK-8591 triphosphate levels will remain above the 0.53 pmol/10^6 cells target for ~25 days postdose. Administration of a 100 mg dose is supported by preclinical safety studies and available clinical safety data from Protocol 001 where single doses up to 400 mg were tested and well tolerated. The projected MK-8591 plasma AUC0-168 hr following a 100 mg dose is 11.0 uM*hr and is ~2-2.3 fold below the NOEL observed in preclinical safety studies. The projected Cmax of a single 100 mg dose is 3.23 uM and is expected to exceed that of the preclinical NOEL by ~2-2.2-fold. While the Cmax is higher than what was observed at the

NOEL, the lack of any Cmax related toxicities in clinical studies combined with fact the Protocol 003 includes a only single dose, supports the administration of this top dose.

[redacted]

Based on ante-mortem and post-mortem findings from the modified 6-M rat study, the 3-mg/kg/day group represents the no observed effect level (NOEL). The corresponding $AUC_{0-168\ hr}$ and Cmax for the 3 mkg/kg are 26µM·hr and 1.43 µM, respectively.

[redacted]

[redacted]

Based on the ante-mortem data to date (SW 23), the NOEL from the ongoing monkey study is 5 mg/kg/dose. The corresponding $AUC_{0\text{-}168\ hr}$ and Cmax for the 5 mg/kg/dose are 22 µM·hr and 1.6 µM, respectively.

Panel C

A dose of 30 mg was administered in Panel C to allow for dose selection flexibility and to explore the higher end of the MK-8591 dose response curve.

Panel D

As of 5-April-2016, 18 HIV patients have been enrolled in PN003 and preliminary viral load data are available. Following single doses of 2 mg (Panel B), 10 mg (Panel A), and 30 mg (Panel C) the respective baseline corrected HIV viral load reductions at Day 7 (168 hours postdose) were 1.35 log10, 1.64 log10, and 1.60 log10. Based on these preliminary data, it is very likely that 10 and 30 mg fall on the plateau of efficacy, and 2 mg falls somewhere near the cusp. In order to best characterize the dose response curve for MK-8591, assessing a dose that falls on the linear region of the efficacy-response curve relative to those already tested is critical. Establishing a clear understanding of MK-8591's dose response is essential for refining dose selection in later phase clinical studies. In order to do this, a dose of 1 mg was proposed for Panel D. Modeling & simulation experiments with available viral load and pharmacokinetic data predict that a 1 mg dose of MK-8591 will result in a Day 7 mean change from baseline reduction in viral load between 0.8-1.4log10 (see Figure 1 below). The 0.8log10 prediction exceeds the efficacy target of 0.5log10 and would outperform other NRTIs tested in previous monotherapy studies. For example, 10 days of once daily monotherapy of 300 mg TDF, the approved clinical dose, resulted in a mean Day 7 VL reduction lower than 0.8log10 and closer to 0.5log10.

The preclinical PK derived target of 0.53 pmol/10^6 cells (2.65 µM) was anticipated to provide a 0.5log10 reduction in VL. Data from Panels A-C indicate that patients who exceed this target had VL drops > 1.3log10. Therefore, we are now targeting a lower PK target to achieve the target response of 0.5log10 reduction in VL. Data from Panel B (2 mg) predict that C168 hr intracellular levels of MK-8591-TP will be ~0.096 pmol/10^6 cells (0.48 uM) after a 1 mg dose. Furthermore, a collective review of pharmacokinetic data for TDF/TAF shows that a minimum concentration of intracellular tenofovir diphosphate of 0.8-1.1 µM is associated with an ~1.0 log10 reduction in VL. The superior potency of MK-8591 to either

TAF or TDF combined with VL data from Panels A and B provide additional confidence in the decision to assess 1 mg. Viral breakthrough or the emergence of resistant mutants 7 days after dosing is not anticipated in any patient enrolled in Panel D.

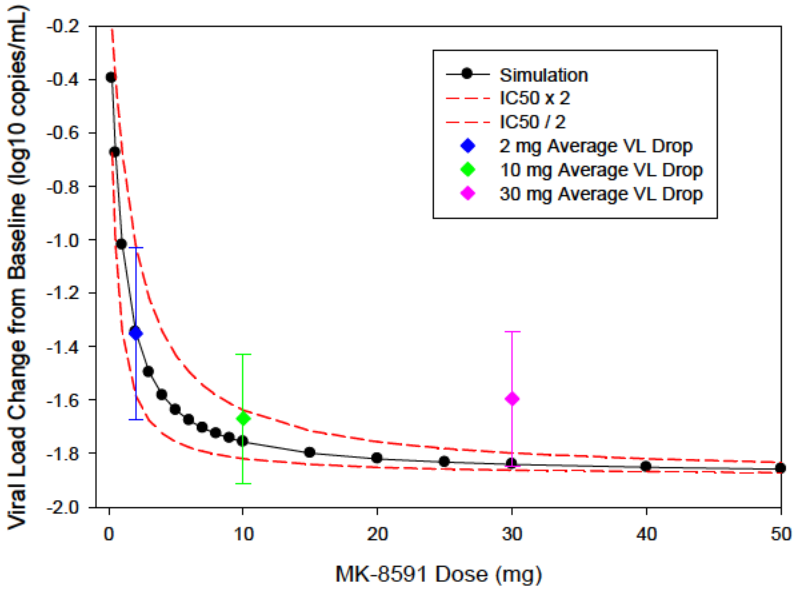

Figure 1: Simulated Viral Load Change from Baseline (log10 copies/mL) versus MK-8591 Dose predicts that a dose of 1 mg MK-8591 will result in a baseline reduction in viral load between 0.8-1.4log10

Subjects that received 1 mg of MK-8591 responded, on average, slightly better than expected based on the simulations. The average viral load reduction was 1.30 log10. The PK parameters for all 4 panels are summarized in Tables 2 and 3 below. The 1 mg patients had slightly higher than expected MK-8591 plasma and MK-8591-TP levels (AUC and Cmax) based on the 2 mg panel. These PK and viral load data were used to update the model and provide the rationale for pursuing doses lower than 1 mg.

Table 2: Summary Pharmacokinetic Parameter Values of Plasma MK-8591 Following Administration of Single Oral Doses of 1mg, 2mg, 10mg and 30mg to Anti-Retroviral Therapy (ART)-Naive, HIV-1 Infected Patients in Fasted State

Dose (mg)	Analyte	N	Geometric Mean (%GCV)			
			AUC0-∞ (hr*nM)	AUC0-last (hr*nM)	AUC0-168hr (hr*nM)	Cmax (nM)
1	MK-8591	6	88.7 (35.1)	81.4 (32)	88.3 (33.8)	38.8 (31.3)
2	MK-8591	6	157 (41.1)	128 (39.2)	143 (39.6)	43.8 (51.2)
10	MK-8591	6	1100 (17.4)	924 (16.5)	1020 (16.8)	235 (32.1)
30	MK-8591	6	3220 (24.7)	2740 (24.9)	3020 (24.6)	678 (29.6)

Table 3: Summary Pharmacokinetic Parameter Values of MK-8591 triphosphate (TP) in PBMC Following Administration of Single Oral Doses of 1mg, 2mg,10mg and 30mg to Anti-Retroviral Therapy (ART)-Naive, HIV-1 Infected Patients in Fasted State

Dose (mg)	N	Geometric Mean (%GCV)					
		AUC0-∞ (hr*pmol/10^6 cells)	AUC0-last (hr*pmol/10^6 cells)	AUC0-168hr (hr*pmol/10^6 cells)	Cmax (pmol/10^6 cells)	C168hr (pmol/10^6 cells)	Apparent Terminal t1/2 (hr)
1	**6**	60 (33.9)	56.5 (32.4)	35.9 (27.6)	0.408 (49.3)	0.164 (31.4)	118 (16.1)
2	**6**	76.2 (33)	71.9 (34.7)	46.9 (38.1)	0.495 (62.9)	0.188 (39.2)	120 (14.7)
10	**6**	445[a] (31.9)	398 (25.3)	227 (33.3)	2.81 (49.9)	0.983 (26)	128[a] (42.2)
30	**6**	1380 (40.3)	1360 (41.4)	926 (47.7)	8.9 (60.3)	4.83 (85.9)	78.5 (31.4)

[a] not calculated for one patient due to insufficient terminal phase data

Panels E and F

Following single doses of 1 mg (Panel D), 2 mg (Panel B), 10 mg (Panel A), and 30 mg (Panel C) the respective baseline corrected HIV viral load reductions at Day 7 were 1.30 log10, 1.35 log10, 1.67 log10, and 1.60 log10. As noted for Panel D, in order to best characterize the dose response curve for MK-8591, assessing a dose that falls on the linear region of the efficacy-response curve relative to those already tested is critical to establish a clear understanding of MK-8591's dose response. In order to do this, a dose of 0.5 mg will be given in Panel E and a dose of 0.25 mg will be given in Panel F upon review of available safety, PK, and PD data in Panel E. Modeling & simulation experiments with available viral load and pharmacokinetic data predict that a 0.5 mg dose of MK-8591 will result in a Day 7 mean change from baseline reduction in viral load between 0.7-1.1log10 (see Figure 2).

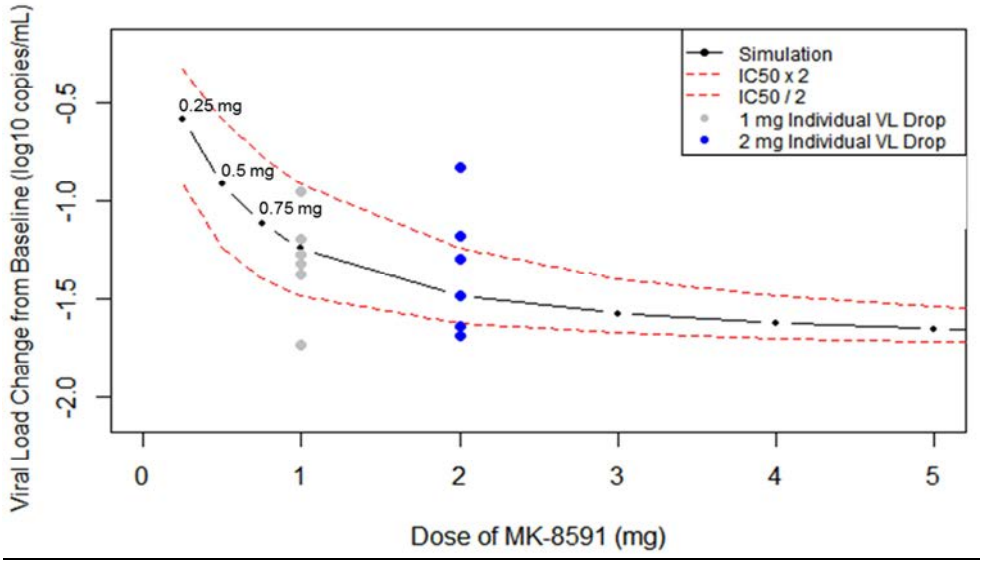

Figure 2: Simulated Viral Load Change from Baseline (log10 copies/mL) versus MK-8591 Dose predicts that a dose of 0.5 mg MK-8591 will result in a baseline reduction in viral load between 0.7-1.1log10

Panel G

Based on emerging results from the ongoing trial, in Panel G, HIV-infected subjects will be given 30 mg MK-8591 and started on ART: 1) at the "end of monotherapy" timepoint of 21 days; 2) after recrudescence of VL above the LLOD; 3) increase in VL above the nadir if this occurs after 10 days post-dose and prior to the end of monotherapy timepoint, at the discretion of the investigator.

For all Panels: As this is a Phase I assessment of MK-8591 in humans, and the pharmacokinetic, pharmacodynamic and safety profiles of the compound are still being evaluated, modifications to the dose or dosing regimen may be required to achieve the scientific goals of the trial objectives and/or to ensure appropriate safety monitoring of the trial subjects. Details of allowed modifications are provided in Section 7.1.5.5 - Trial Design/Dosing/Procedures Modifications Permitted within Protocol Parameters.

4.2.2.1 Rationale for Dose Interval and Trial Design

MK-8591, a highly potent NRTI, is not considered a compound with higher potential for risk of harm to volunteers according to the publication "Guideline on Strategies to Identify and Mitigate Risks for First-in-Human Clinical Trials with Investigational Medicinal Products" (European Medicine Agency guidance released July 2007). It is not a biological molecule, does not exhibit highly species-specific action, nor is it directed towards immune system targets. Furthermore, it acts via a well-established mechanism, allosteric inhibition of HIV-1 reverse transcriptase, for which multiple marketed agents act similarly. Safety assessment toxicity trials and ancillary pharmacology trials with MK-8591 provide no contraindications to the initiation of clinical trials in people with this compound via the oral route. Although dose-limiting toxicities were observed in preclinical rat and dog toxicity trials (described above) preclinical safety margins were obtained to allow for assessment of the doses outlined in this trial.

4.2.3 Rationale for Endpoints

4.2.3.1 Viral Pharmacodynamic Endpoints

A pharmacodynamic endpoint of a ≥0.5 log10 suppression of HIV-1 RNA from baseline on Day 7, relative to historical placebo data, will be used. This target is consistent with prior NRTI monotherapy studies and with past feedback from regulatory agencies that limit NRTI monotherapy studies to 7-10 days in duration.

Assays of HIV-1 viral RNA are well established. This study will utilize the Roche COBAS Ampliprep/COBAS TaqMan HIV-1 test v.2.0 which has a linear range from 20 to 10,000,000 copies/mL. The lower limit of detection has 100% specificity at 20 copies/mL. Additionally, the test increases the probability of detection and expands coverage by targeting two highly conserved regions of the HIV-1 genome to compensate for the possibility of mutations or mismatches. Subjects with a baseline HIV RNA load of ≥ 10,000 copies/mL will be enrolled to ensure an adequate dynamic range by which changes in HIV RNA can be quantified. Periodic blood samples will be collected to assess MK-8591 associated changes in absolute viral load over time and will be compared relative to historical placebo data. Based on the long half-life of MK-8591 triphosphate changes in viral load may be assessed through 21 days for subjects who do not initiate follow-on ART. For these patients, any viral load data that are further collected as part of patient routine follow-up may be transmitted to the sponsor, provided the subject gave appropriate consent. This extra data would only be reviewed to determine when the patient's viral load returned to baseline to provide an exploratory and preliminary understanding of MK-8591's long term effect.

Additionally, the kinetics of viral load reduction vs. dose and exposure will also be determined.

4.2.3.2 Safety Endpoints

This will be the first introduction of MK-8591 to HIV-1 infected subjects. Based on the clean preclinical toxicity profile (refer to IB) along with the preliminary safety data from Protocol 001, single doses of MK-8591 are expected to be well tolerated by subjects. To date, preclinical and clinical testing have demonstrated that MK-8591 has had no significant effects on vital sign measurements, laboratory safety studies and on measures of cardiac conduction or ventricular repolarization (including QTc). Therefore, standard safety assessment measurements will be utilized in this study.

4.2.3.3 Pharmacokinetic Endpoints

While the pharmacokinetic parameter most closely linked to NRTI efficacy has not been rigorously determined, there is a reasonable association between antiviral activities with doses that achieve a Ctrough value above the IC95 determined in the HIV spread assay (performed in 100% human serum). These PK/PD relationships have been most critically developed using an in vitro hollow-fiber assay where exposure to HIV-infected cells to an inhibitor can be carefully controlled.

One objective of this study is to evaluate the initial plasma and intracellular triphosphate PK profile of MK-8591 in HIV-1 infected males and females. This study will establish if the anticipated target concentration can be achieved safely following single doses of MK-8591 to HIV-1 infected subjects. Preclinical studies in rhesus monkeys showed that antiviral efficacy of MK-8591 is related to the trough concentration (C_{trough}) of the active triphosphate moiety in PBMCs, rather than in plasma. PK/PD modeling was performed and predicted a target a geometric mean intracellular C_{168hr} (i.e., C_{trough} for weekly dosing) of 1.1 pmol/10^6 cells (90% CI: 0.53 - 2.5).

To account for the overall uncertainty in the translation of the PK/PD relationship from monkeys to humans the lower bound of the 90% CI (0.53 pmol/10^6 cells) is the MK-8591 PK target. For the PK assessment, active triphosphate in PBMCs may be determined for up to 21 days following single dose administration. Plasma concentrations of unchanged MK-8591 will be determined for up to 7 days. To evaluate the excretion of MK- 8591 by the kidneys, urine will also be collected for potential determination of MK-8591 concentrations.

This study will establish whether achieving the efficacy target is associated with a commensurate viral load reduction worthy of continued clinical development. Hence, assessment of this primary pharmacokinetic parameter will be conducted 7 days after administration of the MK-8591 dose. Additional assessments beyond 7 days (e.g., 14 or 21 days) may be also be performed.

4.2.3.4 Future Biomedical Research

The Sponsor will conduct Future Biomedical Research on specimens routinely and specifically 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.

