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**TITLE:**

A Multiple Rising Dose Study to Assess the Safety and Pharmacokinetics of MK-8591 in Healthy Adults

**EudraCT NUMBER:** 2014-000635-16

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## SUMMARY OF CHANGES

**PRIMARY REASON(S) FOR THIS AMENDMENT:**

| Section Number (s) | Section Title(s) | Description of Change (s) | Rationale |
|---|---|---|---|
| 4.2.1 | Rationale for Amendment | Due to preliminary preclinical dental findings in rats that received MK-8591 at doses resulting in exposures higher than exposures in Panel C subjects, we have asked the Panel C subjects to have a voluntary, standard dental examination. | Due to preliminary preclinical dental findings in rats that received MK-8591 at doses resulting in exposures higher than exposures in Panel C subjects, we have asked the Panel C subjects to have a voluntary, standard dental examination. |
| 6.0 | Study Flow Chart | A standard dental examination for Panel C subjects was added to the post trial visit. | Due to preliminary preclinical dental findings in rats that received MK-8591 at doses resulting in exposures higher than exposures in Panel C subjects, we have asked the Panel C subjects to have a voluntary, standard dental examination. |

**ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:**

No additional changes.

## 1.0 TRIAL SUMMARY

| | |
|---|---|
| Abbreviated Title | Multiple Rising Dose Study to Evaluate Safety and PK of MK-8591 in Healthy Adult Subjects |
| Trial Phase | I |
| Clinical Indication | Treatment of HIV Infection |
| Trial Type | Interventional |
| Type of control | Placebo |
| Route of administration | Oral |
| Trial Blinding | Double-blind |
| Treatment Groups | Three panels of 8 subjects (6 active, 2 placebo) will receive three once weekly doses of MK-8591 and two panels of 8 subjects (6 active, 2 placebo) will receive nine daily doses of MK-8591. |
| Number of trial subjects | Approximately 40 subjects will be enrolled. |
| Estimated duration of trial | The sponsor estimates that the trial will require approximately 7 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 9 weeks from the time the subject signs the Informed Consent Form (ICF) through the final contact. After a screening phase of 3 weeks, subjects in Panels A, B, and C will be receiving assigned treatment for approximately 3 weeks. Subjects in Panels D and E will receive assigned treatment for approximately 9 days. After the end of treatment each subject will be followed for 3 weeks. |

| | |
|---|---|
| Randomization Ratio | 3:1 |

## 2.0 TRIAL DESIGN

### 2.1 Trial Design

This is a randomized, placebo-controlled, serial panel, rising multiple dose, double-blind trial of MK-8591 in healthy adult subjects (men and women of non-childbearing potential). The study will be conducted at a single site in conformance with Good Clinical Practices. Three serial panels (A, B, and C) consisting of 8 subjects each, will be administered three once weekly doses of MK-8591 (n=6) or placebo (n=2) on Days 1, 8, and 15. Two serial panels (D and E) will be administered once daily doses of MK-8591 (n=6) or placebo (n=2) on Days 1-9.

For each panel, safety, tolerability, and pharmacokinetics (when available) will be reviewed by the Investigator and SPONSOR. The decision to proceed to the next panel in the sequence will be contingent on acceptable safety and tolerability from the preceding panel. This includes an assessment of safety laboratory tests and potential adverse events. For Panels A, B, and C at least 10 days will separate the final multiple dose in one panel and the initial multiple dose of the next panel. For Panels D and E at least 7 days will separate the final multiple dose in one panel and the initial multiple dose of the next panel.

Initiation of Panel A will be contingent upon satisfactory evaluation of available clinical and laboratory safety data from MK-8591 Protocol 001, the single rising dose study recently being completed. Available preliminary pharmacokinetic data from Protocol 001 (up to 400 mg) will be used to guide dose escalation in this study and provided to the investigator prior to the start of this study. Review of preliminary pharmacokinetic data from this study may also be used to advance to the next dose.

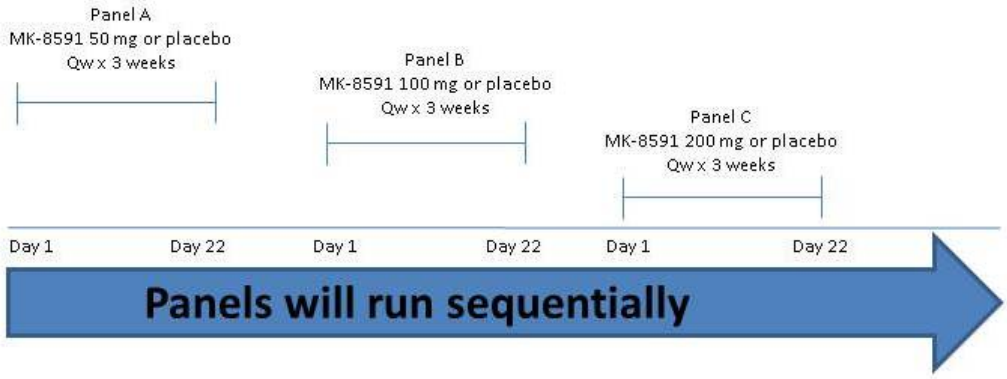
Subjects may participate in only one panel. In all panels, the subjects and investigator will be blinded to the MK-8591/placebo treatment.

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 suggested multiple dose escalation scheme are presented in Figure 1 and Table 1.



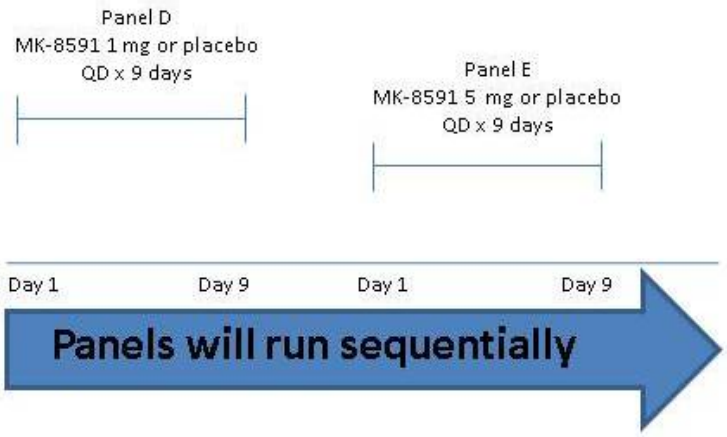



Figure 1 Trial Diagram

Table 1 MK-8591 Multiple Dose Escalation Scheme

| Panel[a] | MK-8591 Dose[b] |
|---|---|
| A | 50[c] mg once weekly on Days 1, 8 and 15 |
| B | 100 [c] mg once weekly on Days 1, 8 and 15 |
| C | 200 [c] mg once weekly on Days 1, 8 and 15 |
| D | 1 mg once daily on Days 1-9 |
| E | 5 mg once daily on Days 1-9 |

[a] Within each treatment period, 6 subjects will be randomized to receive MK-8591 and 2 subjects to receive matching placebo according to a computer-generated allocation schedule.
[b] The suggested doses of MK-8591 may be adjusted downwards based on evaluation of available safety and/or pharmacokinetic data observed in previous panels or from Protocol 001.
[c] Doses have been adjusted downwards to 10 mg once weekly for Panel A, 30 mg once weekly for Panel B, and 100 mg once weekly for Panel C

## 3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

### 3.1 Primary Objective(s) & Hypothesis(es)

1) **Objective:** To assess the safety of a multiple rising dose of MK-8591 in healthy adult subjects.

2) **Objective**: To obtain a preliminary intracellular PK profile of MK-8591 triphosphate and to determine PK parameter values (including $AUC_{0\text{-}24,}$ $AUC0_{\text{-}168}$, $T_{max}$, $C_{max}$, $C_{24hr}$, $C_{168hr}$, and apparent terminal $t_{1/2}$) in peripheral blood mononuclear cells (PBMC) after administration of multiple oral doses of MK-8591 to healthy adult subjects.

**Hypotheses:** The true geometric mean intracellular MK-8591 triphosphate $C_{168hr}$ (Panels A, B, and C) or $C_{24hr}$ (Panels D and E) is $\geq$ 0.53 pmol/$10^6$ cells for at least one dose level that also exhibits an acceptable safety and tolerability profile

3) **Objective:** To obtain a preliminary plasma PK profile of MK-8591 and to determine PK parameter values (including $AUC_{0-24}$, $AUC_{0-168}$, $T_{max}$, $C_{max}$, and apparent terminal $t_{1/2}$) after administration of multiple oral doses of MK-8591 to healthy adult subjects.

**Hypotheses (Estimation):** The preliminary plasma pharmacokinetic PK profile of MK-8591 including $AUC_{0-24}$ ,$AUC_{0-168}$, $T_{max}$, $C_{max}$, and apparent terminal $t_{1/2}$ after administration of multiple oral doses of MK-8591 to healthy adult subjects will be estimated.

### 3.2 Secondary Objective(s) & Hypothesis(es)

There are no secondary objectives or hypotheses.

### 3.3 Exploratory Objectives

(1) To compare the intracellular pharmacokinetics of MK-8591 triphosphate in PBMCs (including $AUC_{0-24hr}$, $AUC_{0-168hr}$, $C_{max}$, $T_{max}$, $C_{24\ hr}$, $C_{168hr}$, and apparent terminal $t_{1/2}$) following a single dose of the MK-8591 solid capsule formulation with that of the oral suspension administered in Protocol 001

(2) To compare the plasma pharmacokinetics (including $AUC_{0-\infty}$, $C_{max}$, $T_{max}$, and apparent terminal $t_{1/2}$) of a single dose of the MK-8591 solid capsule formulation with that of the oral suspension administered in Protocol 001.

(3) To evaluate urinary excretion of intact MK-8591 following multiple dose administration.

## 4.0 BACKGROUND & RATIONALE

### 4.1 Background

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

#### 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 patients 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 Ongoing Clinical Trials

MK-8591 has been tested in a rising single dose study in healthy male and female subjects (Protocol 001). In this study, subjects were randomized to 1 of 3 panels (A, B, or C) consisting of 8 subjects. Within each panel, subjects were administered either MK-8591 (N=6) or placebo (N=2) in a blinded fashion. The actual doses for Protocol 001 were 5, 15, 30, 100, 200, 400, 30mg (with food). MK-8591 is formulated as an oral suspension in Protocol 001.

Preliminary safety data indicate that MK-8591 is generally well tolerated. No serious adverse experiences have been reported and no subject has been discontinued due to an adverse experience. A preliminary summary of the number of subjects reporting adverse experiences that have occurred at each dose level is provided in Table 2. The study is still blinded.

Table 2 Preliminary Summary of Number of Subjects Reporting Adverse Experiences for Each Dose Level in Protocol 001

| | **MK-8591or Placebo[†‡]** | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Panel A, Period 1** | **Panel B, Period 1** | **Panel C, Period 1** | **Panel A, Period 2** | **Panel B, Period 2** | **Panel C, Period 2** | **Panel B, Period 3** |
| **Adverse Experience** | **15 mg** | **30 mg** | **100 mg** | **200 mg** | **400 mg** | **5mg** | **30 mg with food** |
| Abdominal discomfort | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Abdominal pain upper | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Application site irritation | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Back pain | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Catheter site pain | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Contusion | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Eyelid irritation | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Headache | 3 | 3 | 1 | 2 | 4 | 1 | 0 |
| Nasopharyngitis | 2 | 1 | 0 | 0 | 0 | 1 | 0 |
| Oral herpes | 0 | 0 | 2 | 0 | 0 | 0 | 0 |
| Somnolence | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Vessel puncture site pain | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Wound | 0 | 0 | 0 | 0 | 0 | 1 | 0 |

[†]Data for this trial is still blinded, all adverse experiences regardless of causality are listed.
[‡]N = 8 subjects per dose (6 active/2placebo)

A summary of preliminary mean MK-8591 plasma pharmacokinetics from Protocol 001 is provided in Table 3 and Table 4. Preliminary pharmacokinetic data indicate MK-8591 was rapidly absorbed with a median Tmax of 0.5 hour (range of 0.25-1.00). Plasma concentrations decreased in a bi-phasic manner with a rapid initial phase (Cmax reduced by approximately 10-fold within the first 6-8 hours) and a slow terminal phase with an apparent terminal half-life of 50-60 hours. Variability of PK parameters between subjects was considerably small with a coefficient of variation (CV) generally <20%. MK-8591 plasma exposure appeared to increase in an approximately dose-proportional manner between 5 and 400 mg. A high-fat meal co-administered with 30 mg MK-8591 had a minimal impact on MK-8591 plasma AUC and decreased Cmax on the order of ~50%.