4.3 Benefit/Risk

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

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

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male/Female subjects with HIV-1 infection who are naïve to ART between the ages of 18 and 60 years (inclusive) 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. Provide written informed consent. The subject may also provide consent/assent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.

2. Be a male or non-pregnant and non-breast feeding female, 18 to 60 years of age at the pretrial (screening) visit; further:

    a. if female with reproductive potential: subject must demonstrate a serum β-human chorionic gonadotropin (β –hCG) level consistent with the nongravid state at the pretrial (screening) visit and agree to use (and/or have their partner use) two (2) acceptable methods of birth control beginning at the pretrial (screening) visit, throughout the trial and until the post-trial visit. Acceptable methods of birth control are defined in Section 5.7.2.5.1

    b. if postmenopausal female: subject is without menses for at least 1 year and have a documented follicle stimulating hormone (FSH) level in the postmenopausal range at pretrial (screening),

    AND/OR

    c. if surgically sterile female: subject is status post hysterectomy, oophorectomy, or tubal ligation.

    d. NOTE: These procedures must be confirmed with medical records. In the absence of documentation, hysterectomy may be confirmed by pelvic exam or if necessary by ultrasound; oophorectomy may be confirmed by hormone levels, particularly FSH in the post-menopausal range, but tubal ligation subjects without records should be excluded. Information must be captured appropriately within the site's source documents

    e. Male subjects with female partner(s) of childbearing potential must agree to use a medically acceptable method of contraception (refer to Section 5.7.2.5.1) during the study and for 90 days after the last dose of trial drug. **Males** should use a condom **and their partner**, if of child-bearing potential, must additionally be using one of the following methods: hormonal contraception, intrauterine device, diaphragm, or cervical cap. Males should use a condom if their partner is pregnant.

3. Have a Body Mass Index (BMI) $\leq$35 kg/m^2. BMI = weight(kg)/height (m$^)2$.

4. Other than HIV infection, have baseline health judged to be stable based on medical history, physical examination, vital sign measurements, and laboratory safety test(see Section 7.1.3) performed at the prestudy (screening) visit and/or prior to administration of the initial dose of study drug.

5. Have no clinically significant abnormality on the electrocardiogram (ECG) performed at the prestudy (screening) visit and/or prior to administration of the initial dose of study drug.

6. Be documented HIV-1 positive as determined by a positive ELISA or QT-PCR with confirmation (e.g., Western Blot).

7. Have a screening plasma $CD4^+$ T-cell count of >200/$mm^{3.}$

8. Have a screening plasma HIV-1 RNA ≥ 10,000 copies/mL within 30 days prior to the treatment phase of this study. For inclusion in Panel G, subjects must also have a screening plasma HIV-1 RNA ≤ 25,000 copies/mL within 30 days prior to the treatment phase.

9. Be ART-naïve which is defined as having never received any antiretroviral agent **OR** the following:

   ≤30 consecutive days of an investigational antiretroviral agent, excluding an NRTI,

   OR

   ≤60 consecutive days of combination ART not including an NRTI

10. Have not received an investigational agent or marketed ART within 30 days of study drug administration.

11. Be diagnosed with HIV-1 infection ≥ 3 months prior to screening.

12. Be willing to receive no other ART for the duration of the treatment phase of this study.

13. Have no evidence at screening for mutations conferring resistance to NRTIs (e.g., M184V, M184I, etc.) as previously defined [1].

14. Have the following laboratory values at screening as defined by Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events ("DAIDS AE grading table" see attached document in Appendix 12.5) and in accordance with the normal ranges of the clinical laboratory:

    a. INR ≤ 1.6

    b. Hemoglobin ≥ 10.0 g/dL

c. Absolute neutrophil count ≥ 1000/mm3

d. Platelet count ≥ 100,000/mm3

e. Direct bilirubin ≤ 1.0 mg/dL

f. Alkaline phosphatase ≤ 1.5 x upper limit of normal

g. AST (SGOT) and ALT (SGPT) ≤ 2 x upper limit of normal

15. Be willing to comply with the trial restrictions (see Section 5.7 for a complete summary of trial restrictions).

5.1.3 Subject Exclusion Criteria

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

1. Is under the age of legal consent.

2. Is mentally or legally institutionalized / incapacitated, has significant emotional problems at the time of pretrial (screening) visit or expected during the conduct of the trial or has a history of clinically significant psychiatric disorder of the last 5 years. Subjects who have had situational depression may be enrolled in the trial at the discretion of the investigator.

3. Has a history of clinically significant endocrine, gastrointestinal, cardiovascular, hematological, hepatic, immunological (outside of HIV-1 infection), renal, respiratory, genitourinary or major neurological (including stroke and chronic seizures) abnormalities or diseases. Subjects with a history of uncomplicated kidney stones, as defined as spontaneous passage and no recurrence in the last 5 years, or childhood asthma may be enrolled in the trial at the discretion of the investigator.

4. Has a history of cancer (malignancy).

   Exceptions: (1) Subjects with adequately treated non-melanomatous skin carcinoma or carcinoma in situ of the cervix may participate in the trial; (2) Subjects with other malignancies which have been successfully treated ≥10 years prior to the pretrial (screening) visit where, in the judgment of both the investigator and treating physician, appropriate follow-up has revealed no evidence of recurrence from the time of treatment through the time of the pretrial (screening) visit (except those cancers identified at the beginning of exclusion criterion 4); or, (3) Subjects, who, in the opinion of the trial investigator, are highly unlikely to sustain a recurrence for the duration of the trial.

5. Has a history of significant multiple and/or severe allergies (e.g. food, drug, latex allergy), or has had an anaphylactic reaction or significant intolerability to prescription or non-prescription drugs or food.

6. Is positive for hepatitis B surface antigen

7. Patient has a history of chronic Hepatitis C unless there has been documented cure and/or patient with a positive serologic test for HCV has a negative HCV viral load

8. Had major surgery, donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks prior to the pretrial (screening) visit.

9. Has participated in another investigational trial within 4 weeks or 5 half-lives whichever is greater prior to the Day 1 Dosing visit. The 4 week window will be derived from the date of the last trial medication and / or blood collection in a previous trial and/or AE related to trial drug to the Day 1 Dosing visit of the current trial.

10. Is unable to refrain from or anticipates the use of any medication, including prescription and non-prescription drugs or herbal remedies beginning approximately 2 weeks (or 5 half-lives) prior to administration of the initial dose of trial drug, throughout the trial, until the post-trial visit. There may be certain medications that are permitted, see Section 5.5.

11. Consumes greater than 3 glasses of alcoholic beverages (1 glass is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce]) per day. Subjects who consume 4 glasses of alcoholic beverages per day may be enrolled at the discretion of the investigator.

12. Consumes excessive amounts, defined as greater than 6 servings (1 serving is approximately equivalent to 120 mg of caffeine) of coffee, tea, cola, energy-drinks, or other caffeinated beverages per day.

13. Is an excessive smoker (i.e., more than 10 cigarettes/day) and is unwilling to restrict smoking to ≤10 cigarettes per day.

14. Is currently a regular user of any illicit drugs (excluding cannabis) or has a history of drug (including alcohol) abuse within approximately 2 years.

15. Is any concern to the investigator regarding the safe participation of the subject in the trial or if, for any other reason; the investigator considers the subject inappropriate for participation in the trial (e.g. prior NRTI exposure).

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

5.2 Trial Treatment(s)

The treatment to be used in this trial is outlined below in Table 4.

Table 4 Trial Treatment

Panel	Subjects	Dose/Potency	Dose Frequency	Route of Administration
A	N=6	10 mg	Single Dose	Oral
B	N=6	2 mg	Single Dose	Oral
C	N=6	30 mg	Single Dose	Oral
D	N=6	1 mg	Single Dose	Oral
E	N=6	0.5 mg	Single Dose	Oral
F	N=6	0.25 mg	Single Dose	Oral
G	N=6	30 mg	Single Dose	Oral

Trial treatment should begin on the day of randomization or as close as possible to the date on which the subject is allocated/assigned.

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/Modification

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 (Escalation/Titration/Other)

Dose selection will be based on key safety variables including, vital signs, 12-lead ECG, laboratory safety tests, adverse events from the previous dose levels up to at least 24 hours (or longer depending on the compound). Pharmacokinetic and pharmacodynamic data may be included in the dose escalation decisions. See Background & Rationale - Section 4.0.

If, as judged by the Sponsor and principal investigator, the safety and tolerability data do not justify dose escalation, the dose will not be increased as planned. Instead, subjects may:

- receive the same dose level to further explore safety and tolerability at that level;
- receive a lower dose of the trial drug;
- receive the same or lower dose as a divided dose; or
- receive a lower dose with or without food.

Or, dosing may be stopped. Subject discontinuation criteria are outlined in Section 5.8.

Prior to each treatment, the clinical and laboratory safety parameters from the previous dose level will be reviewed by the principal investigator and discussed with the Sponsor to permit a decision on whether to advance to the next higher dose level. No dose escalation will occur without the joint agreement of the principal investigator and the Sponsor.

5.2.2 Trial Blinding/Masking

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

5.3 Randomization or Allocation

Subjects will be assigned randomly according to a computer-generated allocation schedule (Table 5).

Table 5 Sample Allocation Schedule

Subjects	Panel A	Panel B	Panel C	Panel D	Panel E	Panel F	Panel G
N=6	10 mg	2 mg	30 mg	1 mg	0.5 mg	0.25 mg	30 mg
Subjects will only participate in one Panel.							

5.4 Stratification

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

5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

If a subject does not discontinue all prior medications within 14 days or 5 half-lives of starting the trial, he/she may be included in the study if the investigator can rationalize that the specific use of a prior medication is not clinically relevant within the context of the trial.

Concurrent use of any prescription or non-prescription medication, or concurrent vaccination, during the course of the trial (i.e., after randomization or treatment allocation) must first be discussed between the investigator and Sponsor prior to administration, unless appropriate medical care necessitates that therapy or vaccination should begin before the investigator and Sponsor can consult. The subject will be allowed to continue in the trial if both the Sponsor and the investigator agree.

Paracetamol/acetaminophen may be used for minor ailments without prior consultation with the Sponsor Clinical Director.

5.6 Rescue Medications & Supportive Care

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

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

Subjects will fast from all food and drinks, except water, for at least 8 hours prior to trial drug administration (and laboratory safety tests). Subjects will fast from all food and drinks except water between trial drug administration and the first scheduled meal. Meals and snack(s) will be provided by the investigator at timepoints indicated in the trial flowchart. Subjects will fast from all food and drinks except water between meals and snacks. The caloric content and composition of meals will be the same for all subjects. After the 24-hour postdose procedures have been completed, subsequent meals and snacks will be unrestricted in caloric content, composition and timing.

Water will be provided during trial drug administration. Water will be restricted 1 hour prior to and 1 hour after trial drug administration.

Instructions on whether to take MK-8591 with or without food and/or drink may be modified during the trial based on newly available data.

5.7.2 Alcohol, Caffeine, Tobacco, Activity

5.7.2.1 Alcohol Restrictions

Subjects will refrain from consumption of alcohol 24 hours prior to the pre- and post-trial visits and from 24 hours prior to and after trial drug administration. At all other times, alcohol consumption is limited to no more than approximately 3 alcoholic beverages or equivalent (1 glass is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce]) per day.

5.7.2.2 Caffeine Restrictions

Subjects will refrain from consumption of caffeinated beverages from 12 hours prior to and after trial drug administration. At all other times, caffeinated beverages or xanthine-containing products will be limited to no more than 6 units per day amounts (>6 units: 1 unit=120 mg of caffeine).

5.7.2.3 Smoking Restrictions

Smoking should be limited to ≤ 10 cigarettes per day and follow the smoking restrictions defined by the CRU while on site.

5.7.2.4 Activity Restrictions

Subjects will avoid unaccustomed strenuous physical activity (i.e., weight lifting, running, bicycling, etc.) from the pre-trial (screening) visit until the post-trial visit.

5.7.2.5 Contraception and Pregnancy Testing

5.7.2.5.1 Contraception

Women of childbearing potential can be enrolled. However, two (2) acceptable methods of barrier contraception must be used beginning at the pretrial visit, throughout the trial and until 4 weeks after the last dose of trial drug in the last treatment period. Acceptable methods of birth control are two (2) of the following: intrauterine device (IUD-with or without local hormone release), diaphragm, spermicides, cervical cap, contraceptive sponge, and/or condoms. Abstinence is an alternative life style and subjects practicing abstinence may be included in the trial.

Oral contraceptives are not allowed as a method of birth control in this trial.

Subjects must be completely informed of the unknown risks of pregnancy and agree not to become pregnant during the time they are participating in this trial.

If there is any question that a subject will not be reliable in the use of appropriate contraceptive methods, they should not be entered into the trial.

5.7.2.5.2 Pregnancy Testing

Female subjects of childbearing potential will be tested for serum β-human chorionic gonadotropin (hCG) at pretrial, for urine and/or serum β-human chorionic gonadotropin (hCG) predose and at the last trial visit. In the case of a positive or borderline serum β-hCG pregnancy test at the pretrial visit, the subject must not enter the trial; in the case of a positive or borderline serum β-hCG pregnancy test during the trial, the pregnancy test should be repeated and confirmed positive. If the pregnancy has been confirmed the subject must be discontinued from the trial immediately and the pregnancy must be reported the Sponsor as outlined in Section 7.2.2.

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.

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

- The subject withdraws consent.
- 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.

5.8.1 Timing of Dose Administration

Subjects will receive a single dose of MK-8591. The dose will be given in the morning. The trial treatment will be administered in the fasted state with approximately 240mL water. Instructions on whether to take MK-8591 with or without food and/or drink may be modified during the study based on newly available data.

5.9 Subject Replacement Strategy

If a subject discontinues from the trial, a replacement subject may be enrolled if deemed appropriate by the investigator and Sponsor. The replacement subject will generally receive the same treatment or treatment sequence (as appropriate) as the subject being replaced. The replacement subject will be assigned a unique treatment/randomization number. The trial site should contact the Sponsor for the replacement subject's treatment/randomization number.

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

A trial may be paused during review of newly available preclinical/clinical safety, pharmacokinetic, pharmacodynamic, efficacy or biologic data or other items of interest, prior to a final decision on continuation or termination of the trial. It may be necessary to keep the trial open for gathering/reviewing of additional supportive data to optimally complete the objective(s) of the trial. If necessary, the appropriate amendment(s) to the protocol and/or appropriate communication(s) will be generated. The overall trial end will then not be identified until the Sponsor has made the decision to end the trial following this review period. The Competent Authority(ies) and Institutional Review Board(s)/Independent Ethics Committee(s) [IRB(s)/IEC(s)] will be appraised of the maximum duration of the trial beyond the last subject out and the justification for keeping the trial open.

5.11 Clinical Criteria for Early Trial Termination

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

A primary objective of this early Phase I trial is to identify the maximum safe and well-tolerated dose and/or dosing regimen that achieve pharmacokinetic, pharmacodynamic and/or biologic targets in humans based on preclinical or early clinical data. Therefore, it is possible that trial subjects may not receive all doses specified in the protocol if this objective is achieved at lesser dose levels in this trial. This would not be defined as early termination of the trial, but rather an earlier than anticipated achievement of the trial objective(s). If a finding (e.g., pharmacokinetic, pharmacodynamic, efficacy, biologic targets, etc.) from another preclinical or clinical trial using the trial treatment(s), comparator(s), drug(s) of the same class, or methodology(ies) used in this trial, results in the trial(s) or program being stopped for non-safety reasons, this also does not meet the definition of early trial termination.

Early trial termination is defined as a permanent discontinuation of the trial due to unanticipated concerns of safety to the trial subjects arising from clinical or preclinical trials with the trial treatment(s), comparator(s), drug(s) of the same class or methodology(ies) used in this trial.

Enrollment of the trial will be halted in the following circumstances:

1. Two (2) subjects per panel report severe adverse events with a potential causal relationship to study drug.

2. Three (3) or more of the enrolled subjects experience the same adverse event requiring withdrawal from the study, or the same severe adverse event assessed as having a potential causal relationship to study drug.

3. Two (2) severe but not life threatening adverse experiences or severe clinically significant laboratory abnormalities that are similar in nature OR one (1) severe and life threatening adverse experience laboratory abnormality OR participant death thought to be potentially related to the investigational product.

4. Two (2) or more of the enrolled subjects experience confirmed QTcB > 500 ms or QTcB change from baseline >60ms in a given panel.

If one or more of the above conditions are met, enrollment will be halted and all available safety data will be reviewed prior to making a decision about terminating the study. The safety of subjects will be assessed on an ongoing basis, and while conditions that could warrant early trial termination are not limited to those noted above, these criteria are meant to pre-specify circumstances under which the trial may be terminated early.

6.0 TRIAL FLOW CHART

Panels A, B, C, D, E, and F [a]																				
	Scheduled Time																			
				Hours Postdose																
	Prestudy	Pre-dose	0	0.25	0.5	1	2	4	6	8	12	24	48	96	120	144	168	240	336	Post-trial[m]
Administrative Procedures																				
Informed Consent	X																			
Informed Consent for Future Biomedical Research[b]	X																			
Inclusion/Exclusion Criteria	X																			
Subject Identification Card	X																			
Medical History	X																			
Prior/Concomitant Medication Review	X	X----------										-X								
Clinic Procedures/Assessments																				
Full Physical Examination	X	X[c]															X			X
Height	X																			
Weight	X																			
12-Lead Electrocardiogram[d]	X	X				X						X					X			X
Vital Signs (heart rate, blood pressure)[e]	X	X				X						X					X			X
Orthostatic Vital Signs (heart rate, blood pressure)[e]	X	X				X						X					X			X
Vital Signs (respiratory rate, oral/tympanic temperature)	X	X				X						X					X			X
Standard Meals[f]						X----------						X								
MK-8591 Administration			X																	
Adverse Events Monitoring		X----------																		-X
Laboratory Procedures/Assessments																				
Hematology	X	X[g]										X					X			X
Urinalysis	X	X[g]										X					X			X
Chemistry	X	X[g]										X					X			X
Urine /Serum β-Human Chorionic Gonadotropin (β-hCG)[h]	X	X[g]																		X
Serum FSH[i]	X																			
Urine/Blood Drug Screen	X																			
HIV/Hepatitis Screen	X																			
Blood for Future Biomedical Research[b]		X																		
Pharmacokinetic/Pharmacodynamic Evaluations																				
Blood for Plasma MK-8591 Assay[j]		X		X	X	X	X	X		X	X	X	X	X						
Blood for MK-8591 PBMC Assay[n o]								X			X	X		X	X	X	X	X	X	X

Panels A, B, C, D, E, and F [a]																				
	Scheduled Time																			
				Hours Postdose																
	Prestudy	Pre-dose	0	0.25	0.5	1	2	4	6	8	12	24	48	96	120	144	168	240	336	Post-trial[m]
Urine for MK-8591 Assay[k]		X		X----------								X								
Blood for HIV RNA, viral resistance[l o]	X	X						X				X		X	X	X	X	X	X	X
CD-4 cell count	X																			

a. Panel C will occur after completion and review of safety, pharmacokinetic, and viral dynamic data from Panels A and B. Panel D will occur after completion and review of safety, pharmacokinetic, and viral dynamic data from Panel C. Panels E and F will occur after completion and review of safety, pharmacokinetic and viral dynamic data from Panels D and E, respectively.
b. Informed consent for future biomedical research samples must be obtained before the FBR sample. FBR sample for analysis should be obtained on Day 1 (or with the next scheduled blood draw), as the last sample drawn, on randomized subjects only, if the subject agrees to participate in the FBR sub-study.
c. The pre-dose PE may be performed within 24 hour prior to dosing.
d. Pre-dose ECG will be performed within 2 hours prior to study drug administration and will consist of 3 repeat measurements with at least 1 minute intervals between ECG measurements. Recording may commence after the subject has remained in a semi-recumbent position for at least 10 minutes. (See Section 7.1.2 for additional details).
e. Pre-dose semi-recumbent HR and BP will be duplicate measurements obtained at least 1-2 minutes apart. Subjects should be resting in the semi-recumbent position for 10 minutes prior to obtaining HR and BP. Following duplicate measurements of the semi-recumbent HR and BP subjects assume a standing position for 2 minutes and then orthostatic HR and BP will be obtained. See Section 7.1.2 for additional details.
f. Standardized meals will be provided at ~4 and ~10 hours post-dose. A snack will be offered at ~ 7 and 13 hours post-dose. After the 24 hour postdose procedures have been completed, subsequent meal and snacks will be unrestricted in terms of caloric content, composition and timing.
g. Can be conducted on admission (within 24 hours of dosing).
h. For female subjects of childbearing potential only. Urine pregnancy test can be performed at predose.
i. For postmenopausal women only
j. Leftover plasma samples will be stored for future biomedical research at the end of the study, if the subject signs the Future Biomedical Research consent.
k. Urine samples for MK-8591 assay will be collected and archived. Urine will be collected pre-dose and during the 0-24 interval postdose.
l. For all panels blood for HIV-1 viral RNA and viral resistance may be collected up to the post-trial visit if subjects do not start ART.
m. The post-trial visit will occur approximately 21 days following administration of the study drug. Follow up for any clinical or laboratory adverse experiences should occur by phone or in person if the post-trial visit occurs prior to 21 days following the last dose of study drug. For confirmation of viral load return to baseline, additional data from viral load samples collected during routine follow-up visits may be transmitted to the sponsor for those patients who do not begin ART and who provide appropriate informed consent.
n. For all panels PBMC samples may be collected up to the post-trial visit regardless of initiation of ART.
o. For blood collection at 120, 144, 168, 240, and 336 hour timepoints, a window of +/- 4 hrs is acceptable. The 504 hour sample may be collected at the post-trial visit.

Panel G [a]																					
	Scheduled Time																				
			Hours Postdose																		
	Prestudy	Pre-dose	0	0.25	0.5	1	2	4	6	8	12	24	48	96	120	144	168	240	336	408	456	Post-trial[l] [n]
Administrative Procedures																						
Informed Consent	X																					
Informed Consent for Future Biomedical Research[b]	X																					
Inclusion/Exclusion Criteria	X																					
Subject Identification Card	X																					
Medical History	X																					
Prior/Concomitant Medication Review	X	X----------																				----------X
Clinic Procedures/Assessments																						
Full Physical Examination	X	X[c]															X					X
Height	X																					
Weight	X																					
12-Lead Electrocardiogram[d]	X	X				X						X					X					X
Vital Signs (heart rate, blood pressure)[e]	X	X				X						X					X					X
Orthostatic Vital Signs (heart rate, blood pressure)[e]	X	X				X						X					X					X
Vital Signs (respiratory rate, oral/tympanic temperature)	X	X				X						X					X					X
Standard Meals[f]						X----------						X										
MK-8591 Administration			X																			
Adverse Events Monitoring		X----------																				----------X
Laboratory Procedures/Assessments																						
Hematology	X	X[g]										X					X					X
Urinalysis	X	X[g]										X					X					X
Chemistry	X	X[g]										X					X					X
Urine /Serum β-Human Chorionic Gonadotropin (β-hCG)[h]	X	X[g]																				X
Serum FSH[i]	X																					
Urine/Blood Drug Screen	X																					
HIV/Hepatitis Screen	X																					
Blood for Future Biomedical Research[b]		X																				
Pharmacokinetic/Pharmacodynamic Evaluations																						
Blood for Plasma MK-8591 Assay[j]		X		X	X	X	X	X		X	X	X	X	X								

Panel G [a]																						
	Scheduled Time																					
				Hours Postdose																		
	Prestudy	Pre-dose	0	0.25	0.5	1	2	4	6	8	12	24	48	96	120	144	168	240	336	408	456	Post-trial[l, n]
Blood for MK-8591 PBMC Assay[m]								X			X	X		X	X	X	X	X	X	X	X	X
Urine for MK-8591 Assay[k]		X		X----------X																		
Blood for HIV RNA, viral resistance[m, o]	X	X						X				X		X	X	X	X	X	X[o]	X[o]	X[o]	X[o]
CD-4 cell count	X																					X

a. Panel G will occur after completion and review of safety, pharmacokinetic, and viral dynamic data from Panels A-D.
b. Informed consent for future biomedical research samples must be obtained before the FBR sample. FBR sample for analysis should be obtained on Day 1 (or with the next scheduled blood draw), as the last sample drawn, on randomized subjects only, if the subject agrees to participate in the FBR sub-study.
c. The pre-dose PE may be performed within 24 hour prior to dosing.
d. Pre-dose ECG will be performed within 2 hours prior to study drug administration and will consist of 3 repeat measurements with at least 1 minute intervals between ECG measurements. Recording may commence after the subject has remained in a semi-recumbent position for at least 10 minutes. (See Section 7.1.2 for additional details).
e. Pre-dose semi-recumbent HR and BP will be duplicate measurements obtained at least 1-2 minutes apart. Subjects should be resting in the semi-recumbent position for 10 minutes prior to obtaining HR and BP. Following duplicate measurements of the semi-recumbent HR and BP subjects assume a standing position for 2 minutes and then orthostatic HR and BP will be obtained. See Section 7.1.2 for additional details.
f. Standardized meals will be provided at ~4 and ~10 hours post-dose. A snack will be offered at ~ 7 and 13 hours post-dose. After the 24 hour postdose procedures have been completed, subsequent meal and snacks will be unrestricted in terms of caloric content, composition and timing.
g. Can be conducted on admission (within 24 hours of dosing).
h. For female subjects of childbearing potential only. Urine pregnancy test can be performed at predose.
i. For postmenopausal women only
j. Leftover plasma samples will be stored for future biomedical research at the end of the study, if the subject signs the Future Biomedical Research consent.
k. Urine samples for MK-8591 assay will be collected and archived. Urine will be collected pre-dose and during the 0-24 interval postdose.
l. The post-trial visit will occur approximately 21 days following administration of the study drug. Follow up for any clinical or laboratory adverse experiences should occur by phone or in person if the post-trial visit occurs prior to 21 days following the last dose of study drug. For confirmation of viral load return to baseline, additional data from viral load samples collected during routine follow-up visits may be transmitted to the sponsor for those patients who do not wish to begin ART and who provide appropriate informed consent.
m. For blood collection at 120, 144, 168, 240, 336 and 408, and 456 hour timepoints, a window of +/- 4 hrs is acceptable. The 504 hour sample may be collected at the post-trial visit.
n. If HIV-1 RNA levels remain below the lower limit of detection (LLOD) at the post-trial visit (VL as determined at 456 hours postdose), subjects will withhold from ART initiation and followed closely, additional semiweekly assessment of two measurements of VL/timepoint beyond the post-trial visit until levels go above the LLOD, at which point ART will be initiated.
o. For HIV-1 RNA blood samples taken at 336, 408, 456, and 504 (post-trial visit) hours post dose, two samples will be taken per timepoint.

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 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 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 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.

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.

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.

7.1.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee.

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, including any protocol-specified washout requirement, and record prior medication taken by the subject within 28 days before starting the trial.

7.1.1.5.2 Concomitant Medications

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

7.1.1.6 Assignment of Screening Number

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

7.1.1.7 Assignment of Treatment/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)

Administration of trial medication will be witnessed by the investigator and/or trial staff.

7.1.2 Clinical Procedures/Assessments

Physical Exam:

The physical exam assessments will be defined and conducted per the site SOP.

Body Weight and Height

Body weight and height will be obtained with the patient's shoes off, jacket or coat removed.

Body Mass Index (BMI)

BMI equals a person's weight in kilograms divided by height in meters squared. (BMI=kg/m2).

12-Lead ECG

Special care must be taken for proper lead placement by qualified personnel. Skin should be clean and dry prior to lead placement. Subjects may need to be shaved to ensure proper lead placement. Female subjects may need to remove interfering undergarments.

Subjects should be resting in the semi-recumbent position for at least 10 minutes prior to each ECG measurement. The position during ECG collection should be consistent throughout the study.

The correction formula to be used for QTc is Bazett's.

If repeat ECGs are required the clinical site will decide whether to leave the electrodes in place or mark the position of the electrodes for subsequent ECGs. To mark the position of the electrodes, 12-lead electrode sites will be marked on the skin of each subject with an ECG skin marker pen to ensure reproducible electrode placement.

Prior to dose, ECGs will be obtained in triplicate at least 1-2 minutes apart within 1-2 hours prior to dosing MK-8591. The average of these measurements will be used as the baseline. Post-dose ECG measurements will be single measurements.

If a patient demonstrates an increase in QTc interval ≥60 msec compared with mean predose baseline measurement, the ECG will be repeated twice within 5 minutes. The average value of the QTc interval from the 3 ECGs will represent the value at that time point. If the average QTc interval increase from baseline for any postdose time point is ≥60 msec, the patient will continue to be monitored by repeat 12-lead ECGs every 15 minutes for at least 1 hour or until the QTc is within 60 msec of baseline. If prolongation of the QTc interval ≥60 msec persists, a consultation with a study cardiologist may be appropriate and the Sponsor should be notified.

If the QTc interval is ≥500 msec, the Sponsor should be notified and the ECGs should be reviewed by a cardiologist. The patient should be telemetry-monitored (until the QTc is <500 msec) or should be considered for transfer to a location where closer monitoring and definitive care (e.g., a Cardiac or Intensive Care Unit) is available.

If the patient has unstable hemodynamics, or has any clinically significant dysrhythmias noted on telemetry, the subject should be immediately transferred to an acute care setting for definitive therapy.

If prolongation of the QTc is noted, concomitant medications that prolong QTc should be held until the QTc is within 60 msec of baseline and the QTc is <500 msec.

A study cardiologist should be arranged by the Principal Investigator to be available as needed to review ECG tracings with abnormalities.

Body Temperature

Body temperature will be measured with an oral, temporal artery, or tympanic thermometer. The same method must be used for all measurements for each individual subject and should be the same for all subjects.

Vital Sign Measurements (Heart Rate and Blood Pressure)

Subjects should be resting in a semi-recumbent position for at least 10 minutes prior to having vital sign measurements obtained. Semi-recumbent signs will include heart rate (HR) and blood pressure (BP). The correct size of the blood pressure cuff and the correct positioning on the pateints' arm is essential to increase the accuracy of blood pressure measurements. The same method (e.g., manual or automated) must be used for all measurements for each individual subject and should be same for all subjects.

Prior to dosing, HR and BP will be duplicate measurements obtained at least 1-2 minutes apart within 2 hrs of dosing MK-8591. The average of these measurements will be used as the baseline. Post-dose vital sign measurements will be single measurements.

Orthostatic vital signs (HR and BP) will also be obtained. Subjects should be semi-recumbent for at least 10 minutes and then stand upright for 2 minutes prior to measurement of orthostatic vital signs.

Subjects will continue to rest semi-recumbent from dosing until 4 hours postdose except to stand for the measurement of orthostatic vital signs or other trial related procedure. Predose vital signs can be obtained up to 2 hours prior to dosing.

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 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry and urinalysis are specified in Table 6.

Table 6 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Glucose	Hepatitis B surface antigen,
Hemoglobin	Alkaline phosphatase	Protein	Hepatitis C antibodies
Platelet count	Alanine aminotransferase (ALT)	RBC	HIV-1 RNA (prestudy) Plasma for HIV genotype (resistance testing)
WBC:total and differentials including: Absolute neutrophils Absolute Lymphocytes Absolute Monocytes Absolute Eosinophils Absolute Basophils	Aspartate aminotransferase (AST)	WBC	Urine/blood Drug Screen
	Bicarbonate	Microscopic exam, if abnormal results are noted	Follicle Stimulating Hormone (FSH)
	Calcium		Urine / Serum β-hCG
	Chloride		CD4 T cell count at screening for all Panels and post-trial for Panel G only
	Creatinine		INR at screening
	Glucose		
	Lactic Acid		
	Phosphorus		
	Potassium		
	Sodium		
	Total Bilirubin		
	Direct Bilirubin		
	Total protein		
	Urea		

Laboratory safety tests will be performed after at least an 8-hour fast. Pre-dose laboratory procedures can be conducted up to 24 hours prior to dosing.

7.1.3.2 Pharmacokinetic/Pharmacodynamic Evaluations

The decision as to which plasma and/or urine samples collected will be assayed for evaluation of pharmacokinetics/pharmacodynamics will be collaboratively determined by the Departments of Pharmacokinetics, Pharmacodynamics & Drug Metabolism and the appropriate department within Early-Stage Development, (e.g., samples at lower doses may not be assayed if samples at higher doses reveal undetectable drug concentrations). If indicated, these samples may also be assayed and/or pooled for assay in an exploratory manner for metabolites and/or additional pharmacodynamic markers.

7.1.3.2.1 Blood Collection for Plasma MK-8591

Sample collection, storage and shipment instructions for plasma samples will be provided in a Study Specific Procedure Manual.

7.1.3.2.2 Urine Collection for Urinary MK-8591

Sample collection, storage and shipment instructions for urine samples will be provided in a Study Specific Procedure Manual.

7.1.3.3 Blood Collection for PBMC

Sample collection and processing for PBMC samples will be provided in a Study Specific Procedure Manual.

7.1.3.4 Future Biomedical Research

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

- Blood for genomics use
- Leftover main study plasma for future use

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

The investigator or trial coordinator must notify the Sponsor when a subject has been discontinued/withdrawn from the trial. If a subject discontinues for any reason at any time during the course of the trial, the subject may be asked to return to the clinic (or be contacted) for a post-trial visit (approximately 21 days after the last dose of trial drug is given) to have the applicable procedures conducted. However, the investigator may decide to perform the post-trial procedures at the time of discontinuation or as soon as possible after discontinuation. If the post-trial visit occurs prior to 21 days after the last dose of trial drug is given, the investigator should perform a follow-up phone call 21 days after the last dose of trial drug to determine if any adverse events have occurred since the post-trial clinic visit. 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 ([redacted] 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 Domiciling

Subjects will report to the clinical research unit (CRU) the evening prior to the scheduled day of trial drug administration and will remain in the unit until 24 hours post-dose. At the discretion of the investigator, subjects may be requested to remain in the CRU longer.