Table 3 Summary of Preliminary Pharmacokinetic Parameter Values for Plasma MK-8591 Following Administration of Single Oral Doses to Healthy Adult Subjects

| Dose (mg) | Panel/ Period | N | Geometric Mean (%GCV) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | AUC0-∞ (µM*hr) | AUC0-last[§] (µM*hr) | AUC0-168hr[%] (µM*hr) | Cmax (µM) | Tmax[†] (hr) | $t_{1/2}$ (hr) | Cl/F (L/hr) | Vz/F (L) |
| **5** | **C2** | **6** | -- | 0.357[¶] (15.1) | -- | 0.147 (8.2) | 0.50 (0.50, 0.50) | -- | -- | -- |
| **15** | **A1** | **6** | 1.57 (17.8) | 1.25[‡] (22.4) | 1.40 (21.1) | 0.385 (33.1) | 0.50 (0.25, 1.00) | 51.2 (16.8) | 32.5 (17.8) | 2400 (15.2) |
| **30** | **B1** | **6** | 3.84 (15.9) | 3.40 (12.3) | 3.68 (14.2) | 1.05 (19.5) | 0.50 (0.25, 0.50) | 48.7 (13.1) | 26.7 (15.9) | 1870 (6.4) |
| **100** | **C1** | **6** | 11.7 (15.8) | 10.1 (14.4) | 11.0 (15.1) | 3.23 (19.6) | 0.50 (0.25, 0.50) | 58.8 (7.3) | 29.3 (15.8) | 2480 (13.7) |
| **200** | **A2** | **6** | 25.0 (8.8) | 21.7 (9.3) | 23.5 (9.0) | 6.17 (30.9) | 0.50 (0.50, 0.50) | 61.3 (8.3) | 27.3 (8.8) | 2410 (12.7) |
| **400** | **B2** | **6** | 49.0 (15.5) | 44.7 (15.3) | 47.5 (15.5) | 9.76 (11.9) | 0.50 (0.50, 1.00) | 48.5 (7.1) | 27.8 (15.5) | 1950 (17.5) |
| **30 (fed)** | **B3** | **6** | 4.21 (21.1) | 3.43 (15.2) | 3.85 (16.9) | 0.535 (40.0) | 1.25 (0.50, 4.00) | 63.5 (20.7) | 24.3 (21.1) | 2230 (13.9) |
| **GMR Fed/Fasted (30mg)[&]** | | **6** | 1.10 | -- | -- | 0.51 | -- | -- | -- | -- |

N: Number of subjects; %GCV: The geometric mean percent coefficient of variation
[†] Median (Min, Max)
[§] Plasma samples were collected up to 96 hrs.
[%] AUC0-168 was extrapolated from 96hr to 168hr.
-- Values could not be determined due to insufficient data in the terminal phase.
[¶] AUC0-12hr for 4 subjects, AUC0-16hr for 1 subject and AUC0-24hr for 1 subject
[‡] AUC0-48hr for 2 subjects and AUC0-96hr for 4 subjects
[&] Geometric Mean Ratio of Fed/Fasted, calculated by QP2

MK-8591 diphosphate and triphosphate concentrations were assessed in PBMCs. Data are presented in Table 2. Intracellular MK-8591 triphosphate concentrations increased roughly dose proportionally. Half-life was between 116 and 211 hours.

Table 4 Summary Pharmacokinetics for MK-8591 metabolites in PBMCs Following Administration of 15-400 mg Single Oral Doses of MK-8591 to Healthy Fasted Male and Female Subjects (Preliminary Results).

| Dose (mg) | Panel/ Period | Analyte | N | Geometric Mean (%GCV) | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | AUC0-∞[&¶§] (hr*pmol/$10^6$cells) | AUC0-168hr (hr*pmol/$10^6$cells) | C168hr (pmol/$10^6$cells) | Cmax (pmol/$10^6$cells) | Tmax[†] (hr) | $t_{1/2}$ (hr) |
| 5[α] | C2 | MK-8591-MP | 6 | -- | -- | -- | 0.162 (31.8) | 6.00 (6.00, 24.00) | -- |
| | | MK-8591-DP[£] | 6 | 106[‡] (31.5) | 44.8 (30.4) | 0.151 (106.0) | 0.488 (27.4) | 18.00 (6.00, 96.00) | 225[‡] (45.7) |
| | | MK-8591-TP[£] (active moiety) | 6 | 164 (57.3) | 92.5 (49.6) | 0.294 (95.9) | 1.07 (26.1) | 9.00 (6.00, 24.00) | 126 (50.2) |
| 15 | A1 | MK-8591-MP | 6 | 73.6[‡] (20.5) | 28.9 (43.3) | 0.137 (46.0) | 0.590 (22.3) | 6.03 (6.00, 24.00) | 180[‡] (42.1) |
| | | MK-8591-DP | 6 | 501[‡] (42.6) | 241 (21.3) | 0.942 (33.8) | 2.23 (16.4) | 24.00 (6.00, 96.00) | 189[‡] (38.2) |
| | | MK-8591-TP (active moiety) | 6 | 668 (39.1) | 341 (27.1) | 1.24 (38.2) | 3.65 (53.2) | 6.00 (6.00, 48.07) | 161 (29.6) |
| 30 | B1 | MK-8591-MP | 6 | 99.2 (33.6) | 65.6 (13.7) | 0.170 (26.9) | 1.04 (16.8) | 6.00 (6.00, 12.00) | 100 (63.9) |
| | | MK-8591-DP | 6 | 667 (34.4) | 418 (20.5) | 1.39 (30.8) | 5.07 (19.2) | 12.00 (12.00, 12.08) | 105 (32.2) |
| | | MK-8591-TP (active moiety) | 6 | 1410 (19.6) | 870 (11.6) | 2.77 (26.9) | 8.26 (19.4) | 24.00 (6.00, 48.00) | 118 (23.9) |
| 100 | C1 | MK-8591-MP | 6 | 274 (19.5) | 170 (24.3) | 0.558 (27.5) | 3.20 (26.8) | 6.00 (6.00, 6.00) | 123 (11.3) |
| | | MK-8591-DP | 6 | 1540[‡] (25.7) | 884 (34.1) | 3.25 (24.3) | 12.9 (23.9) | 12.00 (12.00, 96.02) | 153[‡] (40.1) |
| | | MK-8591-TP (active moiety) | 6 | 2950[‡] (62.1) | 1320 (20.0) | 4.80 (38.1) | 14.7 (27.6) | 24.00 (12.00, 96.02) | 211[‡] (106.8) |
| 200 | A2 | MK-8591-MP | 6 | 440 (20.1) | 299 (16.8) | 0.611 (30.2) | 7.71 (27.0) | 6.00 (6.00, 6.00) | 112 (15.8) |
| | | MK-8591-DP | 6 | 1930 (36.7) | 1050 (12.3) | 2.40 (131.3) | 12.8 (17.1) | 18.00 (6.00, 48.00) | 155 (34.8) |
| | | MK-8591-TP (active moiety) | 6 | 4820 (28.9) | 3090 (24.5) | 7.73 (17.1) | 37.3 (26.4) | 6.00 (6.00, 12.00) | 116 (13.3) |
| 400 | B2 | MK-8591-MP | 6 | 761 (17.1) | 490 (15.5) | 1.37 (24.4) | 9.90 (39.1) | 6.00 (6.00, 6.08) | 127 (12.6) |
| | | MK-8591-DP | 6 | 3330 (10.9) | 1740 (23.3) | 7.39 (31.0) | 19.5 (22.8) | 6.00 (6.00, 6.08) | 138 (25.9) |
| | | MK-8591-TP | 6 | 9420 (23.9) | 5420 (13.8) | 18.3 (28.2) | 65.0 (23.4) | 12.08 (6.08, 24.13) | 143 (35.8) |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | **(active moiety)** | | | | | | | |
| **30[α] (fed)** | **B3** | **MK-8591-MP** | **6** | -- | -- | -- | 1.68 (29.2) | 6.00 (6.00, 6.00) | -- |
| | | **MK-8591-DP[£]** | **6** | 318[‖] (13.3) | 204[#] (32.2) | 0.832 (18.8) | 2.52 (44.0) | 15.00 (6.00, 24.00) | 110[‖] (49.5) |
| | | **MK-8591-TP[£] (active moiety)** | **6** | 1120[#] (57.6) | 614[$] (35.2) | 2.70[#] (127.0) | 7.90 (23.7) | 18.00 (6.00, 24.00) | 120[#] (72.9) |
| GMR Fed/Fasted (30mg) | | **MK-8591-TP** | **6** | 0.77 | -- | 0.96 | 0.96 | -- | -- |

N: Number of subjects; PBMC: Peripheral Blood Mononuclear Cells; %GCV: The geometric mean percent coefficient of variation
MK-8591-MP: MK-8591Monophosphate; MK-8591-DP: MK-8591Diphosphate;MK-8591 TP: MK-8591Triphosphate
[†] Median (Min, Max)
[α] NCAs (non-compartmental analysis) of 5 mg and 30 mg fed treatments were conducted using prescribed times (relative nominal times) as the actual times were unavailable at the time of the analysis. For other treatments, relative actual times were used for the analysis.
[£] Predose concentrations were greater than 5% of Cmax for some subjects, presumably from the previous treatment period and, therefore, carryover concentrations were estimated and subtracted from the reported concentrations before NCA was conducted.
-- Parameters could not be determined due to insufficient data in the terminal phase
[‡] N=5, as one subject had insufficient data in the terminal phase.
[&] AUC% extrapolation for MK-8591-MP were above 25 % for some subjects; 5 subjects in A1 (36.1, 32.2, 48.3, 47.1, 30.3%) in A1, 2 subjects in B1 (63.1, 29.8%).
[¶] AUC% extrapolation for MK-8591-DP were above 25% for some subjects; 2 subjects in A1 (44.9 and 38.8%), 1 subjects in B1(27.6%), 2 subjects in C1 (37.1, 25.4%), 3 subjects in A2 (32.6, 25.1, 35.8%), 1 subject (37.0%) in B2, 4 subjects (41.0, 25.7, 60.3, 26.7%) in C2, and 2 subjects (33.1, 60.6%) in B3.
[§] AUC% extrapolation for MK-8591-TP were above 25% for some subjects; 1 subject in A1 (40.2%), 3 subjects in C1 (26.7, 55.2, 62.3%), 2 subjects in B2 (27.9, 35.1, 15.1%), and 3 subjects in B3 (35, 30.3, 28.5%).
[‖] N=3, as one subject discontinued the study due to personal reasons after t=96 hr postdose and two subjects had insufficient data in the terminal phase
[#] N=5, as one subject discontinued the study due to personal reasons after t=96 hr postdose
[$] AUC0-168 was extrapolated from 96hr to 168hr for the discontinued subject.

## 4.2 Rationale

### 4.2.1 Rationale for the Trial and Selected Subject Population

MK-8591 is a NRTI being developed as a novel best in class therapy for the treatment of HIV-1 infection. The purpose of this study is to assess the initial safety and pharmacokinetics (plasma and PBMC) of multiple oral doses of MK-8591 in healthy adult subjects. Pharmacokinetic and safety data from this study will be used to appropriately select doses for future studies in healthy subjects and pharmacodynamic/efficacy studies in HIV-1 infected patients. Assessing MK-8591 in healthy volunteers provides an opportunity to collect safety and pharmacokinetic data in a population without interfering variable factors secondary to HIV infection prior to initiating patient studies.

This study will be the first multiple dose administration of MK-8591 to human subjects and will include a new solid capsule formulation. One of the study's exploratory objectives will be to determine any potential differences in plasma and PMBC pharmacokinetic performance between the new formulation and that of the oral suspension used in Protocol 001.

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

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.