7.1.4.4 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:

Vital sign and ECG machines

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

Approximately 4 weeks prior to randomization, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1. Screening procedures may be repeated after consultation with the Sponsor.

7.1.5.2 Treatment Period/Vaccination Visit

7.1.5.2.1 Predose Procedures (All Panels)

Prior to each treatment, the clinical and laboratory safety parameters from the previous dose level and previous treatment panel will be reviewed by the Investigator and the Clinical Team and a mutual decision on whether to advance to the next higher dose level will be made. No dose escalation will occur without agreement of the Investigator and the SPONSOR.

Subjects will report to the CRU the day prior to the scheduled day of administration of the study drug or time specified by the investigator. Subjects will fast from all food and drink, except for water, for a minimum of 8 hours prior to study drug administration and prior to obtaining samples for laboratory safety tests (refer to Section 5.7.1.1).

After the Day 1 predose procedures have been completed, subjects will be assigned a unique randomization/allocation number associated with a specific treatment sequence as defined by a computer-generated allocation schedule. For details on procedures, please refer to the Study Flow Chart (Section 6.0), Procedures (Section 7.1.2) and/or corresponding appendices.

7.1.5.2.2 Treatment Procedures (All Panels)

Procedures for study drug administration and postdose procedures are listed in the Study Flow Chart, Section 6.0 of this protocol.

Subjects will be administered a single dose of MK-8591 in the morning. The exact clock time of dosing should be recorded.

7.1.5.3 Post-Trial

Post-trial procedures are listed in the Study Flow Chart, Section 6.0 of this protocol.

Subjects will be required to return to clinic approximately 21 days after the last dose of trial drug for the post-trial visit. If the post-trial visit occurs less than 21 days after the last dose of trial drug, a subsequent follow-up phone call should be made at 21 days post the last dose of trial drug to determine if any adverse events have occurred since the post-trial clinic visit.

7.1.5.4 Critical Procedures Based on Trial Objectives: Timing of Procedure

For this trial, the blood sample for viral load and the blood sample for MK-8591 PBMC are considered the critical procedures.

At any post-dose timepoint, the blood sample for MK-8591 PBMC needs to be collected as close to the exact timepoint as possible. All other procedures should be completed as close to the prescribed/scheduled time as possible. Trial procedures can be performed prior or after the prescribed/scheduled time.

The order of priority can be changed during the trial with joint agreement of the investigator and the Sponsor Clinical Director.

Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

7.1.5.5 Trial Design/Dosing/Procedures Modifications Permitted within Protocol Parameters

This is a Phase I assessment of MK-8591 in humans, and the pharmacokinetic, pharmacodynamic and safety profiles of the compound is still being elucidated. This protocol is written with some flexibility to accommodate the inherent dynamic nature of Phase I clinical trials. Modifications to the dose, dosing regimen and/or clinical or laboratory procedures currently outlined below may be required to achieve the scientific goals of the trial objectives and/or to ensure appropriate safety monitoring of the trial subjects.

As such, some alterations from the currently outlined dose and/or dosing regimen may be permitted based on newly available data, but the maximum daily dose may not exceed those currently outlined in the protocol.

- Repeat of or decrease in the dose of the trial drug administered
- Interchange of doses between panels
- Entire panel(s) may be omitted
- Instructions to take trial drug with or without food or drink may also be modified based on newly available data
- Decrease in the length of postdose pharmacokinetic/pharmacodynamic sample collection

The pharmacokinetic/pharmacodynamic sampling scheme currently outlined in the protocol may be modified during the trial based on newly available pharmacokinetic or pharmacodynamic data (e.g., to obtain data closer to the time of peak plasma concentrations). If indicated, these collected samples may also be assayed in an exploratory manner for metabolites and/or additional pharmacodynamic markers.

Up to additional 50 mL of blood may be drawn for safety, pharmacokinetic, and/or pharmacodynamic analyses. The total blood volume withdrawn from any single subject will not exceed the maximum allowable volume during his/her participation in the entire trial (Section 12.4).

The timing of procedures for assessment of safety procedures (e.g., vital signs, ECG, safety laboratory tests, etc.) currently outlined in the protocol may be modified during the trial based on newly available safety, tolerability, pharmacokinetic or pharmacodynamic data (e.g., to obtain data closer to the time of peak plasma concentrations). Additional laboratory safety tests may be added to blood samples previously drawn to obtain additional safety information. These changes will not increase the number of trial procedures for a given subject during his/her participation in the entire trial.

It is understood that the current trial may employ some or none of the alterations described above. Any alteration made to this protocol to meet the trial objectives must be detailed by the Sponsor in a letter to the Trial File and forwarded to the investigator for retention. The letter may be forwarded to the IRB/ERC at the discretion of the investigator.

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.

For randomized subjects only, all adverse events that occur after the consent form is signed but before treatment allocation/randomization must be reported by investigator if they 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 21 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Electronic reporting procedures can be found in the Electronic Data Capture (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

The subject has taken (accidentally or intentionally) any drug administered as part of the protocol and exceeding the dose as prescribed by the protocol. It is up to the investigator or the reporting physician to decide whether a dose is to be considered an overdose, in consultation with the Sponsor.

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

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

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

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

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

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. Pregnancies and lactations that occur from the time of treatment allocation/randomization through 21 days following cessation of Sponsor's product must be reported by the investigator. All reported pregnancies must be followed to the

completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

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

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

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

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

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

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

Refer to Table 7 for additional details regarding each of the above criteria.

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

For the time period beginning at treatment allocation/randomization through 21 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 21 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 must trigger 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).

   It may also be appropriate to conduct additional evaluation for an underlying etiology in the setting of abnormalities of liver blood tests including AST, ALT, bilirubin, and alkaline phosphatase that do not meet the criteria noted above. In these cases, the decision to proceed with additional evaluation will be made through consultation between the

study investigators and the Sponsor Clinical Director. However, abnormalities of liver blood tests that do not meet the criteria noted above are not ECIs for this trial).

7.2.3.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events with respect to the elements outlined in Table 7. The investigator's assessment of causality is required for each adverse event. Refer to Table 7 for instructions in evaluating adverse events.

Table 7 Evaluating Adverse Events

Maximum Intensity	**Mild**	awareness of sign or symptom, but easily tolerated (for pediatric trials, awareness of symptom, but easily tolerated)
	Moderate	discomfort enough to cause interference with usual activity (for pediatric trials, definitely acting like something is wrong)
	Severe	incapacitating with inability to work or do usual activity (for pediatric trials, extremely distressed or unable to do usual activities)
Seriousness	A serious adverse event (AE) is any adverse event occurring at any dose or during any use of Sponsor's product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred [Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.]; or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of 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 THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following:	**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).**	
Yes, there is a reasonable possibility of Sponsor's product relationship.	There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.	
No, there is not a reasonable possibility of Sponsor's product relationship	Subject did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a subject with overdose without an associated AE.)	

7.2.5 Sponsor Responsibility for Reporting Adverse Events

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

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan Summary

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

Statistical Methods

Primary Objective (Safety): Incidence of adverse experiences will be descriptively summarized. Summary statistics and plots will be generated for the change from baseline values in the vital signs, ECG parameters, and selected laboratory safety parameters for subjects, as deemed clinically appropriate. Depending on the safety parameter, the difference from baseline will either be computed on the original scale (raw change from baseline) or on the log scale and back-transformed for reporting (percent change from baseline). Summary statistics for the raw laboratory safety tests, ECGs, and/or vital signs may also be computed, as deemed clinically appropriate.

Primary Objective (Pharmacodynamics): The log10 plasma HIV-RNA (copies/mL) measurements from subjects in all panels will be pooled and analyzed based on a longitudinal data analysis model containing fixed effects for dose level, time (pre-dose, 168 hrs post-dose) and dose level by time interaction, and a random effect for patient. The change from baseline for each dose level at 168 hours post-baseline will be estimated from this model. A posterior distribution for the true mean change from baseline at 168 hours will be generated for each dose level using flat priors under a normal likelihood assumption. Historical placebo data from recent monotherapy studies in HIV-1 subjects [redacted] will be separately analyzed based on a longitudinal data analysis model containing fixed effects for study and time (pre-dose, 168 hours post-dose), and a random effect for patient. The change from baseline for placebo at 168 hours post-baseline will be estimated from this model, and a posterior distribution for the true mean change from baseline at 168 hours will be generated using flat priors under a normal likelihood assumption. Using the posterior distributions for each dose level and placebo, the posterior distribution of the true mean difference between each dose level and placebo will be generated, and the posterior probability that the true mean difference in the log10 plasma HIV-1 RNA reduction from baseline between MK-8591 and placebo is at least 0.5 log10 copies/mL will be calculated. An 80% posterior probability for at least one dose level that also exhibits an acceptable safety and tolerability profile will satisfy the primary pharmacodynamics hypothesis. For each dose level, the posterior probability that the true mean log10 plasma HIV-1 RNA reduction from baseline is at least 0.5 log10 copies/mL will also be calculated.

Power

Pharmacodynamic (Primary): If the true SD of the log10 reduction from baseline in plasma HIV-RNA at 168 hours postdose is 0.4 (0.5), there is ~80% power to yield at least 80% posterior probability if the true mean log10 reduction is at least 1.0 log10 (1.1 log10) with N=6 subjects in a Panel.

8.2 Statistical Analysis Plan

The statistical analysis of the data obtained from this study will be conducted by, or under the direct auspices of, the Clinical Pharmacology Statistics Department in collaboration with the Pharmacokinetics, Pharmacodynamics, and Drug Metabolism (PPDM) and Clinical Pharmacology Departments of the Sponsor.

If, after the study has begun, changes are made to the statistical analysis plan stated below, then these deviations to the plan will be listed, along with an explanation as to why they occurred, in the Clinical Study Report.

8.2.1 Hypotheses

Primary

At a dose that is sufficiently safe and generally well tolerated, MK-8591 has superior antiretroviral activity compared to placebo, as measured by change from baseline in plasma HIV-1 RNA (log_{10} copies/mL) at 168 hours postdose. That is, the true mean difference in the plasma HIV-1 RNA reduction from baseline between MK-8591 and placebo is at least 0.5 log_{10} copies/mL.

8.2.2 Analysis Endpoints

Primary Pharmacodynamic

The primary pharmacodynamic variables in this study include plasma HIV-1 RNA pre-dose and 4, 24, 96, 120, 144, 168, 240 and 336 hours post-dose.

Primary Safety

The primary safety endpoints in this study include all types of adverse experiences, in addition to laboratory safety assessments, ECGs, and vital signs.

Secondary Endpoints

The secondary endpoints in this study include MK-8591 plasma and intracellular triphosphate in PBMC $AUC_{0\text{-}168hr}$, T_{max}, C_{max}, C_{168hr}, C_{336hr}, and apparent terminal t1/2 after administration of single oral doses following dosing on Day 1.

8.2.3 Approaches to Analyses

The following populations are defined for the analysis and reporting of data. All subjects will be reported, and their data analyzed, according to the treatment(s) they actually received.

All Subjects as Treated (AST) - All subjects who received at least one dose of the investigational drug. This population will be used for assessments of safety and tolerability.

Per-Protocol (PP) – The set of data generated by the subset of subjects who comply with the protocol sufficiently to ensure that these data will be likely to exhibit the effects of treatment, according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements and absence of major protocol violations. Major protocol violators will be identified to the extent possible prior to unblinding by individuals responsible for data collection/compliance, and its analysis and interpretation. Any subjects or data values excluded from analysis will be identified, along with their reason for exclusion, in the CSR. At the end of the study, all subjects who are compliant with the study procedure as aforementioned and have available data from at least one treatment will be included in the primary analysis dataset. This population will be used for the primary PD, secondary PK and exploratory PK and PD analyses.

8.2.4 Statistical Methods

Primary (Safety)

Incidence of adverse experiences will be descriptively summarized. Summary statistics and plots will be generated for the change from baseline values in the vital signs, ECG parameters, and selected laboratory safety parameters for subjects, as deemed clinically appropriate. Depending on the safety parameter, the difference from baseline will either be computed on the original scale (raw change from baseline) or on the log scale and back-transformed for reporting (percent change from baseline). Summary statistics for the raw laboratory safety tests, ECGs, and/or vital signs may also be computed, as deemed clinically appropriate.

Primary (Pharmacodynamics)

The log10 plasma HIV-RNA (copies/mL) measurements from subjects in all panels will be pooled and analyzed based on a longitudinal data analysis (LDA) model containing fixed effects for dose level, time (pre-dose, 168 hrs post-dose) and dose level by time interaction, and a random effect for patient. The response vector consists of the baseline and 168 hours post-baseline values. Time is treated as a categorical variable so that no restriction is imposed on the trajectory of means over time. The change from baseline for each dose level at 168 hours post-baseline will be estimated from this model. A posterior distribution for the true mean change from baseline at 168 hours will be generated for each dose level using flat priors under a normal likelihood assumption. Historical placebo data from recent monotherapy studies in HIV-1 subjects [redacted] will be separately analyzed based on a

longitudinal data analysis model containing fixed effects for study and time (pre-dose, 168 hrs post-dose), and a random effect for patient. The change from baseline for placebo at 168 hours post-baseline will be estimated from this model, and a posterior distribution for the true mean change from baseline at 168 hours will be generated using flat priors under a normal likelihood assumption. Using the posterior distributions for each dose level and placebo, the posterior distribution of the true mean difference between each dose level and placebo will be generated, and the posterior probability that the true mean difference in the log10 plasma HIV-1 RNA reduction from baseline between MK-8507 and placebo is at least 0.5 log10 copies/mL will be calculated. An 80% posterior probability for at least one dose level that also exhibits an acceptable safety and tolerability profile will satisfy the primary pharmacodynamics hypothesis. For each dose level, the posterior probability that the true mean log10 plasma HIV-1 RNA reduction from baseline is at least 0.5 log10 copies/mL will also be calculated. To address the exploratory objective related to antiretroviral activity at 336 hours post-baseline, a similar analysis will be performed using viral load measurements at baseline and 336 hours post-baseline. Similar exploratory analyses may be performed at timepoints earlier than 168 hours post-baseline.

Secondary (Pharmacokinetic)

MK-8591 plasma and intracellular triphosphate in PBMC pharmacokinetic parameters C_{168hr}, C_{336hr}, $AUC_{0\text{-}168hr}$, and C_{max} from subjects in all panels will be pooled, log-transformed and analyzed based on a linear model containing a fixed effect for dose level. The 95% confidence intervals for the means will be constructed on the natural log scale and will reference the t-distribution. Exponentiating the means will yield estimates for the population geometric means on the original scale. The posterior probability that the true GM C_{168hr} triphosphate in PBMC is at least 0.53 pmol/10^6 cells will be calculated for each dose level using flat priors under a normal likelihood assumption. Data will be examined for departures from the assumptions of the statistical model(s) as appropriate; e.g., heteroscedasticity, nonnormality of the error terms. Distribution-free methods may be used if a serious departure from the assumptions of the model(s) is observed, or suitable data transformation may be applied.

Individual values will be listed for each MK-8591 plasma and intracellular triphosphate in PBMC PK parameter (C_{168hr}, C_{336hr}, $AUC_{0\text{-}168hr}$, C_{max}, T_{max}, and apparent terminal t1/2) by dose level, and the following (non-model-based) descriptive statistics will be provided: N (number of subjects with non-missing data), arithmetic mean, standard deviation, arithmetic percent CV (calculated as 100 x standard deviation/arithmetic mean), median, minimum, maximum, geometric mean, and geometric percent CV (calculated as 100 x sqrt(exp(s^2) - 1), where s^2 is the observed variance on the natural log-scale).

Secondary and Exploratory (Pharmacokinetic/Pharmacodynamic)

The pharmacokinetic-pharmacodynamic and dose-pharmacodynamic association of MK-8591will be explored. Graphs to visualize the association of the reduction in log10 plasma HIV-1 RNA levels with various plasma and intracellular triphosphate in PBMC parameters (e.g., C_{168hr}, C_{336hr}, $AUC_{0-168hr}$, and C_{max}) and dose will be generated. Exploratory linear and/or non-linear model fits may be considered, as appropriate. Exposure levels and doses that result in various proportions of the population (e.g., 80%, 90%) that have at least 0.5 log10 reduction from baseline in plasma HIV-1 RNA levels with high confidence may be estimated.

The duration of antiretroviral suppression after a single dose of 30 mg MK-8591 in Panel G will be evaluated with individual plots across time.