**Rationale for Amendment**

For Amendment 01, the primary reason for amending the protocol is to assess the multiple dose safety, tolerability, and pharmacokinetics of MK-8591 administered once daily for 9 days in Panels D and E. This will allow for the potential of administering MK-8591 once daily as an alternative dosing regimen in future studies.

An additional reason for amending is to allow for the use of 1 mg dose potency capsule. The lower potency provides greater flexibility in dose.

For Amendment 03, due to preliminary preclinical dental findings in rats that received MK-8591 at doses resulting in exposures higher than exposures in Panel C subjects, we have asked the Panel C subjects to have a voluntary, standard dental examination.

### 4.2.2 Rationale for Dose Selection/Regimen

The primary objectives of this study are to assess the preliminary safety and pharmacokinetics (plasma and PBMC) of MK-8591 following three once weekly doses and once daily administration for 9 days.

Panels A, B, C (Once weekly administration)

Based on the predicted long half-life (~90h) of MK-8591 intracellular triphosphate, three weeks of dosing will help to quantify the steady state pharmacokinetics and evaluate the safety of longer term administration.

The proposed once weekly multiple doses of 50, 100, and 200 mg correspond to 0.83 to 3.34 mg/kg in a 60 kg subject. These doses were selected for safety considerations as well as a desire to bracket the projected therapeutic dose. Data from preclinical experiments, combined with an assumption that MK-8591 potency against SIV and HIV is similar, predict a human efficacious dose between 30 to 300 mg. It is expected that a dose within this range will reach the C168 hr intracellular triphosphate target of 0.53 pmol/$10^6$ cells that achieved efficacy in the monkey SIV model. While the intracellular triphosphate levels are the primary driver of efficacy, MK-8591 plasma concentrations are used for preclinical and clinical safety monitoring. The corresponding MK-8591 plasma AUC0-168 and Cmax predicted to achieve the target C168 hr triphosphate are 1.3-12.8 uM·hr and 0.2-2.5uM, respectively.

Panels D and E (once daily administration)

Based on the predicted long half-life (~120 hr) intracellular triphosphate levels are predicted to achieve steady at ~21 days. However, dosing in Panels D and E will be limited to 9 once daily doses as this was the number of doses administered in the 29-day monkey toxicity study. While this is less than what is needed to achieve steady state, 9 days of dosing should provide a good approximation of MK-8591's safety and pharmacokinetics upon once daily dosing.

The proposed once daily doses for Panels D and E are 1 and 5 mg and correspond to 0.017 to 0.083 mg/kg. These doses were selected for safety considerations as well as a desire to bracket the projected therapeutic dose. It is therefore expected that a dose within 1 to 5 mg will reach the intracellular triphosphate target of 0.53 pmol/$10^6$ cells at 24 hours postdose.. Based on the preliminary plasma pharmacokinetic data from Protocol 001, a single 5 mg dose of MK-8591 is anticipated to achieve a Day 9 plasma MK-8591$AUC_{0\text{-}24}$ hr of ~0.51 uM·hr and a Cmax of ~0.15 uM . If MK-8591 plasma pharmacokinetics scale down in a proportional manner, a 1 mg dose is anticipated to result in a Day 9 $AUC_{0\text{-}24}$ of ~0.1 uM·hr and a Cmax ~0.03uM.

All doses of MK-8591 administered in this study, either once weekly or once daily, are expected to be well tolerated. Preliminary data from Protocol 001 indicate that single doses of up to 400 mg have been well tolerated. Additionally, selected doses are supported by preclinical toxicity studies in rats and monkeys, which have explored the potential toxicities that might occur in this clinical trial.

In a 7 day exploratory toxicity study in rats, MK-8591 was administered at 0, 10, 30, or 100 mg/kg/day. There were no pathology changes at 10 or 30 mg/kg. At 100 mg/kg, very slight degeneration of the glandular mucosa of the stomach was observed. The mean plasma $AUC_{0\text{-}24}$ and Cmax at 100 mg/kg were 213 µM•hr and 28.3 µM, respectively. This provides a ~417.6 margin to the predicted therapeutic $AUC_{0\text{-}24}$ and a ~135 margin to the predicted Cmax following administration of 5 mg once daily for 9 days.

In the 29 day rat toxicity study, MK-8591 was administered once a day at 0, 3 10, or 50 mg/kg/day. MK-8591 was well tolerated and there were no adverse findings up to 50 mg/kg/day. [redacted] Based on the lack of adverse findings in the 29-day study in rats and the ability to monitor the very slight, non-adverse clinical pathology changes, the NOAEL for rats was ≥50 mg/kg/day ($AUC_{0\text{-}24\ hr}$: 86.5 µM•hr [**AUC0-168 hr**: 605.5 µM•hr] and Cmax of 18.9 µM). This provides a ~47 to 468-fold margin to the predicted clinical plasma $AUC_{0\text{-}24}$/$AUC_{0\text{-}168\ hr}$ target and a ~7.6 to 95-fold margin to predicted clinical Cmax.

In an exploratory oral rising-dose toxicity study in monkeys, MK-8591 was administered once daily for 10 days. Monkeys received 10 mg/kg/day for 3 days, 30 mg/kg/day for 4 days, and 75 mg/kg/day for 3 days with no washout interval between dose levels. [redacted]. Based on the mean plasma levels observed at 10 mg/kg (20.7 uM·hr)and 75 mg/kg (222.33 uM·hr), there is an ~41.4 to ~444.7 fold margin to what is expected following once daily administration and 5 mg on Day 9.

In the 29 day monkey toxicity study, MK-8591 was administered orally once every three (q3d) days at 0, 5, 20, or 75 mg/kg/dose. Overall, MK-8591 was well tolerated in monkeys. [redacted] Following completion of the study, there were no gross observations, organ weight changes, or histomorphologic changes at any dose level. [redacted] the NOEL as well as the NOAEL was 20 mg/kg/dose ($AUC_{0\text{-}72\ hr}$: 37.4 µM•hr [**AUC0-168hr: 87.3 µM•hr**] and Cmax of 8.4 µM). This provides a ~7 to 67-fold margin to the predicted clinical plasma $AUC_{0\text{-}72\ hr}$/$AUC_{0\text{-}168\ hr}$ target and provides a ~3 to 42-fold margin to the predicted clinical Cmax of 0.2 to 2.5 µM.

[redacted]. Exposures from the exploratory studies were significantly higher than those from the 28/29-day studies. For example, in the 29-day monkey study, the MK-8591 plasma $AUC_{0\text{-}72}$ ranged from 10.1 µM•hr to 210 µM•hr for the 10 and 75 mg/kg/day doses, respectively. These values are significantly lower than the corresponding $AUC_{0\text{-}24}$ exposures (10 to 75 mg/kg/dose: 20.7 µM•hr to 222.23 µM•hr) obtained from the exploratory toxicity study. Similarly in the rat 28-

day study, the highest dose tested (50 mg/kg/day) was associated with an exposure ($AUC_{0-24\ hr}$ 86.5 µM•hr) that was ~2.5-fold lower than that observed with 100 mg/kg/day (213 µM•hr) in the exploratory study.

Administration of 1-mg and 5-mg MK-8591 qd for 9 days is expected to safe and well tolerated based on the substantial preclinical safety Plasma concentrations (AUC and Cmax) following administration of 1 mg and 5 mg are predicted to be between ~40 to 400-fold lower than those obtained in any of the preclinical toxicity studies. Subjects safety will be monitored using routine clinical safety assessments (e.g., adverse experience reporting, laboratory safety assessments, and vital signs).

[redacted] routine vital sign assessments will be performed throughout the current study to monitor for potential changes in subjects.

In addition to the preclinical toxicity data, clinical safety and pharmacokinetic data from Protocol 001 will also be used to guide dosing and dose escalation in the present study. Because significant accumulation of plasma MK-8591 is not expected the exposures associated with multiple dosing should approximate those observed in Protocol 001. The expectation is that multiple doses of 50-200 mg administered once weekly and 1 and 5 mg administered once daily should remain below those established from preclinical toxicity studies.

An additional objective of this study is to compare the pharmacokinetic performance of the new solid capsule formulation to that of an oral suspension. Pharmacokinetic data from this study will be compared to that obtained in Protocol 001. Doses of 5 and 100 mg will allow for a direct dose comparison between these studies.

The currently outlined doses may be reduced based on data from Protocol 001 and/or from panels in the current study. Safety data from previous dose levels will be reviewed prior to each subsequent dose escalation. Pharmacokinetic data, when available, will also be reviewed.

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.

### 4.2.3 Starting and Maximum Doses

Panels A, B, and C

The proposed starting dose for this trial is 50 mg administered once weekly for three weeks. Prior to the initiation of dosing in Protocol 002 safety and plasma pharmacokinetic data through 400 mg will be available and evaluated. A 50 mg dose corresponds to 0.83 mg/kg in a 60 kg human. Administration of this starting dose is supported by the preclinical toxicity studies in rats and monkeys along with the preliminary safety data from Protocol 001. To date the highest dose administered in Protocol 001 is 400 mg, which is 8-fold higher than the starting dose for this trial. A 400 mg single dose has been well tolerated in human subjects and is described in Section 4.1.2.

The proposed maximum dose of 200 mg administered once weekly for three weeks corresponds to 3.34 mg/kg in a 60 kg human. Administration of this dose is contingent on safety and pharmacokinetic data from Protocol 001 along with safety and available pharmacokinetic data from preceding panels in Protocol 002. Prior to each dose escalation, all available clinical safety data and pharmacokinetic data will be carefully reviewed to permit a decision on whether to advance to the next higher dose level. Because this is the first multiple dose administration of MK-8591 to humans at doses predicted to achieve therapeutic concentrations, the dose levels may be adjusted downwards based on available safety and/or pharmacokinetic data from previous periods of this study, or from Protocol 001. Specifically, pharmacokinetic data from Protocol 001 and Protocol 002 (if available) will be used to assure that the AUC0-168 hr exposure cap of 87.3 µM•hr is not exceeded in the present study.

Panels D and E

The proposed once daily starting dose for this trial is 1 mg administered for nine days. A 1 mg dose corresponds to 0.017 mg/kg in a 60 kg human. Administration of this dose is supported by the preclinical toxicity studies in rats and monkeys along with the preliminary safety data from Protocol 001. To date the highest dose administered in Protocol 001 is 400 mg, which is 400-fold higher than the starting once daily dose for this trial. A 400 mg single dose has been well tolerated in human subjects and is described in Section 4.1.2.

The proposed maximum once daily dose of 5 mg administered for nine days corresponds to 0.083 mg/kg in a 60 kg human. Administration of this dose is contingent on safety and pharmacokinetic data from Protocol 001 along with safety and available pharmacokinetic data from Panel D. Prior to dose escalation, all available clinical safety data and pharmacokinetic data will be carefully reviewed to permit a decision on whether to advance to Panel E. Because this is the first once daily multiple dose administration of MK-8591 to humans at doses predicted to achieve therapeutic concentrations, the dose maximum level may be adjusted downwards based on available safety and/or pharmacokinetic data from previous periods of this study, or from Protocol 001. Specifically, pharmacokinetic data from Protocol 001 and Protocol 002 (if available) will be used to assure that the $AUC_{0-24}$ hr exposure cap of 12.4 µM•hr is not exceeded in the present study.

### 4.2.4 Rationale for Endpoints

#### 4.2.4.1 Safety Endpoints

This will be the first multiple dose assessment of MK-8591 to humans. No meaningful physical or biochemical signs were observed in the 28/29-day oral toxicity studies in rats and monkeys. Available safety data from Protocol 001 and from previous panels in Protocol 002 will be used to guide dosing and dose escalation in the present study. To date, single doses of 5 up to 400 mg have been well tolerated in Protocol 001 (refer to Section 4.1.2).

Based on the data from the preclinical safety assessment studies it is expected that oral administration of MK-8591 will be well tolerated in humans. Changes in heart rate and blood pressure observed in rat and monkey telemetry experiments will require close monitoring with vital sign assessments in the present clinical study.

The primary objective of this study is to evaluate the safety of MK-8591 in healthy subjects when administered in multiple doses. Safety will be assessed throughout the study by monitoring adverse experiences, physical examinations, vital signs, 12-Lead electrocardiograms, laboratory safety tests. Only after careful review of these data will dose escalation proceed. If available, pharmacokinetic data may also be used for dose escalation. Because of the anticipated long half-life of intracellular MK-8591 triphosphate, the post trial visit is scheduled to occur 21 days following the last dose of study drug.

There are no mechanism-related events that are known to be associated with HIV-1 nucleoside reverse transcriptase inhibition.

#### 4.2.4.2 Pharmacokinetic Endpoints

A primary objective of this study is to evaluate the initial plasma and intracellular triphosphate PK profile of MK-8591 in healthy young males and females of nonchildbearing potential. This study will establish if the anticipated target concentration can be achieved safely following multiple doses of MK-8591.

Preclinical studies in rhesus monkeys showed that antiviral efficacy of MK-8591 is related to the trough concentration ($C_{trough}$) of the active moiety (triphosphate) in PBMCs, rather than to trough concentrations in plasma. PK/PD modeling was performed and predicted a target intracellular $C_{168hr}$ (i.e., $C_{trough}$ for weekly dosing) or $C_{24hr}$ (i.e., Ctrough for once daily 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) will be used as the PK target in the study. For the PK assessment, active triphosphate in PBMCs may be determined for up to 14 days following the last multiple dose. Plasma concentrations of unchanged MK-8591 may 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 following multiple doses.

#### 4.2.4.3 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), 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.

## 5.0 METHODOLOGY

### 5.1 Entry Criteria

#### 5.1.1 Diagnosis/Condition for Entry into the Trial

Healthy male/female subjects 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. Understand the study procedures and agree to participate in the study by giving written informed consent, including for Future Biomedical Research.

2. Be a male or female of non-childbearing potential, 18 to 60 years of age at the pretrial (screening) visit.

    a. Females of non-childbearing potential are defined as:

        i. a female who is postmenopausal without menses for at least 1 year and has a follicle stimulating hormone (FSH) value in the postmenopausal range upon pretrial (screening) evaluation,

        ***AND/OR***

        ii. a female who is status post hysterectomy, oophorectomy or tubal ligation.

        *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*.

3. Have a Body Mass Index (BMI) $\leq$32 kg/m$^2$. BMI = weight (kg)/height (m)$^2$.

4. Be judged to be in good health based on medical history, physical examination, vital sign measurements and ECG performed prior to randomization. Section 12.4 provides a table of 12-Lead Electrocardiogram Abnormality Criteria.

5. Be judged to be in good health based on laboratory safety tests (Section 7.1.3.1) obtained at screening and/or prior to administration of the initial dose of trial drug. Section 12.6 provides an algorithm for the assessment of out-of-range laboratory values.

6. Be a nonsmoker and/or has not used nicotine or nicotine-containing products (e.g., nicotine patch) for at least approximately 3 months.

7. 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 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. Subject has an estimated creatinine clearance of ≤ 80 mL/min based on the Cockcroft-Gault equation; the Cockcroft-Gault equation is as follows (multiply by 0.85 for female subjects):

$$ClCr = \frac{(140-age[yr])(body\ wt\ [kg])}{(72)(serum\ creat\ [mg/dL])}$$

*When creatinine is measured in micromole/litre, use the following formula:*

$$ClCr = \frac{(140-age[yr])(body\ wt[kg])}{(72)(serum\ creatinine\ [micromol/L] \times 0.0113)}$$

   An actual creatinine clearance, as determined by a 24-hour urine collection, may be used in place of, or in conjunction with, the Cockcroft-Gault equation; subjects who have an actual or estimated creatinine clearance up to 10% below 80 mL/min may be enrolled in the study at the discretion of the investigator.

4. Has a history of clinically significant endocrine, gastrointestinal, cardiovascular, hematological, hepatic, immunological, 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.

5. Has a history of cancer (malignancy).

6. 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.

7. Is positive for hepatitis B surface antigen, hepatitis C antibodies or HIV-1.

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) prior to the pretrial screening 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 pretrial/screening visit of the current trial.

10. Has QTc (bazett) interval ≥ 470 msec (for males) or ≥ 480 msec (for females)

11. Is unable to refrain from or anticipates the use of any medication, including prescription and non-prescription drugs or herbal remedies (such as St. John's Wort [hypericum perforatum]) beginning approximately 4 weeks (or 5 half-lives) prior to administration of the initial dose of trial drug, throughout the trial (including washout intervals between treatment periods), until the posttrial visit. There may be certain medications that are permitted, see Section 5.5.

12. 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. Patients who consume 4 glasses of alcoholic beverages per day may be enrolled at the discretion of the investigator.

13. 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.

14. Is currently a regular user (including "recreational use") of any illicit drugs 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 for any other reason the investigator considers the subject inappropriate for participation in the trial.

16. Has participated in MK-8591 P001.

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

## 5.2 Trial Treatment(s)

This is a randomized, double-blind, placebo-controlled, serial panel, rising multiple dose trial of MK-8591. Three panels (A, B, and, C), consisting of 8 subjects each, will receive three once weekly doses of MK-8591 (n=6) or matching placebo (n=2) on Day 1, 8, and 15. Two panels (D and E), consisting of 8 subjects each, will receive once daily doses of MK-8591 (n=6) or matching placebo (n=2) on Days 1-9. All subjects will be randomized to receive MK-8591 (n=6) or matching placebo (n=2) in a blinded fashion according to a randomized allocation schedule.

Subjects may only participate in one panel. Trial treatments are outlined in Table 1.

All study drugs will be administered with ~240 mL of water after at least an 8 hour fast. Additional water may be given if needed. The additional amount of water must be documented.

In Panels A, B and C, subjects will receive MK-8591 or matching placebo once in the morning in the clinical research unit on Days 1, 8 and 15. Water will be restricted for 1 hour prior to and 1 hour after dosing and subjects will continue to fast for 4 hours post-dose at which time a standard lunch will be served. Subjects will remain semi-recumbent for 4 hours post dose during these days, except for brief moments to ambulate to the restroom and assessment of orthostatic vital signs. Subjects will remain in the clinical research unit until 24 hours postdose on Days 1 and 15, and until 4 hours postdose on Day 8, when they will be discharged at the discretion of the investigator. Subjects may be required to return to the clinical research unit for completion of study mandated procedures (e.g., pharmacokinetic blood samples).

In Panels D and E, subjects will receive MK-8591 or matching placebo once in the morning on Days 1 to 9. Water will be restricted for 1 hour prior to and 1 hour after dosing. On Days 1 and 9 subjects will continue to fast for 4 hours post-dose at which time a standard lunch will be served. Subjects will remain semi-recumbent for 4 hours post dose during these days, except for brief moments to ambulate to the restroom and assessment of orthostatic vital signs. Subjects may be required to return to the clinical research unit for completion of study mandated procedures (e.g., pharmacokinetic blood samples).

Subjects will return on ambulant visits on the Days 2 to 8 to receive MK-8591 or matching placebo. On Days 3 and 5, subjects will complete select predose procedures prior to receiving the dose of study drug. Water will be restricted for 1 hour prior to and 1 hour after dosing. On Days 2 to 8, subjects will continue to fast until 2 hours post-dose.

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)

Dose escalation decisions will be based on key safety variables including orthostatic and semi-recumbent vital signs, 12-lead ECG, laboratory safety tests (chemistry, hematology, urinalysis), physical examinations, 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 Timing of Dose Administration

### 5.2.3 Trial Blinding/Masking

A double-blind/masking technique will be used. MK-8591 and placebo will be dispensed in a blinded fashion by an unblinded pharmacist or qualified trial site personnel. The subject, the investigator and Sponsor personnel or delegate(s) who are involved in the treatment administration or clinical evaluation of the subjects are unaware of the group assignments.

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

## 5.3 Randomization or Treatment Allocation

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

The sample allocation schedule is shown below in Table 5 for Panels A through C and Table 6 for Panels D and E. When possible, male subjects will be assigned in ascending order and females will be assigned in descending order within each panel. Please note that the gender in the minority should be allocated within the same randomization block.

Table 5 Sample Allocation Schedule Panels A-C

| Subjects [a] | A[b, c] | B[b, c] | C[b, c] |
|---|---|---|---|
| N=2<br><br>N=6 | Placebo on Days 1, 8 and 15<br><br>MK-8591 50 mg q weekly on Days 1, 8 and 15 | | |
| N=2<br><br>N=6 | | Placebo on Days 1, 8 and 15<br><br>MK-8591 100 mg q weekly on Days 1, 8<br>and 15 | |
| N=2<br><br>N=6 | | | Placebo on Days 1, 8 and 15<br><br>MK-8591 200 mg q weekly on Days 1, 8<br>and 15 |

[a] Different subjects will participate in each panel (A to C).
[b] The dose of MK-8591 may be adjusted *downwards* for Panels A-C based on available safety, tolerability and pharmacokinetic data.
[c] Doses have been adjusted downwards to 10 mg once weekly for Panel A, 30 mg once weekly for Panel B, and 100 mg once weekle for Panel C. As noted in Protocol Clarification Letters 1-3.
q weekly = Once a week (in the morning)

Table 6 Sample Allocation Schedule Panels D and E

| Subjects[a] | Panel | |
|---|---|---|
| | D | E[b] |
| N=2<br><br>N=6 | Placebo on Days 1-9<br><br>MK-8591 1 mg daily on Days 1-9 | |
| N=2<br><br>N=6 | | Placebo on Days 1-9<br><br>MK-8591 5 mg daily on Days 1-9 |

[a] Different subjects will participate in each panel (D to E).
[b] The dose of MK-8591 may be adjusted *downwards* for Panels E based on available safety, tolerability and pharmacokinetic data.

## 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 allocation) must first be discussed between the investigator and Sponsor Clinical Director prior to administration, unless appropriate medical care necessitates that therapy or vaccination should begin before the investigator and Sponsor Clinical Director can consult. The subject will be allowed to continue in the trial if both the Sponsor Clinical Director 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 and Fruit Juice Restrictions

#### 5.7.1.1 Diet

On full pharmacokinetic sampling days, i.e. Days 1 (all panels), Day 9 (Panels D and E), and 15 (Panels A-C), subjects will fast from all food and drinks except water for at least 8 hours prior to dosing and water will be restricted 1 hour prior to and 1 hour after trial drug administration. A standard lunch and dinner will be provided at ~4 and ~10 hours postdose, respectively, and a snack will be offered at ~7 and ~13 hours postdose; subjects will fast from all food and drink except water between meals and snacks. The caloric content and composition of meals will be the same on each full pharmacokinetic sampling day in each panel. After the 24-hour postdose procedures have been completed, subsequent meals and snacks will be unrestricted in caloric content and composition.

On Day 8 (Panels A-C), subjects will fast from all food and drinks except water for at least 8 hours prior to dosing and water will be restricted 1 hour prior to and 1 hour after trial drug administration. Food will be restricted until after the 4 hour postdose procedures are completed.

On Days 2 – 8 (Panels D and E), subjects will fast from all food and drinks except water for at least 8 hours prior to dosing and water will be restricted 1 hour prior to and 1 hour after trial drug administration. Food will be restricted until 2 hours after trial drug administration.

Dependent on the pharmacokinetic data collected from previous studies subjects may be administered trial drug with or without food.

#### 5.7.1.2 Fruit Juice Restrictions

Subjects will refrain from consumption of grapefruit juice, grapefruits and grapefruit products beginning approximately 2 weeks prior to administration of the initial dose of trial drug, throughout the trial and until the post-trial visit. On dosing days, i.e. Days 1, 8 and 15 (Panel A-C) or Days 1-9 (Panel D and E), subjects will refrain from consumption of all juices 24 hours prior to and after administration of trial drug.

All fruits except for grapefruits are allowed on all days of the trial.

### 5.7.2 Alcohol, Caffeine, Tobacco, Activity

#### 5.7.2.1 Alcohol Restrictions

Subjects will refrain from consumption of alcohol 24 hours prior to trial drug administration on Day 1 up through 48 hours after trial drug administration on Day 15 (Panel A-C) or Day 9 (Panel D and E).

In addition, subjects will refrain from consumption of alcohol 24 hours prior to the pre- and post-trial visits. 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

On dosing days, i.e. Days 1, 8 and 15 (Panel A-C) or Days 1-9 (Panel D and E), subjects will refrain from consumption of caffeinated beverages from 12 hours prior to and after trial drug administration.