8.2.5 Multiplicity

Since there is only one primary pharmacodynamic hypothesis, no multiplicity adjustment will be made.

8.2.6 Power

Pharmacodynamic (Primary): If the true SD of the log10 reduction from baseline in plasma HIV-RNA at 168 hours postdose is 0.4 (0.5), there is ~80% power to yield at least 80% posterior probability if the true mean log10 reduction is at least 1.0 log10 (1.1 log10) with N=6 subjects in a Panel.

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 8.

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Clinical supplies will be packaged to support enrollment and replacement subjects as required. When a replacement subject is required, the Sponsor or designee needs to be contacted prior to dosing the replacement supplies.

Table 8 Product Descriptions

Product Name & Potency	Dosage Form
MK-8591 1mg	Capsule
MK-8591 10mg	Capsule
MK-8591 100mg	Capsule
MK-8591 0.25 mg	Capsule
Note: Sponsor may provide MK-8591 0.25mg capsule for dose selection flexibility, if it is required. Additionally, ART that is initiated during the study will be sourced locally by the clinical site.	

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 supply. 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 and strength (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 by the subjects and the amount remaining at the conclusion of the trial. For all trial sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

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 Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. 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 FDAMA/FDAAA 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 FDAMA/FDAAA are that of the Sponsor and agrees not to submit any information about this trial or its results to the Clinical Trials Data Bank.

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

No references listed.

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 DNA and leftover plasma specimen(s) collected in the current trial will be used to study various causes for how subjects may respond to a drug/vaccine. The DNA and leftover plasma specimen(s) will be stored to provide a resource for future trials conducted by Merck focused on the study of biomarkers responsible for how a drug/vaccine enters and is removed by the body, how a drug/vaccine works, other pathways a drug/vaccine may interact with, or other aspects of disease. The specimen(s) may be used for future assay development and/or drug/vaccine development.

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

3. Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

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

b. Informed Consent

Informed consent for specimens (i.e., DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all subjects, 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 (PPD and a form will be provided by Merck to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. A letter will be sent from Merck to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

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

7. Retention of Specimens

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

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

8. Data Security

Separate databases for specimen information and for results from the Future Biomedical Research sub-trial will be maintained by Merck. This is done to separate the future exploratory test results (which include genetic data) from the clinical trial database thereby maintaining a separation of subject number and these results. The separate databases are accessible only to the authorized Sponsor and the designated trial administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based in international standards (e.g., ISO17799) to protect against unauthorized access. The Merck Entrusted Keyholder maintains control over access to all specimen data. These

data are collected for future biomedical research purposes only as specified in this sub-trial will not be used for any other purpose.

9. Reporting of Future Biomedical Research Data to Subjects

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

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

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

10. Gender, Ethnicity and Minorities

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

11. Risks Versus Benefits of Future Biomedical Research

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

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

It is necessary for subject-related data (i.e., ethnicity, diagnosis, drug therapy and dosage, age, toxicities, etc.) to be re-associated to double coded specimens at the time of data analysis. These subject data will be kept in a separate, secure Merck database, and all

specimens will be stripped of subject identifiers. No information concerning results obtained from future biomedical research will be entered into clinical records, nor will it be released to outside persons or agencies, in any way that could be tied to an individual subject.

12. Self-Reported Ethnicity

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

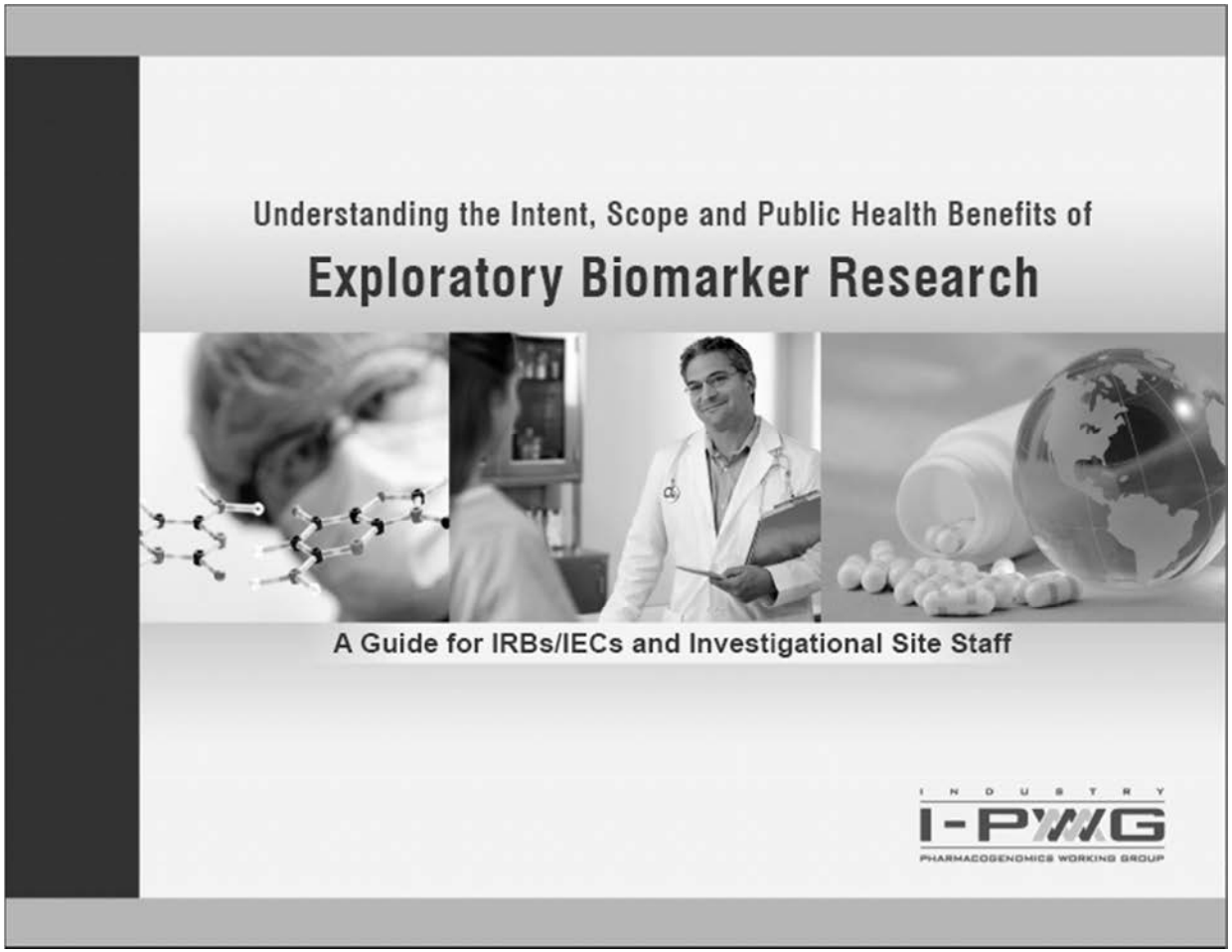
13. Questions

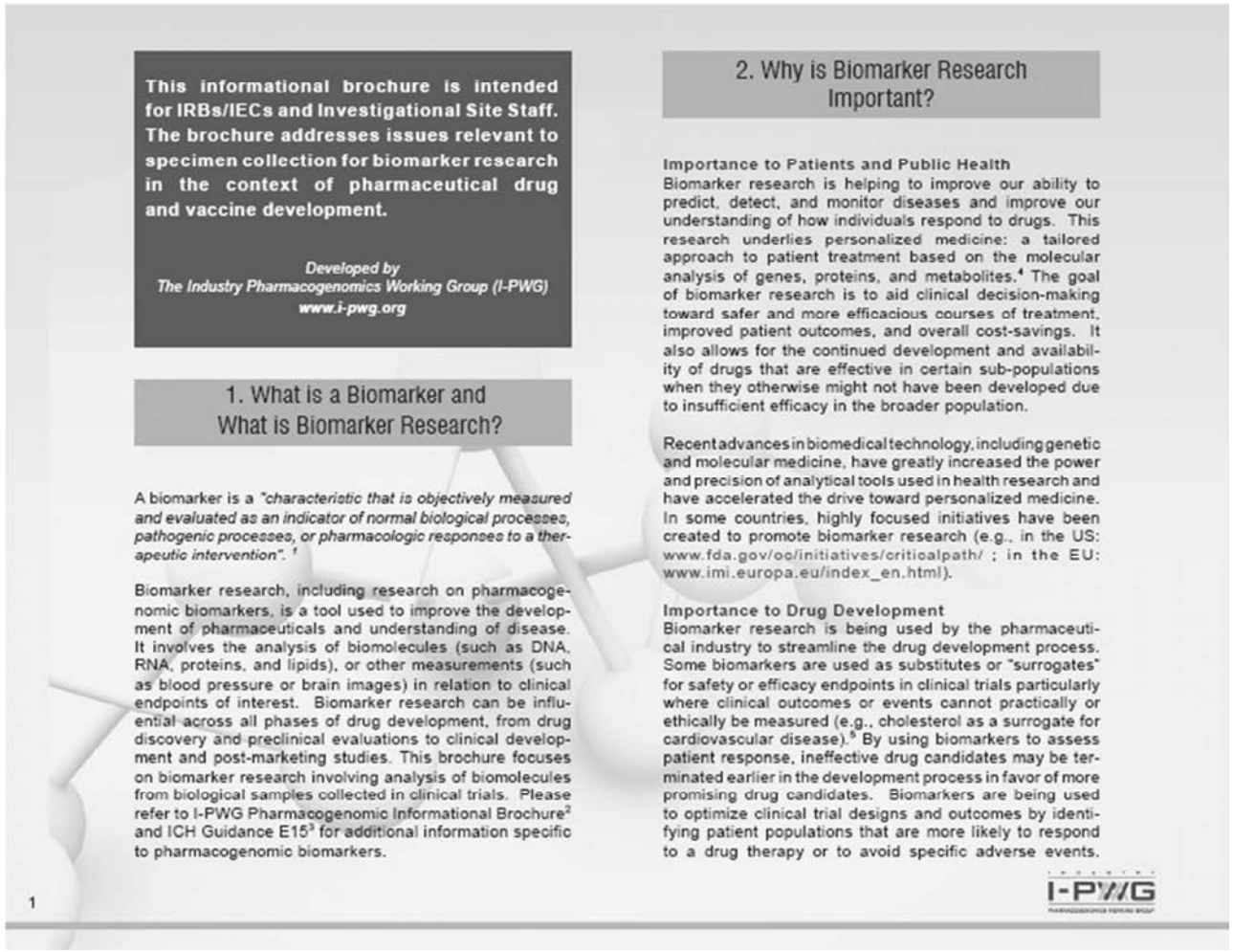
Any questions related to the future biomedical research should be e-mailed directly to PPD

14. References

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

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





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

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

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

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

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

2. Why is Biomarker Research Important?

Importance to Patients and Public Health

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

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

Importance to Drug Development

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

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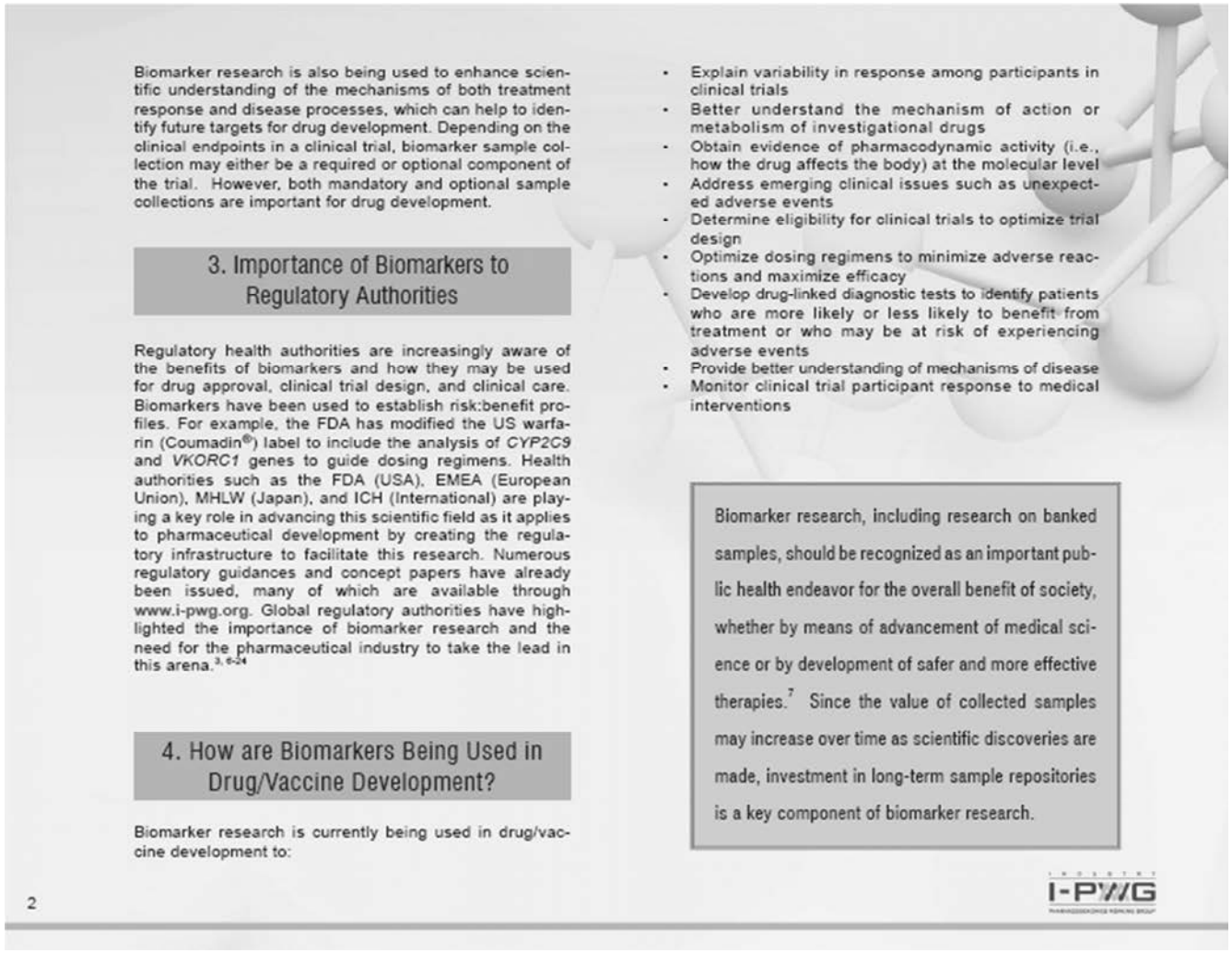
Biomarker research is also being used to enhance scientific understanding of the mechanisms of both treatment response and disease processes, which can help to identify future targets for drug development. Depending on the clinical endpoints in a clinical trial, biomarker sample collection may either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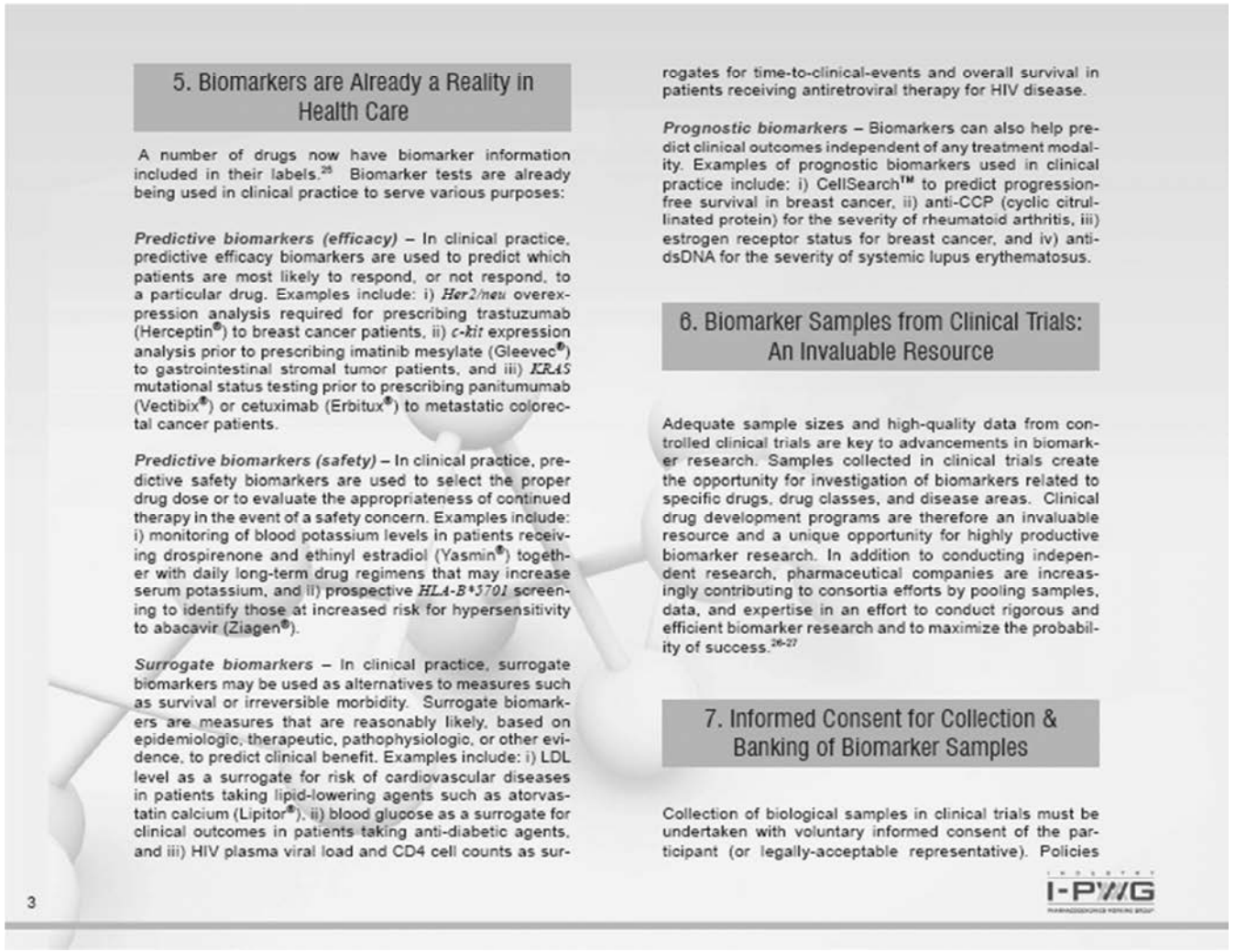