On intermediate days, caffeinated beverages will be limited to no more than 6 units per day amounts (1 unit=120 mg of caffeine).

In addition, subjects will refrain from consumption of caffeinated beverages from 12 hours prior to the pre- and post-trial visits. At all other times, caffeinated beverages will be limited to no more than 6 units per day amounts (1 unit=120 mg of caffeine).

#### 5.7.2.3 Smoking Restrictions

Smoking is not permitted during the trial.

#### 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 administration of the initial dose of trial drug, throughout the trial and until the post-trial visit.

## 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 or legal representative (such as a parent or legal guardian) withdraws consent.

## 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 randomization number. The trial site should contact the Sponsor for the replacement subject's 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.

## 6.0 TRIAL FLOW CHART

| Panels A-C | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Day 1, 8[f] and 15 (Hours Postdose) | | | | | | | | | | | | | | |
| | Screening 1 | Screening 2[d] | Pre-dose | 0 | 0.25 | 0.5 | 1 | 2 | 4 | 6 | 12 | 16 | 24 | 48 | 96 | 168 | 336 | Post-trial[i] |
| **Administrative Procedures** | | | | | | | | | | | | | | | | | | |
| Informed Consent | X | | | | | | | | | | | | | | | | | |
| Informed Consent for Future Biomedical Research[a] | X | | | | | | | | | | | | | | | | | |
| Inclusion/Exclusion Criteria | X | | | | | | | | | | | | | | | | | |
| Subject Identification Card (per site SOP) | X | | | | | | | | | | | | | | | | | |
| Medical History | X | | | | | | | | | | | | | | | | | |
| Concomitant Medication Review | X | | X---------- | | | | | | | | | | | | | | | ----X |
| **Clinic Procedures/Assessments** | | | | | | | | | | | | | | | | | | |
| Full Physical Examination | X | | X[b] | | | | | | | | | | | | | X[h] | | X |
| Height | X | | | | | | | | | | | | | | | | | |
| Weight | X | | | | | | | | | | | | | | | | | X |
| 12-Lead Electrocardiogram | X | | X | | | X | | X | | | | | | | | X[h] | | X |
| Vital Signs (heart rate, blood pressure) | X | | X | | X | X | | X | X | | | | | | | X[h] | | X |
| Orthostatic Vital Signs (heart rate, blood pressure) | X | | X | | | X | | X | | | | | | | | X[h] | | X |
| Vital Signs (respiratory rate, oral/tympanic temperature) | X | | X | | | X | | X | | | | | | | | X[h] | | X |
| Standard Meals | | | | | | | | | X---------- | | | | ----X | | | | | |
| MK-8591/Placebo Administration | | | | X[g] | | | | | | | | | | | | | | |
| Standard dental examination (**Panel C only)** | | | | | | | | | | | | | | | | | | X[k] |
| Adverse Events Monitoring | X---------- | | | | | | | | | | | | | | | | | ----X |
| **Laboratory Procedures/Assessments** | | | | | | | | | | | | | | | | | | |
| Hematology | X | X | X[b] | | | | | | | | | | | | X | X[h] | | X |
| Urinalysis | X | X | X[b] | | | | | | | | | | | | X | X[h] | | X |
| Chemistry | X | X | X[b] | | | | | | | | | | | | X | X[h] | | X |
| Serum Follicle Stimulating Hormone (FSH)[c] | X | | | | | | | | | | | | | | | | | |
| Alcohol/Drug Screen (per site SOP)[e] | X | | X | | | | | | | | | | | | | | | |
| HIV/Hepatitis Screen (per site SOP) | X | | | | | | | | | | | | | | | | | |
| Blood for Future Biomedical Research [a] | | | X | | | | | | | | | | | | | | | |
| **Pharmacokinetics Evaluations** | | | | | | | | | | | | | | | | | | |
| Blood for Plasma MK-8591 assay [a] | | | X | | X | X | X | X | | X | X | X | X | X | X | X[h] | | |
| Blood for PBMC assay (Day1) | | | | | | | | | | X | X | | X | X | X | X | | |
| Blood for PBMC assay (Day 15) | | | X | | | | | | | X | X | | X | X | X | X | X | |

| Panels A-C | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Day 1, 8[f] and 15 (Hours Postdose) | | | | | | | | | | | | | | |
| | Screening 1 | Screening 2[d] | Pre-dose | 0 | 0.25 | 0.5 | 1 | 2 | 4 | 6 | 12 | 16 | 24 | 48 | 96 | 168 | 336 | Post-trial[i] |
| Urine for Urinary MK-8591 Assay[j] | | | X | X----------X | | | | | | | | | | | | | | |

a. Informed consent for future biomedical research samples must be obtained before the DNA sample. DNA sample for analysis should be obtained on Day 1 (or with the next scheduled blood draw) on randomized subjects only. Any leftover plasma from PK evaluations will be stored for future research at the end of the study
b. PE and safety labs can be conducted on admission (within 24 hours prior to dosing). If subjects are admitted to the unit 24h prior to dosing, screening 2 is not required.
c. For postmenopausal women only.
d. If screening 1 occurs within 72hrs prior to the initial dose of trial drug, Screening 2 is not required.
e. Screening Urine Drug Screen (UDS) is mandatory, any additional UDS are conducted per site SOP.
f. On Day 8, subjects will complete the following safety procedures up through 4 hours postdose: vital signs (semi-recumbent and orthostatic) and 12-Lead electrocardiogram. Subjects will then be discharged after the 4 hours postdose, procedures are completed, at the discretion of the investigator.
g. All procedures from previous dose must be completed prior to subsequent dosing.
h. After Day 15 only.
i. The post-trial visit will occur approximately 21 days following administration of the last dose of study drug (Day 15). 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.
j. Urine samples for the MK-8591 assay will be collected from subjects in Panels A-C on Day 15 only. Urine will be collected pre-dose and for the following intervals post-dose: 0-4, 4-8, 8-12,12-24 and 24-48 hours postdose. For the 24-48 hour interval, subjects will collect urine at home. Additional sample collection timepoints may be added based on PK results from previous panels.
k. **Panel C** subjects may have a voluntary, standard dental examination after the posttrial visit. The exact timing of the dental exam will be made by the investigator and/or by the treating dentist. Informed consent for the dental examination must be obtained prior to the dental examination. Additional dental examinations and/or any dental procedures for subjects in Panel C will be performed at the recommendation of the treating dentist(s). In this case, the Sponsor will be informed (or: involved in the decision) prior to having any additional exams taking place.

| Panels D-E | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Day 1 and 9 (Hours Postdose) | | | | | | | | | | | | | | |
| | Screening 1 | Screening 2[d] | Pre-dose | 0 | 0.25 | 0.5 | 1 | 2 | 4 | 6 | 12 | 16 | 24 | 48 | 96 | 168 | 336 | Post-trial[i] |
| **Administrative Procedures** | | | | | | | | | | | | | | | | | | |
| Informed Consent | X | | | | | | | | | | | | | | | | | |
| Informed Consent for Future Biomedical Research[a] | X | | | | | | | | | | | | | | | | | |
| Inclusion/Exclusion Criteria | X | | | | | | | | | | | | | | | | | |
| Subject Identification Card (per site SOP) | X | | | | | | | | | | | | | | | | | |
| Medical History | X | | | | | | | | | | | | | | | | | |
| Concomitant Medication Review | X | | X---------- | | | | | | | | | | | | | | | ----------X |
| **Clinic Procedures/Assessments** | | | | | | | | | | | | | | | | | | |
| Full Physical Examination | X | | X[b, f] | | | | | | | | | | | | | | | X |
| Height | X | | | | | | | | | | | | | | | | | |
| Weight | X | | | | | | | | | | | | | | | | | X |
| 12-Lead Electrocardiogram | X | | X[f] | | | X | | X | | | | | | | | | | X |
| Vital Signs (heart rate, blood pressure) | X | | X[f] | | X | X | | X | X | | | | | | | | | X |
| Orthostatic Vital Signs (heart rate, blood pressure) | X | | X[f] | | | X | | X | | | | | | | | | | X |
| Vital Signs (respiratory rate, oral/tympanic temperature) | X | | X[f] | | | X | | X | | | | | | | | | | X |
| Standard Meals | | | | | | | | | X---------- | | | | ----------X | | | | | |
| MK-8591/Placebo Administration **(Days 1-9)** | | | | X[g, l] | | | | | | | | | | | | | | |
| Adverse Events Monitoring | X---------- | | | | | | | | | | | | | | | | | ----------X |
| **Laboratory Procedures/Assessments** | | | | | | | | | | | | | | | | | | |
| Hematology | X | X | X[b, f] | | | | | | | | | | X[h] | | | X[h] | | X |
| Urinalysis | X | X | X[b, f] | | | | | | | | | | X[h] | | | X[h] | | X |
| Chemistry | X | X | X[b, f] | | | | | | | | | | X[h] | | | X[h] | | X |
| Serum Follicle Stimulating Hormone (FSH)[c] | X | | | | | | | | | | | | | | | | | |
| Alcohol/Drug Screen (per site SOP)[e] | X | | X | | | | | | | | | | | | | | | |
| HIV/Hepatitis Screen (per site SOP) | X | | | | | | | | | | | | | | | | | |
| Blood for Future Biomedical Research [a] | | | X | | | | | | | | | | | | | | | |
| **Pharmacokinetics Evaluations** | | | | | | | | | | | | | | | | | | |
| Blood for Plasma MK-8591 assay [a] | | | X[f, j] | | X | X | X | X | | X | X | X | X | X[h] | X[h] | X[h] | | |
| Blood for PBMC assay | | | X[f, j, k] | | | | | | | X | X | | X | X[h] | X[h] | X[h] | X[h] | |

a. Informed consent for future biomedical research samples must be obtained before the DNA sample. DNA sample for analysis should be obtained on Day 1 (or with the next scheduled blood draw) on randomized subjects only. Any leftover plasma from PK evaluations will be stored for future research at the end of the study
b. Predose PE and safety labs can be conducted on admission (within 24 hrs prior to dosing). If subjects are admitted to the unit 24hrs prior to dosing, screening 2 is not required. Predose PE and safety labs will not be collected on Day 9, only on Day 1 and Day 5.
c. For postmenopausal women only.

| Panels D-E | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Day 1 and 9 (Hours Postdose) | | | | | | | | | | | | | | |
| | Screening 1 | Screening 2[d] | Pre-dose | 0 | 0.25 | 0.5 | 1 | 2 | 4 | 6 | 12 | 16 | 24 | 48 | 96 | 168 | 336 | Post-trial[i] |

d. If screening 1 occurs within 72hrs prior to the initial dose of trial drug, Screening 2 is not required.
e. Screening Urine Drug Screen (UDS) is mandatory, any additional UDS are conducted per site SOP.
f. On Day 5, subjects will complete the following **predose** only procedures: PE, vital signs (semi-recumbent and orthostatic), 12-Lead electrocardiogram, lab safety tests, blood samples for plasma MK-8591 assay and for PBMC assay. No postdose sample collections or procedures will take place on Day 5. Subjects may be discharged after dosing at the discretion of the investigator.
g. All procedures from previous dose must be completed prior to subsequent dosing.
h. After Day 9 only.
i. The post-trial visit will occur approximately 21 days following administration of the last dose of study drug (Day 9). 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.
j. A predose Plasma MK-8591 and PBMC sample will also be collected on **Day 3. No other predose procedures will be performed on Day 3.**
k. There will be no **predose** Day 1 PBMC samples collected, only on Day 3, 5, and 9.
l. MK-8591/placebo will administered in the morning on every day from day 1 to day 9, at approximately the same time.

# 7.0 TRIAL PROCEDURES

## 7.1 Trial Procedures

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

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

### 7.1.1 Administrative Procedures

#### 7.1.1.1 Informed Consent

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

##### 7.1.1.1.1 General Informed Consent

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

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

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

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

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

#### 7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

### 7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

### 7.1.1.3 Subject Identification Card

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

### 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 14 days prior to administration of the initial dose of trial drug .

#### 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 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.

When possible, male subjects will be assigned in ascending order and females will be assigned in descending order within each panel.

#### 7.1.1.8 Trial Compliance

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

### 7.1.2 Clinical Procedures/Assessments

**Body Weight and Height**

Body weight and height will be obtained with the subjects shoes off, jacket or coat removed. Body weight will be taken after an 8 hour fast and the subject has voided.

**Body Mass Index (BMI)**

BMI equals a person's weight in kilograms divided by height in meters squared. (BMI=kg/$m^2$). Body weight and height will be obtained with the subjects shoes off, jacket or coat removed.

**Body Temperature**

Body temperature will be measured with a thermometer (e.g., oral, tympanic, or temporal artery) and recorded in degrees Celsius. The same method (e.g., oral) must be used for all measurements for each individual subject and should be the same for all subjects.

**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. ECG instrument calibration (including updating date and time) should be performed and documented according to local procedures.

Subjects should be resting in the semi-recumbent position for at least 10 minutes prior to each ECG measurement. Subject position during ECG collection (e.g., semi-recumbent or supine) 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.

Predose ECGs on Day 1 will be obtained in triplicate at least 1-2 minutes apart within 3 hours prior to dosing MK-8591. The average of these measurements will be used as the baseline. Post-dose vital sign measurements will be single measurements.

If a subject 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 subject 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 subject 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 subject 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. See Appendix 12.6 for 12-Lead ECG abnormality criteria.

**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 vital signs will include heart rate (HR) and blood pressure (BP). The correct size of the blood pressure cuff and the correct positioning on the subjects' 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.

On Day 1 the pre-dose (baseline) semi-recumbent HR and BP will be the average of duplicate measurements obtained at least 1-2 minutes apart within 60 minutes of dosing MK-8591. Post-dose vital sign measurements will be single measurements.

Orthostatic vital signs (HR and BP) will also be obtained at indicated time points. 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 post-dose except to stand for the measurement of orthostatic measurements or other trial related procedures, or for brief breaks (e.g, restroom breaks).

### 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 7.

Table 7 Laboratory Tests

| Hematology | Chemistry | Urinalysis | Other |
|---|---|---|---|
| Hematocrit | Albumin | Blood | Follicle Stimulating Hormone (FSH)* |
| Hemoglobin | Alkaline phosphatase | Glucose | Hepatitis* |
| Platelet count | Alanine aminotransferase (ALT) | Protein | HIV* |
| WBC (total and differential) | Amylase | Microscopic exam, if abnormal results are noted | Urine Drug Screen |
| Red blood cells | Aspartate aminotransferase (AST) | | |
| | Bicarbonate | | |
| | Calcium | | |
| | Chloride | | |
| | Creatinine | | |
| | Glucose | | |
| | Lipase | | |
| | Phosphorus | | |
| | Potassium | | |
| | Sodium | | |
| | Total Bilirubin | | |
| | Direct Bilirubin, if total bilirubin is elevated above the upper limit of normal | | |
| | Total protein | | |
| | Urea | | |
| * only collected at prestudy. | | | |

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** Blood Collection for Plasma MK-8591

Sample collection, storage and shipment instructions for plasma samples will be provided in the Appendix Section 12.7.

**7.1.3.3** Blood Collection for Plasma PBMC

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

#### 7.1.3.4 Urine Collection for Urinary MK-8591

Sample collection, storage and shipment instructions for urine samples will be provided in the Appendix Section 12.8.

#### 7.1.3.5 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 14 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 14 days after the last dose of trial drug is given, the investigator should perform a follow-up phone call 14 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 (clinical.specimen.management@merck.com), and a form will be provided by the Sponsor to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. A letter will be sent from the Sponsor to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

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

### 7.1.4.2 Blinding/Unblinding

Supplies will be provided with random code/disclosure envelopes or lists containing drug disclosure information. The Sponsor will provide one sealed envelope to the investigator for each randomization number .

Random code/disclosure envelopes or lists must be received by a designated person at the trial site and kept in a secured location to which only the investigator and delegate(s) have access. The random code/disclosure envelopes or lists should be opened only in the case of an emergency. Drug identification information is to be unblinded ONLY in the event that this is required for subject safety.

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

At the end of the trial, random code/disclosure envelopes or lists and unblinding logs are to be returned to the Sponsor or designee.

#### 7.1.4.3 Domiciling

**Panel A, B and C**

On Days 1 and 15, subjects will report to the clinical research unit (CRU) the evening prior to the scheduled day of trial drug administration and remain in the unit until 24 hours post-dose. On Day 8, subjects may report to the CRU the evening prior to, or the morning of, trial drug administration and will remain in the unit until 4 hours post-dose. For all doses, subjects may be requested to remain in the CRU longer at the discretion of the investigator.

**Panel D and E**

On Days 1 and 9, subjects will report to the clinical research unit (CRU) the evening prior to the scheduled day of trial drug administration and remain in the unit until 24 hours post-dose. On all other treatment days, subjects may report to the CRU the evening prior to, or the morning of, trial drug administration and may be discharged following dosing. For all doses, subjects may be requested to remain in the CRU longer at the discretion of the investigator.

#### 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 with the study documentation 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 3 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. Subjects will report to the Clinical Research Unit (CRU) within -72 hours prior to Day 1 to confirm eligibility for study participation.

#### 7.1.5.2 Treatment Period

##### 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 morning or evening prior to the scheduled day of administration of each dose of 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 (refer to Section 5.7.1.1).

After the Day 1 predose procedures have been completed, subjects will be assigned a unique randomization 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 single doses of MK-8591 or matching placebo in the morning. The exact clock time of dosing should be recorded, and the same dosing time should be observed across treatment panels for each subject.

#### 7.1.5.3 Post-Trial

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 PBMC blood sample for MK-8591 is the critical procedure.

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 in any given period/panel
- Interchange of doses between panels
- Entire panel(s) may be omitted
- Decrease in the length of postdose pharmacokinetic (plasma or PBMC) sample collection
- Decrease in the duration of trial drug administration (e.g., number of days)
- Addition of pharmacokinetic pause
- Instructions to take trial drug with or without food or drink may also be modified based on newly available data

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.

Fifty (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 (e.g., adding creatinine kinase to serum chemistry panel that was already drawn. 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 the course of the use of the Sponsor's product in clinical trials or within the follow-up period specified by the protocol, or prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Adverse events may also occur in screened subjects during any pre-allocation baseline period as a result of a protocol-specified intervention, including washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

All adverse events will be recorded from the time the consent form is signed through 21 days following cessation of treatment and 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.

### 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 within 24 hours to the Sponsor either by electronic media or paper. Sponsor Contact information can be found in the Investigator Trial File Binder (or equivalent).

### 7.2.2 Immediate Reporting of Adverse Events to the Sponsor

#### 7.2.2.1 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 a cancer;
- Is associated with an overdose;
- Is an other important medical event

Refer to Table 8 for additional details regarding each of the above criteria.

Any serious adverse event, or follow up to a serious adverse event, including death due to any cause that occurs to any subject from the time the consent is signed through 21 days following cessation of treatment, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor either by electronic media or paper. Sponsor Contact information can be found in the Investigator Trial File Binder (or equivalent).

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.

#### 7.2.2.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Event case report forms/worksheets and reported within 24 hours to the Sponsor either by electronic media or paper. Sponsor Contact information can be found in the Investigator Trial File Binder (or equivalent).

Events of clinical interest for this trial include:

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

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

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

#### 7.2.3 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events with respect to the elements outlined in Table 8. The investigator's assessment of causality is required for each adverse event. Refer to Table 8 for instructions in evaluating adverse events.

Table 8 Evaluating Adverse Events

| | | |
|---|---|---|
| **Maximum Intensity** | **Mild** | awareness of sign or symptom, but easily tolerated (for pediatric trials, awareness of symptom, but easily tolerated) |
| | **Moderate** | discomfort enough to cause interference with usual activity (for pediatric trials, definitely acting like something is wrong) |
| | **Severe** | incapacitating with inability to work or do usual activity (for pediatric trials, extremely distressed or unable to do usual activities) |
| **Seriousness** | A serious adverse event (AE) is any adverse event occurring at any dose or during any use of Sponsor's product that: | |
| | †**Results in death**; or | |
| | †**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred [Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.]; or | |
| | †**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or | |
| | †**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of 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; or** | |
| | **Is associated with an overdose** (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. 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<br>**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?<br>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?<br>If yes, did the AE resolve or improve?<br>If yes, this is a positive dechallenge. If no, this is a negative dechallenge.<br>(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?<br>If yes, did the AE recur or worsen?<br>If yes, this is a positive rechallenge. If no, this is a negative rechallenge.<br>(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.)<br>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 there is another obvious cause of the AE. (Also entered for a subject with overdose without an associated AE.) | |

### 7.2.4 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations.

## 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).

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 (Pharmacokinetics):

**Panels A, B, C:** MK-8591 PBMC and plasma $AUC_{0\text{-}168hr}$, $C_{max}$ and $C_{168hr}$ will be log transformed and analyzed based on a linear mixed effects model containing a fixed effect for treatment, day (Day 1, Day 8 and Day 15 for $C_{168hr}$, and Day 1 and Day 15 for $AUC_{0\text{-}168hr}$ and $C_{max}$) and treatment by day interaction, and a random effect for subject. The point estimates and the corresponding 90% confidence intervals will be obtained from the model for geometric means of each dose level on each day. The posterior probability that the true GM PBMC $C_{168hr}$ is ≥ 0.53 pmol/$10^6$ cells will be calculated for each dose level at Day 1, Day 8 and Day 15 using a non-informative (Jeffrey's) prior under an assumption of normality. A 70% posterior probability that the true Day 15 PBMC GM $C_{168hr}$ is ≥ 0.53 pmol/$10^6$ cells for at least one dose level that also exhibits an acceptable safety and tolerability profile will satisfy the primary pharmacokinetic hypothesis.

**Panels D, E:** MK-8591 PBMC and plasma $AUC_{0\text{-}24hr}$, $C_{max}$ and $C_{24hr}$ will be log transformed and analyzed based on a linear mixed effects model containing a fixed effect for treatment, day (Day 1, Day 2, Day 4, Day 8, and Day 9 for $C_{24hr}$, and Day 1 and Day 9 for $AUC_{0\text{-}24hr}$ and $C_{max}$) and treatment by day interaction, and a random effect for subject. The point estimates and the corresponding 90% confidence intervals will be obtained from the model for geometric means of each dose level on each day. The posterior probability that the true GM PBMC $C_{24hr}$ is ≥ 0.53 pmol/$10^6$ cells will be calculated for each dose level at Day 1, Day 2, Day 4, Day 8, and Day 9 using a non-informative (Jeffrey's) prior under an assumption of normality. A 70% posterior probability that the true Day 9 PBMC GM $C_{168hr}$ is ≥ 0.53 pmol/$10^6$ cells for at least one dose level that also exhibits an acceptable safety and tolerability profile will satisfy the primary pharmacokinetic hypothesis.

**Power**

Pharmacokinetics: If the true CV is 50% (75%), there is ≥80% power to yield at least 70% posterior probability if the true GM triphosphate in PBMC $C_{168hr}$ (or $C_{24hr}$) is at least 0.7 (0.8) pmol/$10^6$ cells.

## 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 Pharmacokinetic**

The true geometric mean intracellular MK-8591 triphosphate $C_{168hr}$ (Panels A, B, and C) or $C_{24hr}$ (Panels D and E) is $\geq$ 0.53 pmol/$10^6$ cells for at least one dose level that also exhibits an acceptable safety and tolerability profile

Estimation:

The preliminary PBMC pharmacokinetic profile of MK-8591, including $AUC_{0\text{-}24,,}$ $AUC0_{\text{-}168}$, $T_{max}$, $C_{max}$, $C_{24hr}$, $C_{168hr}$, and apparent terminal $t_{1/2}$, following multiple oral doses will be estimated.

The preliminary plasma pharmacokinetic profile of MK-8591, including $AUC_{0\text{-}24,,}$ $AUC0_{\text{-}168}$, $T_{max}$, $C_{max}$, $C_{24hr}$, $C_{168hr}$, and apparent terminal $t_{1/2,}$ following multiple oral doses will be estimated.

### 8.2.2 Analysis Endpoints

**Primary (Safety)**

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

**Primary (Pharmacokinetics)**

Panels A, B, C: The primary pharmacokinetic variables will include both the MK-8591 PBMC and plasma $C_{168hr}$ following dosing on Day 1, Day 8 and Day 15; and $AUC_{0\text{-}168hr}$, $C_{max}$, $T_{max}$, and apparent terminal $t_{1/2}$ following dosing on Day 1 and Day 15.