5. Biomarkers are Already a Reality in Health Care

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

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

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

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

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

6. Biomarker Samples from Clinical Trials: An Invaluable Resource

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

7. Informed Consent for Collection & Banking of Biomarker Samples

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

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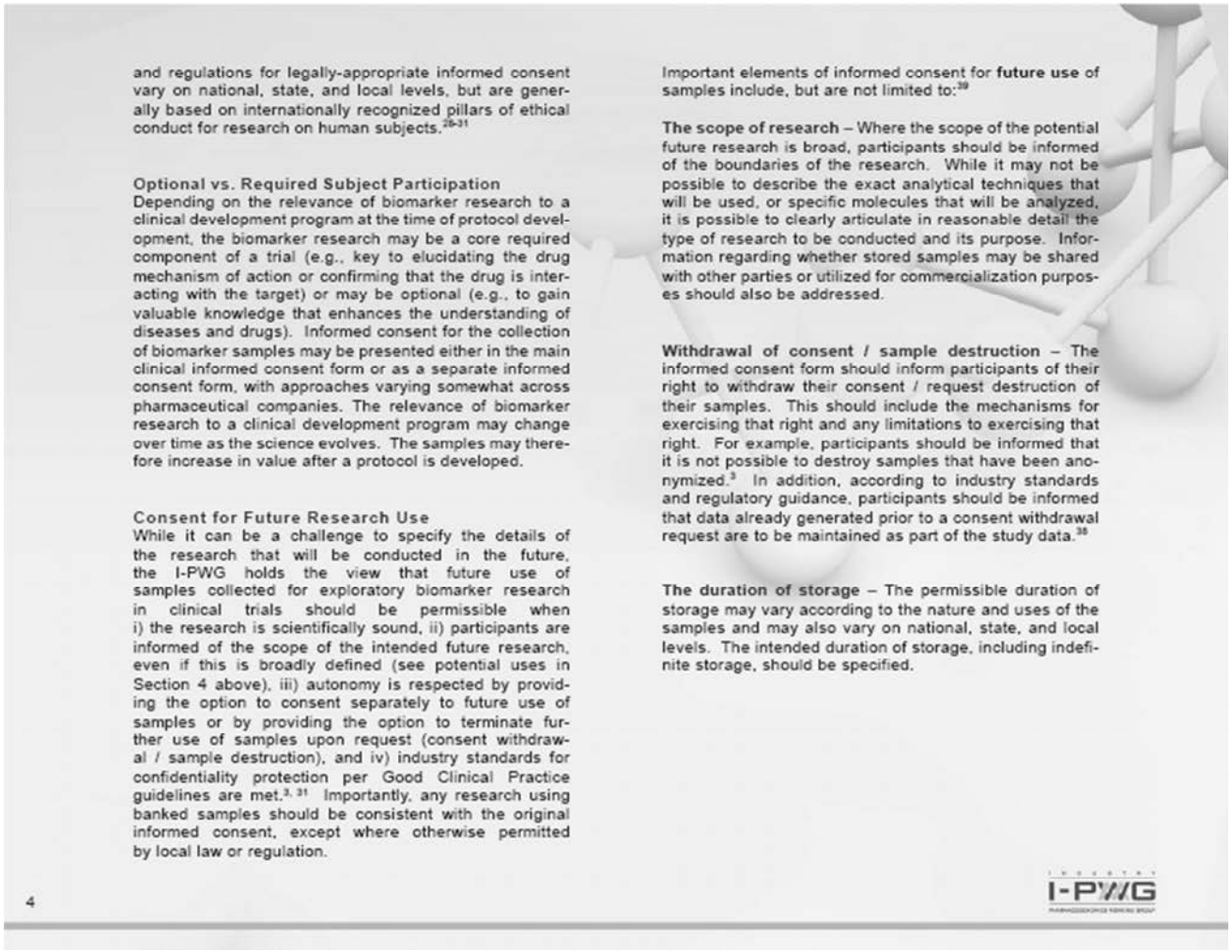

and regulations for legally-appropriate informed consent vary on national, state, and local levels, but are generally based on internationally recognized pillars of ethical conduct for research on human subjects.[28-31]

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

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

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

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

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

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

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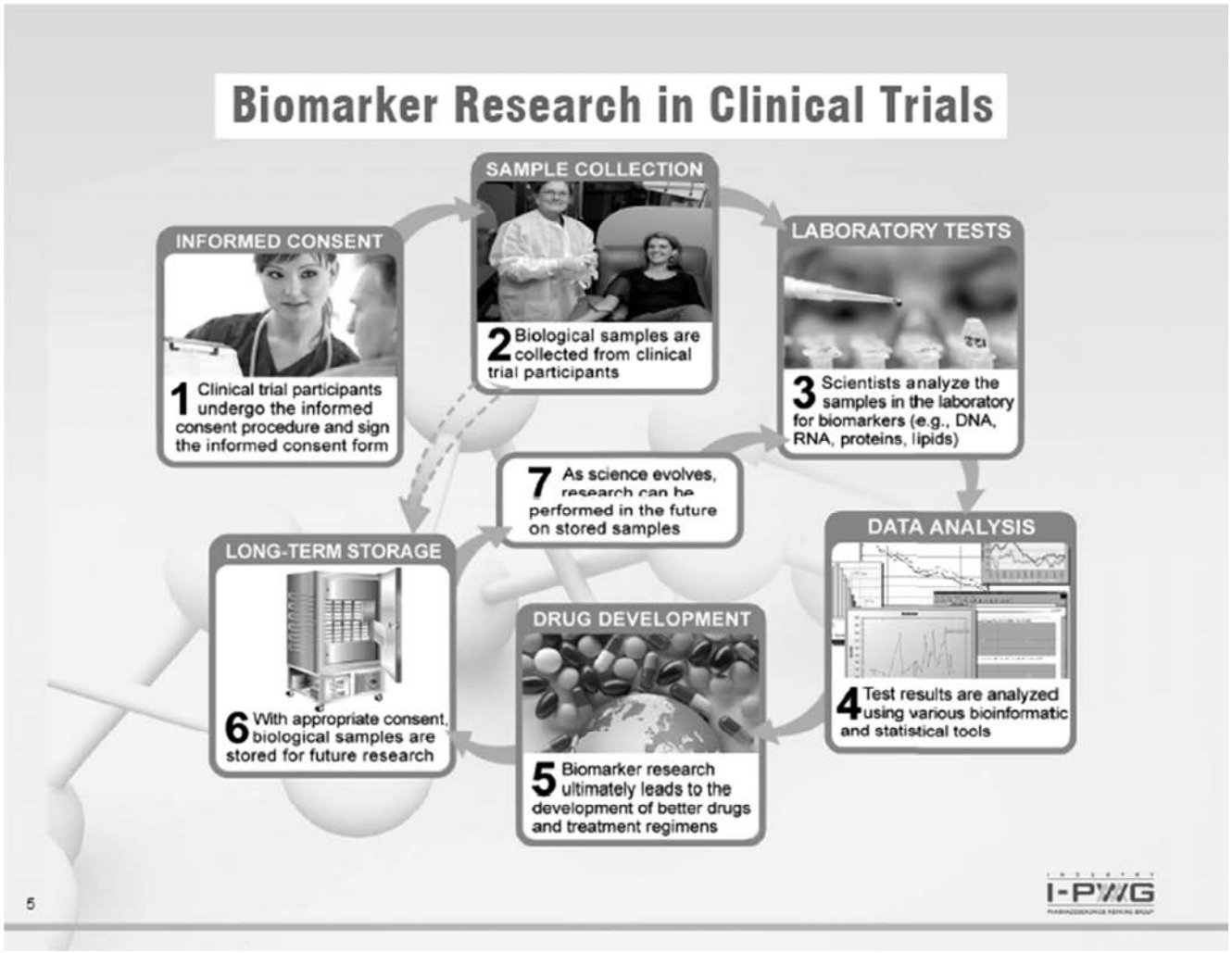
Biomarker Research in Clinical Trials
SAMPLE COLLECTION
2 Biological samples are collected from clinical trial participants
LABORATORY TESTS
3 Scientists analyze the samples in the laboratory for biomarkers (e.g., DNA, RNA, proteins, lipids)
INFORMED CONSENT
1 Clinical trial participants undergo the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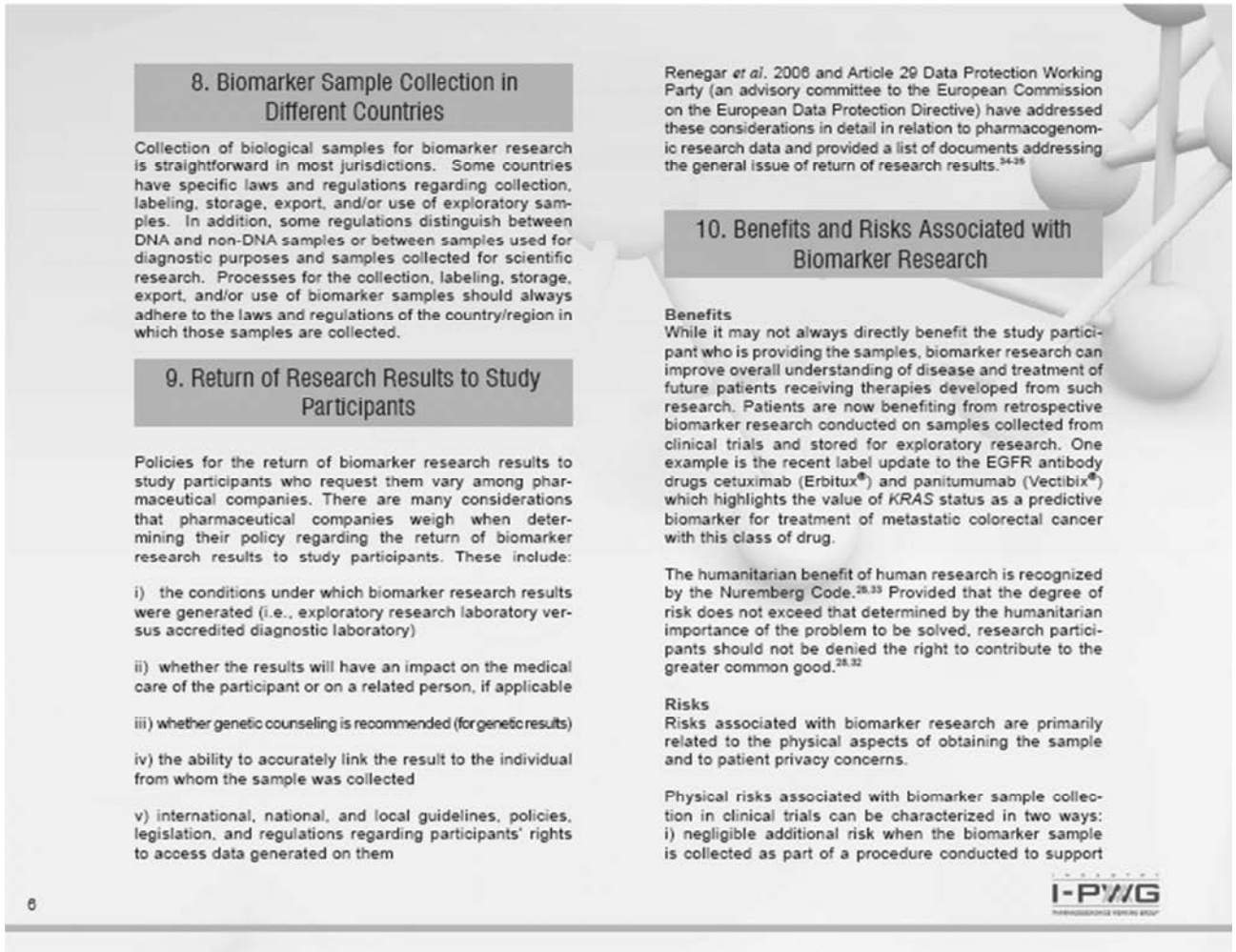

8. Biomarker Sample Collection in Different Countries

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

9. Return of Research Results to Study Participants

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

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

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

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

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

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

Renegar *et al*. 2006 and Article 29 Data Protection Working Party (an advisory committee to the European Commission on the European Data Protection Directive) have addressed these considerations in detail in relation to pharmacogenomic research data and provided a list of documents addressing the general issue of return of research results.[34-36]

10. Benefits and Risks Associated with Biomarker Research

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

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

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

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

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

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

11. Privacy, Confidentiality, and Patient Rights

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

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

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

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

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

12.Where to Get More Information?

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

13. What is I-PWG?

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

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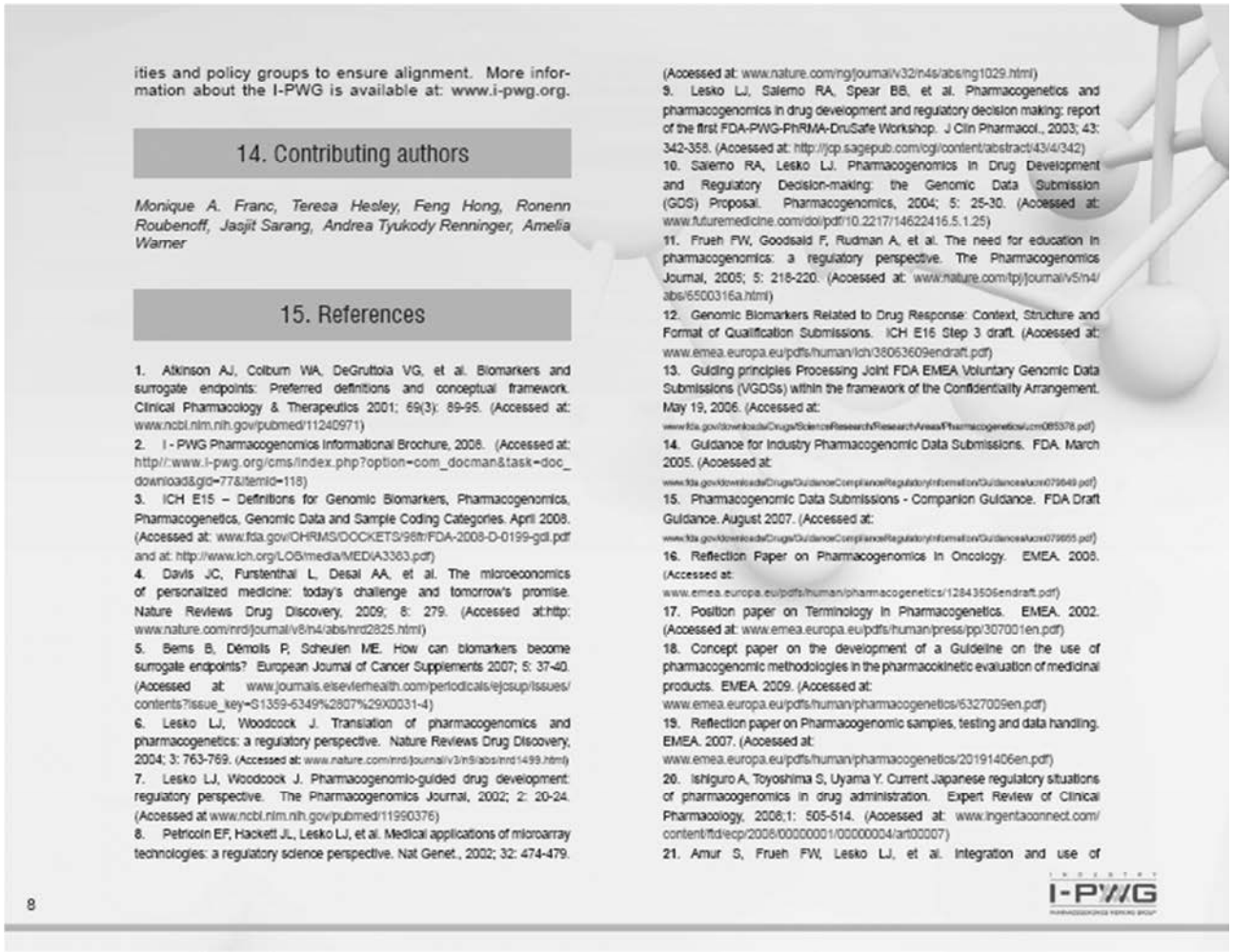

ities and policy groups to ensure alignment. More information about the I-PWG is available at: www.i-pwg.org.