Panels D, E: The primary pharmacokinetic variables will include both the MK-8591 PBMC and plasma $C_{24hr}$ following dosing on Day 1, Day 2, Day 4, Day 8, and Day 9; and $AUC_{0\text{-}24hr}$, $C_{max}$, $T_{max}$, and apparent terminal $t_{1/2}$ following dosing on Day 1 and Day 9.

### 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 PK analyses.

### 8.2.4 Statistical Methods

**Analysis Overview**

All references within this data analysis section to the log transformation or log function pertain to the natural log. If log transformation is used, the confidence intervals for the means (mean differences) will be constructed on the natural log scale and will reference the t-distribution. Exponentiating the least-squares means (mean differences) and lower and upper limits of these confidence intervals will yield estimates for the population geometric means (population geometric mean ratios) and confidence intervals about the geometric means (geometric mean ratios) on the original scale.

If linear mixed modeling is employed for an analysis and statistical inferences are based on t-statistics, Kenward & Roger's approximation will be used to compute the degree-of-freedom.

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 models(s) is observed, or suitable data transformations may be applied.

**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 (Pharmacokinetics)**

**Panels A, B, C:** MK-8591 triphosphate in PBMC $C_{168hr}$ will be log-transformed and analyzed based on a linear mixed effects model containing fixed effects for treatment, day (Day 1, Day 8 and Day 15) and treatment by day interaction, and a random effect for subject. The 90% confidence intervals for the geometric means of MK-8591 triphosphate in PBMC $C_{168hr}$ will be constructed at each dose level on Day 1, Day 8 and Day 15. The posterior probability that the true GM PBMC $C_{168hr}$ is > 0.53 pmol/$10^6$ cells will be calculated for each dose level on Day 1, Day 8 and Day 15 using a non-informative (Jeffrey's) prior under an assumption of normality. A 70% posterior probability that the true Day 15 PBMC GM $C_{168hr}$ is ≥ 0.53 pmol/$10^6$ cells for at least one dose level that also exhibits an acceptable safety and tolerability profile will satisfy the primary pharmacokinetic hypothesis. PBMC $AUC_{0\text{-}168hr}$ and $C_{max}$, as well as plasma MK-8591 $C_{168hr}$, $AUC_{0\text{-}168hr}$ and $C_{max}$, will be analyzed in a similar manner.Individual values will be listed for each plasma and PBMC PK parameter ($AUC_{0\text{-}168hr}$, $C_{max}$, $C_{168hr}$, $T_{max}$, and apparent terminal $t_{½}$) by *treatment, day and gender (if more than 2 females are enrolled in a panel)*, and the following (non-model-based) descriptive statistics will be provided by treatment and day, separately by gender (if more than 2 females are enrolled in a panel), as well as combined across genders: 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).

**Panels D, E:** MK-8591 triphosphate in PBMC $C_{24hr}$ will be log-transformed and analyzed based on a linear mixed effects model containing fixed effects for treatment, day (Day 1, Day 2, Day 4, Day 8, and Day 9) and treatment by day interaction, and a random effect for subject. The 90% confidence intervals for the geometric means of MK-8591 triphosphate in PBMC $C_{24hr}$ will be constructed at each dose level on Day 1, Day 2, Day 4, Day 8, and Day 9. The posterior probability that the true GM PBMC $C_{24hr}$ is > 0.53 pmol/$10^6$ cells will be calculated for each dose level on Day 1, Day 2, Day 4, Day 8, and Day 9 using

a non-informative (Jeffrey's) prior under an assumption of normality. A 70% posterior probability that the true Day 15 PBMC GM $C_{24hr}$ is > 0.53 pmol/$10^6$ cells for at least one dose level that also exhibits an acceptable safety and tolerability profile will satisfy the primary pharmacokinetic hypothesis. PBMC $AUC_{0\text{-}24hr}$ and $C_{max}$, as well as plasma MK-8591 $C_{24hr}$, $AUC_{0\text{-}24hr}$ and $C_{max}$, will be analyzed in a similar manner.

Individual values will be listed for each plasma and PBMC PK parameter ($AUC_{0\text{-}24hr}$, $C_{max}$, $C_{24hr}$, $T_{max}$, and apparent terminal $t_{½}$) by *treatment, day and gender (if more than 2 females are enrolled in a panel)*, and the following (non-model-based) descriptive statistics will be provided by treatment and day, separately by gender (if more than 2 females are enrolled in a panel), as well as combined across genders: 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).

**Exploratory (Pharmacokinetics)**

Single dose PBMC and plasma PK of tablet versus liquid formulations: Day 1 pharmacokinetic parameters $AUC_{0\text{-}168hr}$, $C_{max}$ and $C_{168hr}$ from MK-8591 Protocol 001 using a liquid formulation and from MK-8591 Protocol 002 using a tablet formulation will be log-transformed and analyzed using a linear effects model containing fixed effects for formulation, dose and the interaction of formulation and dose (if more than one dose level is tested in both 001 and 002). The point estimates and the corresponding 95% confidence intervals will be obtained from the model for the geometric means of each dose and formulation. The geometric mean ratios of the pharmacokinetic parameters of the tablet versus liquid formulation for each MK-8591 dose level tested in both Protocol 001 and Protocol 002 will be estimated from the model.

*Other PK parameter summaries and listings*

*Time to Steady State (Pharmacokinetics)*

Time to reach steady state will be assessed separately at each studied dose level of MK-8507 using the following specified methods.

If the assumption of linear pharmacokinetics is tenable for the doses examined in this study, two methods will be used in the assessment of time to steady state. For the primary method, the effective rate of drug accumulation will be obtained for each subject from their accumulation ratio of $AUC_{0\text{-}168hr}$ (Panels A, B, C) or $AUC_{0\text{-}24hr}$ (Panels D, E) and this value will be used to estimate the approach to steady state. Modeling of the trough plasma concentrations ($C_{168hr}$ for Panels A, B, C or $C_{24hr}$ for Panels D, E) collected during multiple-dose administration will also be performed as a secondary approach. If the estimates of time to steady state are consistent between the two methods, only the results calculated from the primary method will be reported. Otherwise, a further examination of the data will be

conducted in order to determine the reasons for any discrepancies. The final results will then be based upon the method that best characterizes the data.

The individual $AUC_{0\text{-}168hr}$ values (Panels A, B, C) or $AUC_{0\text{-}24hr}$ values (Panels D, E) will be used to estimate the effective rate of drug accumulation, $\eta_i$, for each subject *i* using the following relationship:

$$AUC_{X,i} / AUC_{Y,i} = \left(1 - \exp(-X\eta_i\tau)\right) / \left(1 - \exp(-Y\eta_i\tau)\right)$$

where $\tau$ = 168 hours (Panels A, B, C) or $\tau$ = 24 hours (Panels D, E) is the length of the dosing interval, X is the total number of dosing intervals, and Y = 1.

The value of $\eta_i$, solved from the above equation, will be used to estimate the fraction of steady state, $f_{ss,i}$, attained after each dosing interval N for subject$_i$ as follows:

$$f_{ss,i} = 1 - \exp(-N\eta_i\tau) \text{ for } N = 1, 2, \ldots, X.$$

The proportion of subjects who have reached 90% of theoretical steady state will be summarized for each dosing interval $N = 1, 2, \ldots, X$.

The number of dosing intervals needed to reach 90% of steady state, *T90*, will be calculated for each subject as

$$T90_i = \ln(10) / (\eta_i\tau)$$

Median, minimum, and maximum will be provided for T90 at each dose level.

As a secondary approach, $C_{168hr}$ values (Panels A, B, C) or $C_{24hr}$ values (Panels D, E) will be analyzed with a nonlinear mixed effects model using the following relationship:

$$C_{N_i} = C_{ss_i}\left(1 - \exp^{-2.3N/T90_i}\right)\exp^{\varepsilon_i}$$

where $C_{N_i}$ is the trough concentration value for subject *i* collected after drug administration in dosing interval $N = 1, 2, \ldots, X$., $C_{ss_i}$ is a function of the true population steady-state trough concentration and the random effect of subject *i*, $T90_i$ is a function of the true time required to reach 90% of theoretical steady state and the random effect of subject *i*. Both $C_{ss_i}$ and $T90_i$ are assumed to be log normally distributed. $\varepsilon_i$ is the error term that follows a normal distribution. A 95% confidence interval for *T90* will also be calculated. In addition, individual $C_{168hr}$ values will be plotted over time for each subject to further characterize the approach to steady state. As with the primary method, the fraction of steady state achieved and the percentage of subjects at 90% of steady state will be calculated for each dosing interval.

If there is reason to believe that the kinetics of the compound are not linear, time to steady state will be assessed using a method that does not require any assumptions about the underlying compartmental model (e.g., step-wise tests of linear trend in $C_{168hr}$ for Panels A, B, C or $C_{24hr}$ for Panels D, E).

*Assessment of Dose Proportionality (Pharmacokinetics)*

**Panels A, B, C:** The assessment of dose proportionality will be conducted using Day 15 data [steady state] only in an exploratory manner. The primary assessment of dose proportionality for MK-8591 $AUC_{0-168hr}$ will be performed using the power law model with ln(AUC) as the dependent variable and ln(dose) as an explanatory variable. A point estimate of the slope associated with ln(dose) will be provided together with a 95% confidence interval from the power law model.

A plot of the observed PK data versus dose will be provided along with an estimated regression line on the raw scale and a 95% Schéffe confidence band. The assessment of the dose proportionality of MK-8591 $C_{max}$ and $C_{168hr}$ will be carried out in the same manner as that used for MK-8591 $AUC_{0-168hr}$.

### 8.2.5 Multiplicity

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

### 8.2.6 Power

Pharmacokinetics: If the true CV is 50% (75%), there is ≥80% power to yield at least 70% posterior probability if the true GM triphosphate in PBMC $C_{168hr}$ is at least 0.7 (0.8) pmol/$10^6$ cells.

## 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 9.

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 9 Product Descriptions

| Product Name & Potency | Dosage Form |
|---|---|
| MK-8591 1mg | Capsule |
| MK-8591 10 mg | Capsule |
| MK-8591 100 mg | Capsule |
| MK-8591 1mg, 10 mg Placebo (Standard Image Placebo) | Capsule |
| MK-8591 100 mg Placebo (Standard Image Placebo) | Capsule |

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

All other supplies not indicated in Table 7 above will be provided centrally by the Sponsor or locally by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements.

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

### 9.2 Packaging and Labeling Information

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

Site will receive Open label supply. No kitting is required. Site will blind the supplies for the subjects.

### 9.3 Clinical Supplies Disclosure

This trial is blinded but provided open label; therefore, an unblinded pharmacist or qualified trial site personnel will be used to blind supplies. Treatment identity (name, strength or potency) is included in the label text; random code/disclosure envelopes or lists are 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.

## 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

1. Saydah SH, Fradkin J, Cowie CC. Poor control of risk factors for vascular disease among adults with previously diagnosed diabetes. JAMA 2004;291(3):335-42.

# 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 or legal guardians, at a trial visit by the investigator or his or her designate. Informed consent for Future Biomedical Research should be presented to the subjects on Visit 1. If delayed, present consent at next possible Subject Visit. Informed consent must be obtained prior to collection of all Future Biomedical Research specimens. Consent forms signed by the subject will be kept at the clinical trial site under secure storage for regulatory reasons. Information contained on the consent form alone cannot be traced

to any specimens, test results, or medical information once the specimens have been rendered de-identified.

Subjects are not required to participate in the Future Biomedical Research sub-trial in order to participate in the main trial. Subjects who decline to sign the Future Biomedical Research informed consent will not have the specimen collected nor will they be discontinued from the main trial.