14. Contributing authors

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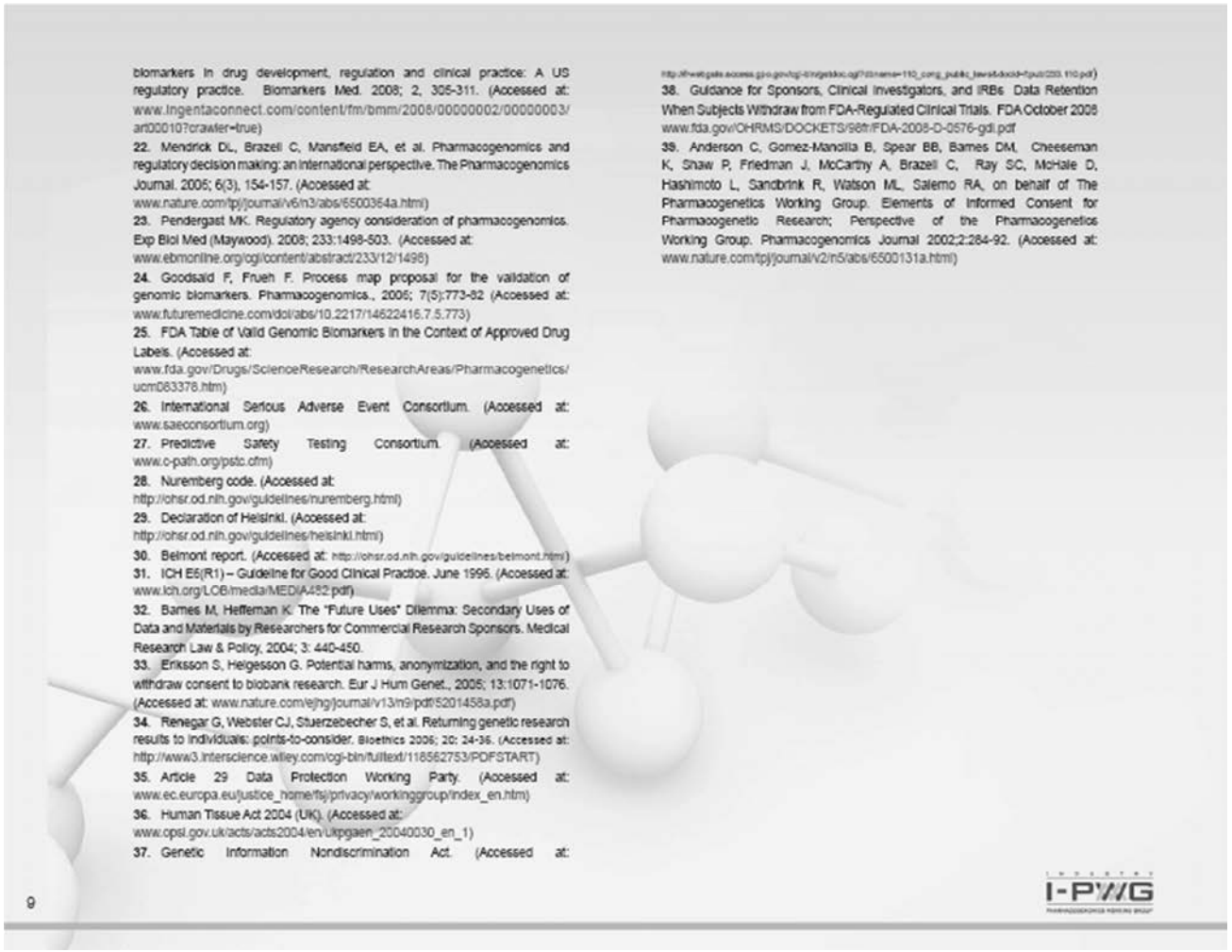

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12.4 Approximate Blood Volumes Collected by Trial Visit and by Sample Types

Panels A, B, C, D, E, and F	Pre-trial	Treatment Periods	Post-trial	Total Collections	mL Per Collection	Total mL/ Test
Laboratory Safety Tests‡	1	3	1	5	12.5	62.5
Serum b-Human Chorionic Gonadotropin (β-hCG)	1	1	1	3	5	15
Blood for MK-8591 Plasma	0	11	0	11	4	44
Blood for MK-8591 PBMC	0	9	1	10	16	160
Blood for HIV RNA, viral resistance§	1	9	1	11	10	110
Blood for Future Biomedical Research	1	0	0	1	8.5	8.5
Maximum Total Blood Volume Per Patient for Panels A, B, C, and D†						400 mL

† If additional pharmacokinetic/pharmacodynamic and/or safety analysis is necessary, up to 50 mL of additional blood may be obtained.
‡ Blood for FSH and CD4 cell count are included in the Laboratory Safety blood draw volume.
§ For all panels blood for HIV-1 viral RNA and viral resistance may be collected up to the post-trial visit if subjects do not start ART. For Panel A, if ART is initiated, samples for HIV-1 viral RNA and viral resistance for blood for HIV-1 viral RNA and viral resistance will only be collected up to 10 days postdose. For Panel B samples for HIV-1 viral RNA and viral resistance will be collected up to 21 days postdose, regardless of ART. The timing of collection for Panels C, D, E and F will be based on the selected dose.

Panel G	Pre-trial	Treatment Periods	Post-trial	Total Collections	mL Per Collection	Total mL/ Test
Laboratory Safety Tests‡	1	3	1	5	12.5	62.5
Serum b-Human Chorionic Gonadotropin (β-hCG)	1	1	1	3	5	15
Blood for MK-8591 Plasma	0	11	0	11	4	44
Blood for MK-8591 PBMC	0	11	1	12	16	192
Blood for HIV RNA, viral resistance§	1	14	2	17	10	170
Blood for Future Biomedical Research	1	0	0	1	8.5	8.5
Maximum Total Blood Volume Per Patient for Panel G†						492 mL

† If additional pharmacokinetic/pharmacodynamic and/or safety analysis is necessary, up to 50 mL of additional blood may be obtained.
‡ Blood for FSH and CD4 cell count are included in the Laboratory Safety blood draw volume.
§ If a subject's VL is below LLOD at the post-trial visit, two additional blood samples (totaling 20mL) will be collected for HIV-RNA at each semiweekly visit in order to monitor VL closely until ART is initiated. If subjects initiate ART earlier than 21 days, the blood collected for HIV-RNA may be less than indicated in the treatment and post-trial periods.

12.5 Division of AIDS Table for Grading Severity of Adult and Pediatric Adverse

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

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events ("DAIDS AE Grading Table") is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

This clarification of the DAIDS Table for Grading the Severity of Adult and Pediatric AE's provides additional explanation of the DAIDS AE Grading Table and clarifies some of the parameters.

I. Instructions and Clarifications

Grading Adult and Pediatric AEs

The DAIDS AE Grading Table includes parameters for grading both Adult and Pediatric AEs. When a single set of parameters is not appropriate for grading specific types of AEs for both Adult and Pediatric populations, separate sets of parameters for Adult and/or Pediatric populations (with specified respective age ranges) are given in the Table. If there is no distinction in the Table between Adult and Pediatric values for a type of AE, then the single set of parameters listed is to be used for grading the severity of both Adult and Pediatric events of that type.

> **Note:** In the classification of adverse events, the term "**severe**" is not the same as "**serious**." Severity is an indication of the intensity of a specific event (as in mild, moderate, or severe chest pain). The term "**serious**" relates to a participant/event outcome or action criteria, usually associated with events that pose a threat to a participant's life or functioning.

Addenda 1-3 Grading Tables for Microbicide Studies

For protocols involving topical application of products to the female genital tract, male genital area or rectum, strong consideration should be given to using Appendices I-III as the primary grading scales for these areas. The protocol would need to specifically state that one or more of the Appendices would be primary (and thus take precedence over the main Grading Table) for items that are listed in both the Appendix and the main Grading Table.

- Addendum 1 - Female Genital Grading Table for Use in Microbicide Studies - PDF
- Addendum 2 - Male Genital Grading Table for Use in Microbicide Studies - PDF
- Addendum 3 - Rectal Grading Table for Use in Microbicide Studies - PDF

Grade 5

For any AE where the outcome is death, the severity of the AE is classified as Grade 5.

Estimating Severity Grade for Parameters Not Identified in the Table

In order to grade a clinical AE that is not identified in the DAIDS AE grading table, use the category "Estimating Severity Grade" located on Page 3.

Determining Severity Grade for Parameters "Between Grades"

If the severity of a clinical AE could fall under either one of two grades (e.g., the severity of an AE could be either Grade 2 or Grade 3), select the higher of the two grades for the AE. If a laboratory value that is graded as a multiple of the ULN or LLN falls between two grades, select the higher of the two grades for the AE. For example, Grade 1 is 2.5 x ULN and Grade 2 is 2.6 x ULN for a parameter. If the lab value is 2.53 x ULN (which is between the two grades), the severity of this AE would be Grade 2, the higher of the two grades.

Values Below Grade 1

Any laboratory value that is between either the LLN or ULN and Grade 1 should not be graded.

Determining Severity Grade when Local Laboratory Normal Values Overlap with Grade 1 Ranges

In these situations, the severity grading is based on the ranges in the DAIDS AE Grading Table, even when there is a reference to the local lab LLN.

For example: Phosphate, Serum, Low, Adult and Pediatric > 14 years (Page 20) Grade 1 range is 2.50 mg/dL - < LLN. A particular laboratory's normal range for Phosphate is 2.1 – 3.8 mg/dL. A participant's actual lab value is 2.5. In this case, the value of 2.5 exceeds the LLN for the local lab, but will be graded as Grade 1 per DAIDS AE Grading Table.

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II. Definitions of terms used in the Table:

Basic Self-care Functions	Adult Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding. Young Children Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).
LLN	Lower limit of normal
Medical Intervention	Use of pharmacologic or biologic agent(s) for treatment of an AE.
NA	Not Applicable
Operative Intervention	Surgical OR other invasive mechanical procedures.
ULN	Upper limit of normal
Usual Social & Functional Activities	Adult Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc. Young Children Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
ESTIMATING SEVERITY GRADE				
Clinical adverse event NOT identified elsewhere in this DAIDS AE Grading Table	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death
SYSTEMIC				
Acute systemic allergic reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with medical intervention indicated OR Mild angioedema with no medical intervention indicated	Generalized urticaria OR Angioedema with medical intervention indicated OR Symptomatic mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Fatigue Malaise	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating fatigue/ malaise symptoms causing inability to perform basic self-care functions
Fever (oral/axillary)	37.7 – 38.6°C	38.7 – 39.3°C	39.4 – 40.5°C	> 40.5°C
Pain (indicate body site) DO NOT use for pain due to injection (See Injection Site Reactions: Injection site pain) See also Headache, Arthralgia, and Myalgia	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization (other than emergency room visit) indicated

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Unintentional weight loss	NA	5 – 9% loss in body weight from baseline	10 – 19% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated [e.g., tube feeding or total parenteral nutrition (TPN)]
INFECTION				
Infection (any other than HIV infection)	Localized, no systemic antimicrobial treatment indicated AND Symptoms causing no or minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated AND Symptoms causing inability to perform usual social & functional activities OR Operative intervention (other than simple incision and drainage) indicated	Life-threatening consequences (e.g., septic shock)
INJECTION SITE REACTIONS				
Injection site pain (pain without touching) Or Tenderness (pain when area is touched)	Pain/tenderness causing no or minimal limitation of use of limb	Pain/tenderness limiting use of limb OR Pain/tenderness causing greater than minimal interference with usual social & functional activities	Pain/tenderness causing inability to perform usual social & functional activities	Pain/tenderness causing inability to perform basic self-care function OR Hospitalization (other than emergency room visit) indicated for management of pain/tenderness
Injection site reaction (localized)				
Adult > 15 years	Erythema OR Induration of 5x5 cm – 9x9 cm (or 25 cm^2 – 81cm^2)	Erythema OR Induration OR Edema > 9 cm any diameter (or > 81 cm^2)	Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)
Pediatric ≤ 15 years	Erythema OR Induration OR Edema present but ≤ 2.5 cm diameter	Erythema OR Induration OR Edema > 2.5 cm diameter but < 50% surface area of the extremity segment (e.g., upper arm/thigh)	Erythema OR Induration OR Edema involving ≥ 50% surface area of the extremity segment (e.g., upper arm/thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Pruritis associated with injection See also Skin: Pruritis (itching - no skin lesions)	Itching localized to injection site AND Relieved spontaneously or with < 48 hours treatment	Itching beyond the injection site but not generalized OR Itching localized to injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA
SKIN – DERMATOLOGICAL				
Alopecia	Thinning detectable by study participant (or by caregiver for young children and disabled adults)	Thinning or patchy hair loss detectable by health care provider	Complete hair loss	NA
Cutaneous reaction – rash	Localized macular rash	Diffuse macular, maculopapular or morbilliform rash OR Target lesions	Diffuse macular, maculopapular or morbilliform rash with vesicles or limited number of bullae OR Superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Toxic epidermal necrolysis (TEN)
Hyperpigmentation	Slight or localized	Marked or generalized	NA	NA
Hyperpigmentation	Slight or localized	Marked or generalized	NA	NA
Pruritis (itching – no skin lesions) (See also Injection Site Reactions: Pruritis associated with injection)	Itching causing no or minimal interference with usual social & functional activities	Itching causing no or minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA
CARDIOVASCULAR				
Cardiac arrhythmia (general) (By ECG or physical exam)	Asymptomatic AND No intervention indicated	Asymptomatic AND Non-urgent medical intervention indicated	Symptomatic, non-life-threatening AND Non-urgent medical intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Cardiac-ischemia/infarction	NA	NA	Symptomatic ischemia (stable angina) OR Testing consistent with ischemia	Unstable angina OR Acute myocardial infarction

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Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hemorrhage (significant acute blood loss)	NA	Symptomatic AND No transfusion indicated	Symptomatic AND Transfusion of ≤ 2 units packed RBCs (for children ≤ 10 cc/kg) indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs (for children > 10 cc/kg) indicated
Hypertension				
Adult > 17 years (with repeat testing at same visit)	140 – 159 mmHg systolic OR 90 – 99 mmHg diastolic	160 – 179 mmHg systolic OR 100 – 109 mmHg diastolic	≥ 180 mmHg systolic OR ≥ 110 mmHg diastolic	Life-threatening consequences (e.g., malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
Correction: In Grade 2 to 160 - 179 from > 160-179 (systolic) and to ≥ 100 -109 from > 100-109 (diastolic) and in Grade 3 to ≥ 180 from > 180 (systolic) and to ≥ 110 from > 110 (diastolic).				
Pediatric ≤ 17 years (with repeat testing at same visit)	NA	91st – 94th percentile adjusted for age, height, and gender (systolic and/or diastolic)	≥ 95th percentile adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences (e.g., malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
Hypotension	NA	Symptomatic, corrected with oral fluid replacement	Symptomatic, IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Pericardial effusion	Asymptomatic, small effusion requiring no intervention	Asymptomatic, moderate or larger effusion requiring no intervention	Effusion with non-life threatening physiologic consequences OR Effusion with non-urgent intervention indicated	Life-threatening consequences (e.g., tamponade) OR Urgent intervention indicated
Prolonged PR interval				
Adult > 16 years	PR interval 0.21 – 0.25 sec	PR interval > 0.25 sec	Type II 2nd degree AV block OR Ventricular pause > 3.0 sec	Complete AV block
Pediatric ≤ 16 years	1st degree AV block (PR > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block	Complete AV block

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Prolonged QTc				
Adult > 16 years	Asymptomatic, QTc interval 0.45 – 0.47 sec OR increase interval < 0.03 sec above baseline	Asymptomatic, QTc interval 0.48 – 0.49 sec OR increase in interval 0.03 – 0.05 sec above baseline	Asymptomatic, QTc interval ≥ 0.50 sec OR increase in interval ≥ 0.06 sec above baseline	Life-threatening consequences, e.g. Torsade de pointes or other associated serious ventricular dysrhythmia
Pediatric ≤ 16 years	Asymptomatic, QTc interval 0.450 – 0.464 sec	Asymptomatic, QTc interval 0.465 – 0.479 sec	Asymptomatic, QTc interval ≥ 0.480 sec	Life-threatening consequences, e.g. Torsade de pointes or other associated serious ventricular dysrhythmia
Thrombosis/embolism	NA	Deep vein thrombosis AND No intervention indicated (e.g., anticoagulation, lysis filter, invasive procedure)	Deep vein thrombosis AND intervention indicated (e.g., anticoagulation, lysis filter, invasive procedure)	Embolic event (e.g., pulmonary embolism, life-threatening thrombus)
Vasovagal episode (associated with a procedure of any kind)	Present without loss of consciousness	Present with transient loss of consciousness	NA	NA
Ventricular dysfunction (congestive heart failure)	NA	Asymptomatic diagnostic finding AND intervention indicated	New onset with symptoms OR Worsening symptomatic congestive heart failure	Life-threatening congestive heart failure
GASTROINTESTINAL				
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated [e.g., tube feeding or total parenteral nutrition (TPN)]
Comment: Please note that, while the grading scale provided for Unintentional Weight Loss may be used as a guideline when grading anorexia, this is not a requirement and should not be used as a substitute for clinical judgment.				
Ascites	Asymptomatic	Symptomatic AND intervention indicated (e.g., diuretics or therapeutic paracentesis)	Symptomatic despite intervention	Life-threatening consequences

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Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Cholecystitis	NA	Symptomatic AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis or perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)
Diarrhea				
Adult and Pediatric ≥ 1 year	Transient or intermittent episodes of unformed stools OR increase of ≤ 3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR increase of 4 – 6 stools over baseline per 24-hour period	Bloody diarrhea OR increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
Pediatric < 1 year	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Liquid stools resulting in severe dehydration with aggressive rehydration indicated OR Hypotensive shock
Dysphagia-Odynophagia	Symptomatic but able to eat usual diet	Symptoms causing altered dietary intake without medical intervention indicated	Symptoms causing severely altered dietary intake with medical intervention indicated	Life-threatening reduction in oral intake
Mucositis/stomatitis (clinical exam) Indicate site (e.g., larynx, oral) See Genitourinary for Vulvovaginitis See also Dysphagia-Odynophagia and Proctitis	Erythema of the mucosa	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Tissue necrosis OR Diffuse spontaneous mucosal bleeding OR Life-threatening consequences (e.g., aspiration, choking)
Nausea	Transient (< 24 hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 – 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Pancreatitis	NA	Symptomatic AND Hospitalization not indicated (other than emergency room visit)	Symptomatic AND Hospitalization indicated (other than emergency room visit)	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)
Proctitis (functional-symptomatic) Also see Mucositis/stomatitis for clinical exam	Rectal discomfort AND No intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social & functional activities OR Operative intervention indicated	Life-threatening consequences (e.g., perforation)
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
NEUROLOGIC				
Alteration in personality-behavior or in mood (e.g., agitation, anxiety, depression, mania, psychosis)	Alteration causing no or minimal interference with usual social & functional activities	Alteration causing greater than minimal interference with usual social & functional activities	Alteration causing inability to perform usual social & functional activities	Behavior potentially harmful to self or others (e.g., suicidal and homicidal ideation or attempt, acute psychosis) OR Causing inability to perform basic self-care functions
Altered Mental Status For Dementia, see Cognitive and behavioral/attentional disturbance (including dementia and attention deficit disorder)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR obtundation, OR coma
Ataxia	Asymptomatic ataxia detectable on exam OR Minimal ataxia causing no or minimal interference with usual social & functional activities	Symptomatic ataxia causing greater than minimal interference with usual social & functional activities	Symptomatic ataxia causing inability to perform usual social & functional activities	Disabling ataxia causing inability to perform basic self-care functions

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Cognitive and behavioral/attentional disturbance (including dementia and attention deficit disorder)	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
CNS ischemia (acute)	NA	NA	Transient ischemic attack	Cerebral vascular accident (CVA, stroke) with neurological deficit
Developmental delay – **Pediatric ≤ 16 years**	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated (other than emergency room visit) OR Headache with significant impairment of alertness or other neurologic function
Insomnia	NA	Difficulty sleeping causing greater than minimal interference with usual social & functional activities	Difficulty sleeping causing inability to perform usual social & functional activities	Disabling insomnia causing inability to perform basic self-care functions
Neuromuscular weakness (including myopathy & neuropathy)	Asymptomatic with decreased strength on exam OR Minimal muscle weakness causing no or minimal interference with usual social & functional activities	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Neurosensory alteration (including paresthesia and painful neuropathy)	Asymptomatic with sensory alteration on exam or minimal paresthesia causing no or minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizure: (new onset) **– Adult ≥ 18 years** See also Seizure: (known pre-existing seizure disorder)	NA	1 seizure	2 – 4 seizures	Seizures of any kind which are prolonged, repetitive (e.g., status epilepticus), or difficult to control (e.g., refractory epilepsy)
Seizure: (known pre-existing seizure disorder) **– Adult ≥ 18 years** For worsening of existing epilepsy the grades should be based on an increase from previous level of control to any of these levels.	NA	Increased frequency of pre-existing seizures (non-repetitive) without change in seizure character OR infrequent break- through seizures while on stable medication in a previously controlled seizure disorder	Change in seizure character from baseline either in duration or quality (e.g., severity or focality)	Seizures of any kind which are prolonged, repetitive (e.g., status epilepticus), or difficult to control (e.g., refractory epilepsy)
Seizure **– Pediatric < 18** years	Seizure, generalized onset with or without secondary generalization, lasting < 5 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting 5 – 20 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting > 20 minutes	Seizure, generalized onset with or without secondary generalization, requiring intubation and sedation
Syncope (not associated with a procedure)	NA	Present	NA	NA
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
RESPIRATORY				
Bronchospasm (acute)	FEV1 or peak flow reduced to 70 – 80%	FEV1 or peak flow 50 – 69%	FEV1 or peak flow 25 – 49%	Cyanosis OR FEV1 or peak flow < 25% OR intubation
Dyspnea or respiratory distress				
Adult ≥ 14 years	Dyspnea on exertion with no or minimal interference with usual social & functional activities	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities	Dyspnea at rest causing inability to perform usual social & functional activities	Respiratory failure with ventilatory support indicated
Pediatric < 14 years	Wheezing OR minimal increase in respiratory rate for age	Nasal flaring OR intercostal retractions OR Pulse oximetry 90 – 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilatory support indicated
MUSCULOSKELETAL				
Arthralgia See also Arthritis	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis See also Arthralgia	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Bone Mineral Loss				
Adult ≥ 21 years	BMD t-score -2.5 to -1.0	BMD t-score < -2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Pediatric < 21 years	BMD z-score -2.5 to -1.0	BMD z-score < -2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Myalgia (non-injection site)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Osteonecrosis	NA	Asymptomatic with radiographic findings AND No operative intervention indicated	Symptomatic bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions
GENITOURINARY				
Cervicitis (symptoms) (For use in studies evaluating topical study agents) For other cervicitis see Infection: Infection (any other than HIV infection)	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions
Cervicitis (clinical exam) (For use in studies evaluating topical study agents) For other cervicitis see Infection: Infection (any other than HIV infection)	Minimal cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption < 25% of total surface	Moderate cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption of 25 – 49% total surface	Severe cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption 50 – 75% total surface	Epithelial disruption > 75% total surface
Inter-menstrual bleeding (IMB)	Spotting observed by participant OR Minimal blood observed during clinical or colposcopic examination	Inter-menstrual bleeding not greater in duration or amount than usual menstrual cycle	Inter-menstrual bleeding greater in duration or amount than usual menstrual cycle	Hemorrhage with life-threatening hypotension OR Operative intervention indicated
Urinary tract obstruction (e.g., stone)	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Vulvovaginitis (symptoms) (Use in studies evaluating topical study agents) For other vulvovaginitis see Infection: Infection (any other than HIV Infection)	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions
Vulvovaginitis (clinical exam) (Use in studies evaluating topical study agents) For other vulvovaginitis see Infection: Infection (any other than HIV Infection)	Minimal vaginal abnormalities on examination OR Epithelial disruption < 25% of total surface	Moderate vaginal abnormalities on examination OR Epithelial disruption of 25 - 49% total surface	Severe vaginal abnormalities on examination OR Epithelial disruption 50 - 75% total surface	Vaginal perforation OR Epithelial disruption > 75% total surface
OCULAR/VISUAL				
Uveitis	Asymptomatic but detectable on exam	Symptomatic anterior uveitis OR Medical intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Visual changes (from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)
ENDOCRINE/METABOLIC				
Abnormal fat accumulation (e.g., back of neck, breasts, abdomen)	Detectable by study participant (or by caregiver for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious changes on casual visual inspection	NA
Diabetes mellitus	NA	New onset without need to initiate medication OR Modification of current medications to regain glucose control	New onset with initiation of medication indicated OR Diabetes uncontrolled despite treatment modification	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma)

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Gynecomastia	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA
Hyperthyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., thyroid storm)
Hypothyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., myxedema coma)
Lipoatrophy (e.g., fat loss from the face, extremities, buttocks)	Detectable by study participant (or by caregiver for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

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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/mm^3 *300 – 400/µL*	200 – 299/mm^3 *200 – 299/µL*	100 – 199/mm^3 *100 – 199/µL*	< 100/mm^3 *< 100/µL*
Absolute lymphocyte count – **Adult and Pediatric > 13 years** (HIV NEGATIVE ONLY)	600 – 650/mm^3 *0.600 x 10^9/L – 0.650 x 10^9/L*	500 – 599/mm^3 *0.500 x 10^9/L – 0.599 x 10^9/L*	350 – 499/mm^3 *0.350 x 10^9/L – 0.499 x 10^9/L*	< 350/mm^3 *< 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/mm^3 *1.000 x 10^9/L – 1.300 x 10^9/L*	750 – 999/mm^3 *0.750 x 10^9/L – 0.999 x 10^9/L*	500 – 749/mm^3 *0.500 x 10^9/L – 0.749 x 10^9/L*	< 500/mm^3 *< 0.500 x 10^9/L*
Infant*†, 2 – ≤ 7 days	1,250 – 1,500/mm^3 *1.250 x 10^9/L – 1.500 x 10^9/L*	1,000 – 1,249/mm^3 *1.000 x 10^9/L – 1.249 x 10^9/L*	750 – 999/mm^3 *0.750 x 10^9/L – 0.999 x 10^9/L*	< 750/mm^3 *< 0.750 x 10^9/L*
Infant*†, ≤1 day	4,000 – 5,000/mm^3 *4.000 x 10^9/L – 5.000 x 10^9/L*	3,000 – 3,999/mm^3 *3.000 x 10^9/L – 3.999 x10^9/L*	1,500 – 2,999/mm^3 *1.500 x 10^9/L – 2.999 x 10^9/L*	< 1,500/mm^3 *< 1.500 x 10^9/L*
Comment: Parameter changed from "Infant, < 1 day" to "Infant, ≤1 day"				
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

* 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**
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 - 5.52 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				
Infant*†, **36 – 56 days** (HIV POSITIVE OR NEGATIVE)	8.5 – 9.4 g/dL *5.24 – 5.80 mmol/L*	7.0 – 8.4 g/dL *4.31 – 5.23 mmol/L*	6.0 – 6.9 g/dL *3.72 – 4.30 mmol/L*	< 6.00 g/dL *< 3.72 mmol/L*
Infant*†, **22 – 35 days** (HIV POSITIVE OR NEGATIVE)	9.5 – 10.5 g/dL *5.87 - 6.54 mmol/L*	8.0 – 9.4 g/dL *4.93 – 5.80 mmol/L*	7.0 – 7.9 g/dL *4.34 – 4.92 mmol/L*	< 7.00 g/dL *< 4.34 mmol/L*
Infant*†, **≤ 21 days** (HIV POSITIVE OR NEGATIVE)	12.0 – 13.0 g/dL *7.42 – 8.09 mmol/L*	10.0 – 11.9 g/dL *6.18 – 7.41 mmol/L*	9.0 – 9.9 g/dL *5.59- 6.17 mmol/L*	< 9.0 g/dL *< 5.59 mmol/L*
Correction: Parameter changed from "Infant < 21 days" to "Infant ≤ 21 days"				
International Normalized Ratio of prothrombin time (INR)	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 3.0 x ULN	> 3.0 x ULN
Methemoglobin	5.0 – 10.0%	10.1 – 15.0%	15.1 – 20.0%	> 20.0%
Prothrombin Time (PT)	1.1 – 1.25 x ULN	1.26 – 1.50 x ULN	1.51 – 3.00 x ULN	> 3.00 x ULN
Partial Thromboplastin Time (PTT)	1.1 – 1.66 x ULN	1.67 – 2.33 x ULN	2.34 – 3.00 x ULN	> 3.00 x ULN
Platelets, decreased	100,000 – 124,999/mm^3 *100.000 x 10^9 – 124.999 x 10^9/L*	50,000 – 99,999/mm^3 *50.000 x 10^9 – 99.999 x 10^9/L*	25,000 – 49,999/mm^3 *25.000 x 10^9 – 49.999 x 10^9/L*	< 25,000/mm^3 *< 25.000 x 10^9/L*
WBC, decreased	2,000 – 2,500/mm^3 *2.000 x 10^9 – 2.500 x 10^9/L*	1,500 – 1,999/mm^3 *1.500 x 10^9 – 1.999 x 10^9/L*	1,000 – 1,499/mm^3 *1.000 x 10^9 – 1.499 x 10^9/L*	< 1,000/mm^3 *< 1.000 x 10^9/L*

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† 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
Infant*†, ≤ 14 days (non-hemolytic)	NA	20.0 – 25.0 mg/dL *342 – 428 µmol/L*	25.1 – 30.0 mg/dL *429 – 513 µmol/L*	> 30.0 mg/dL *> 513.0 µmol/L*
Infant*†, ≤ 14 days (hemolytic)	NA	NA	20.0 – 25.0 mg/dL *342 – 428 µmol/L*	> 25.0 mg/dL *> 428 µmol/L*
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*
Infant*†, < 7 days	11.5 – 12.4 mg/dL *2.88 – 3.10 mmol/L*	12.5 – 12.9 mg/dL *3.11 – 3.23 mmol/L*	13.0 – 13.5 mg/dL *3.245 – 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*
Infant*†, < 7 days	6.5 – 7.5 mg/dL *1.63 – 1.88 mmol/L*	6.0 – 6.4 mg/dL *1.50 – 1.62 mmol/L*	5.50 – 5.90 mg/dL *1.38 – 1.51 mmol/L*	< 5.50 mg/dL *< 1.38 mmol/L*
Comment: Do not adjust Calcium, serum, low or Calcium, serum, high for albumin				

* 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**
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 – 3.00 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

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

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

Comment: Added ULN to Grade 1 parameter				
LDL cholesterol (fasting)				
Adult ≥ 18 years	130 – 159 mg/dL 3.37 – 4.12 mmol/L	160 – 190 mg/dL 4.13 – 4.90 mmol/L	≥ 190 mg/dL ≥ 4.91 mmol/L	NA
Pediatric > 2 - < 18 years	110 – 129 mg/dL 2.85 – 3.34 mmol/L	130 – 189 mg/dL 3.35 – 4.90 mmol/L	≥ 190 mg/dL ≥ 4.91 mmol/L	NA
Lipase	1.1 – 1.5 x ULN	1.6 – 3.0 x ULN	3.1 – 5.0 x ULN	> 5.0 x ULN
Magnesium, serum, low	1.2 – 1.4 mEq/L 0.60 – 0.70 mmol/L	0.9 – 1.1 mEq/L 0.45 – 0.59 mmol/L	0.6 – 0.8 mEq/L 0.30 – 0.44 mmol/L	< 0.60 mEq/L < 0.30 mmol/L
Pancreatic amylase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN
Phosphate, serum, low				
Adult and Pediatric > 14 years	2.5 mg/dL – < LLN 0.81 mmol/L – < LLN	2.0 – 2.4 mg/dL 0.65 – 0.80 mmol/L	1.0 – 1.9 mg/dL 0.32 – 0.64 mmol/L	< 1.00 mg/dL < 0.32 mmol/L
Pediatric 1 year – 14 years	3.0 – 3.5 mg/dL 0.97 – 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

* 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
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/m^2/24 h *0.201 – 0.400 g/d*	500 – 799 mg/m^2/24 h *0.500 – 0.700 g/d*	800 – 1,000 mg/m^2/24 h *0.800 – 1.000 g/d*	> 1,000 mg/m^2/24 h *> 1.000 g/d*

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

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

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	