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

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

c. eCRF Documentation for Future Biomedical Research Specimens

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

d. Future Biomedical Research Specimen Collections

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

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

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

**4. Confidential Subject Information for Future Biomedical Research**

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

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

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

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

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

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

**5. Biorepository Specimen Usage**

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

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

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

**6. Withdrawal From Future Biomedical Research**

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

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

**7. Retention of Specimens**

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

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

**8. Data Security**

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

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

## 9. Reporting of Future Biomedical Research Data to Subjects

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

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

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

## 10. Gender, Ethnicity and Minorities

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

## 11. Risks Versus Benefits of Future Biomedical Research

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

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

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

## 12. Self-Reported Ethnicity

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

## 13. Questions

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

## 14. References

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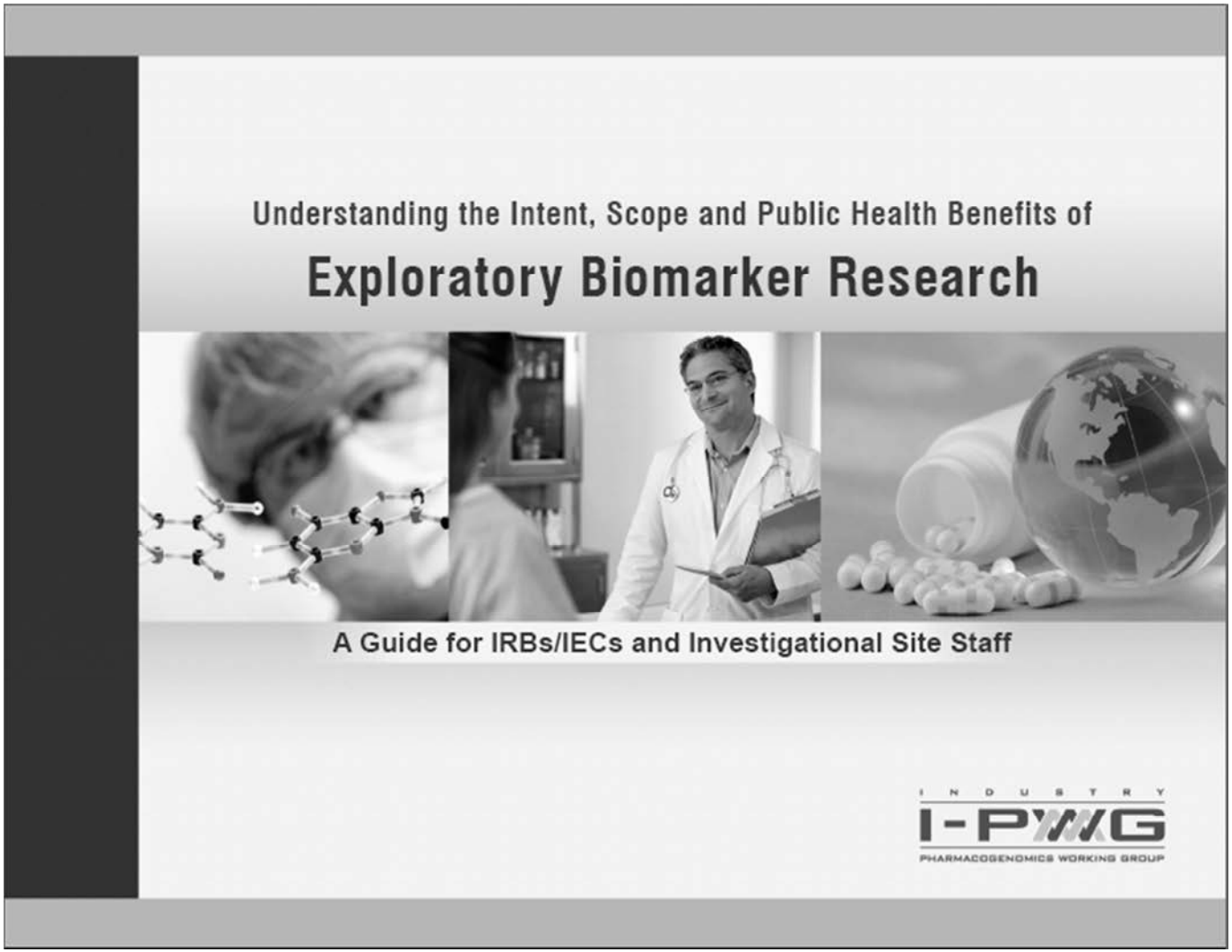
## 12.3 Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff



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

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

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

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

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

## 2. Why is Biomarker Research Important?

**Importance to Patients and Public Health**

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

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

**Importance to Drug Development**

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

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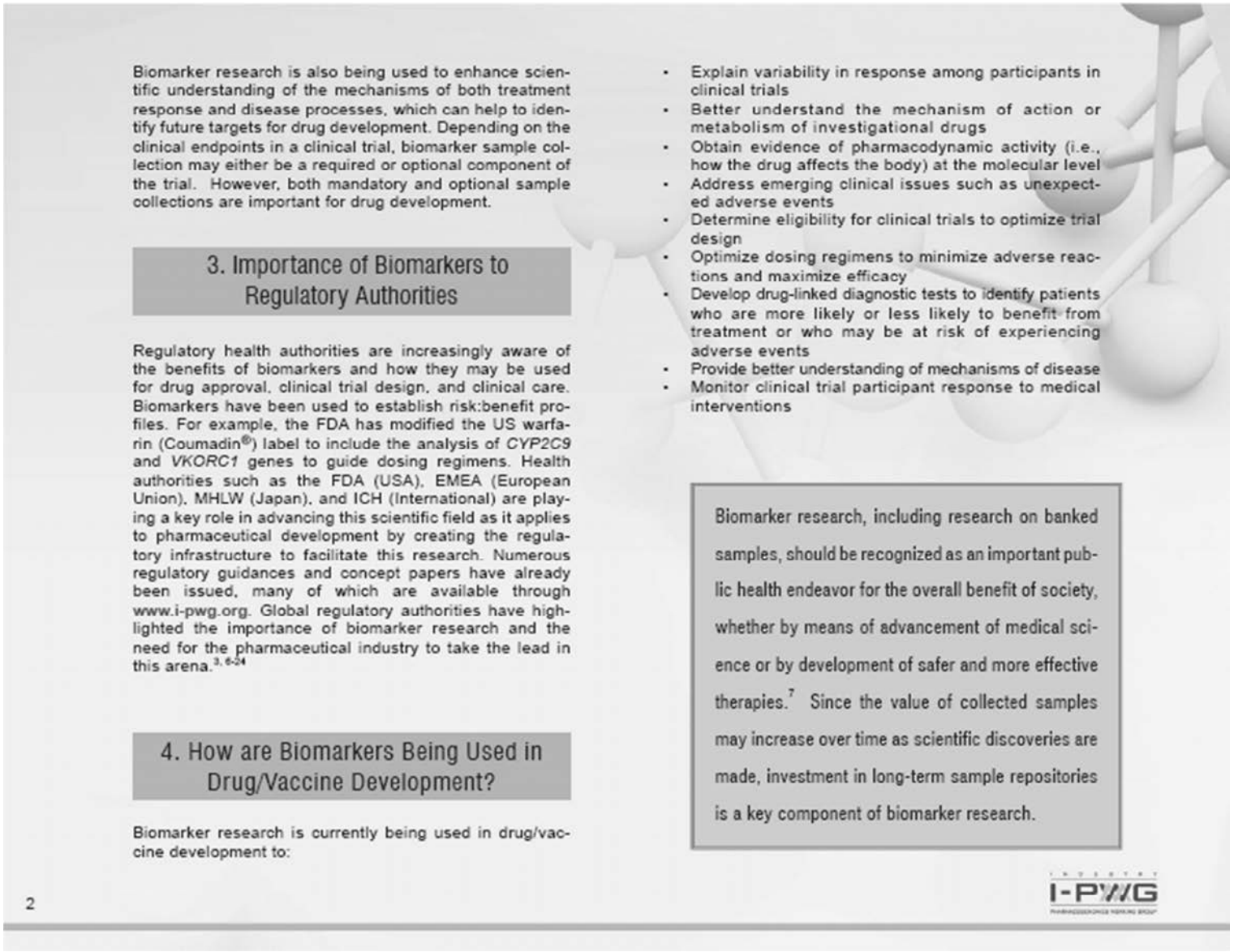
Biomarker research is also being used to enhance scientific understanding of the mechanisms of both treatment response and disease processes, which can help to identify future targets for drug development. Depending on the clinical endpoints in a clinical trial, biomarker sample collection may either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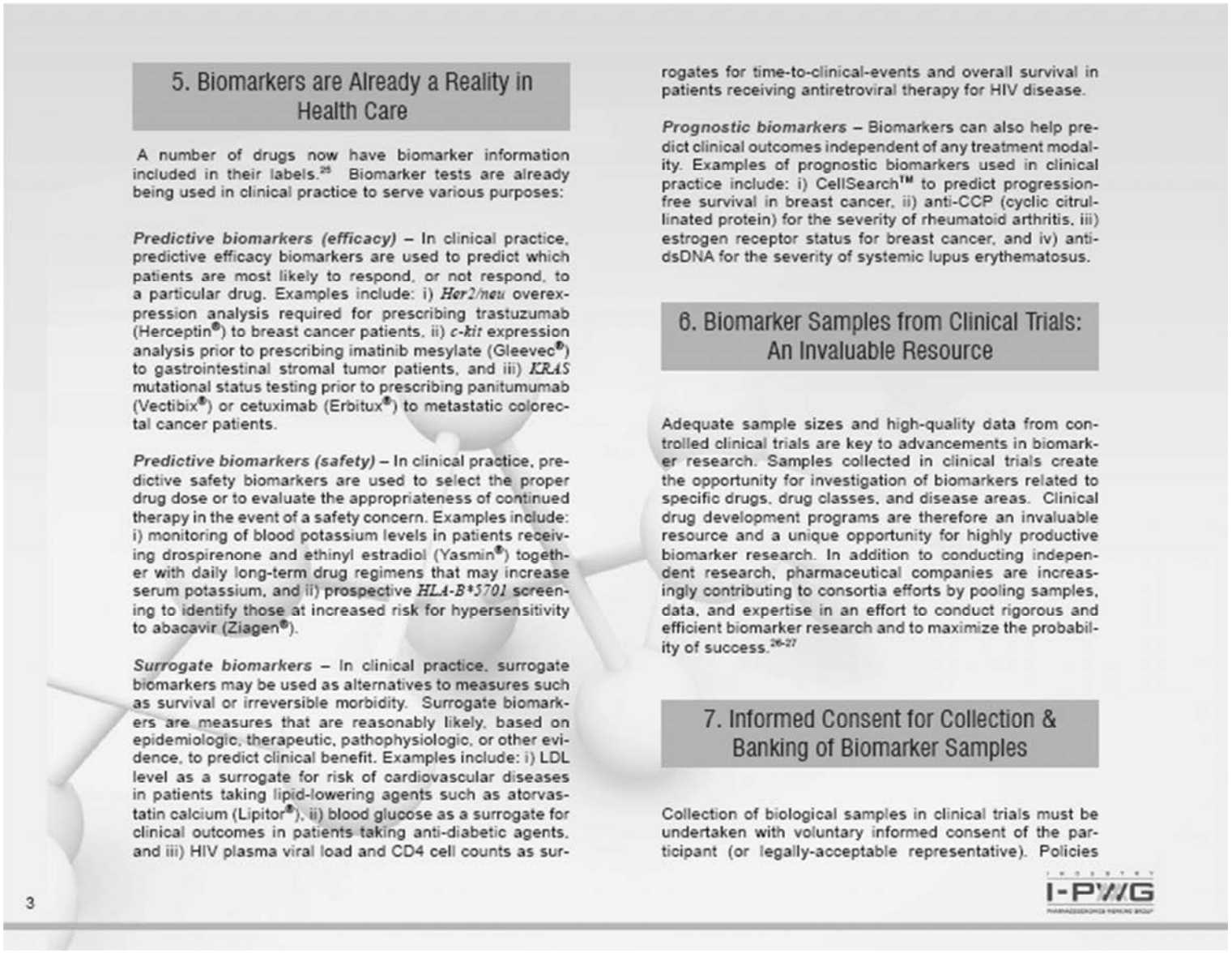

## 5. Biomarkers are Already a Reality in Health Care

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

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

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

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

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

## 6. Biomarker Samples from Clinical Trials: An Invaluable Resource

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

## 7. Informed Consent for Collection & Banking of Biomarker Samples

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

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

### Optional vs. Required Subject Participation

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

### Consent for Future Research Use

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

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

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

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

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

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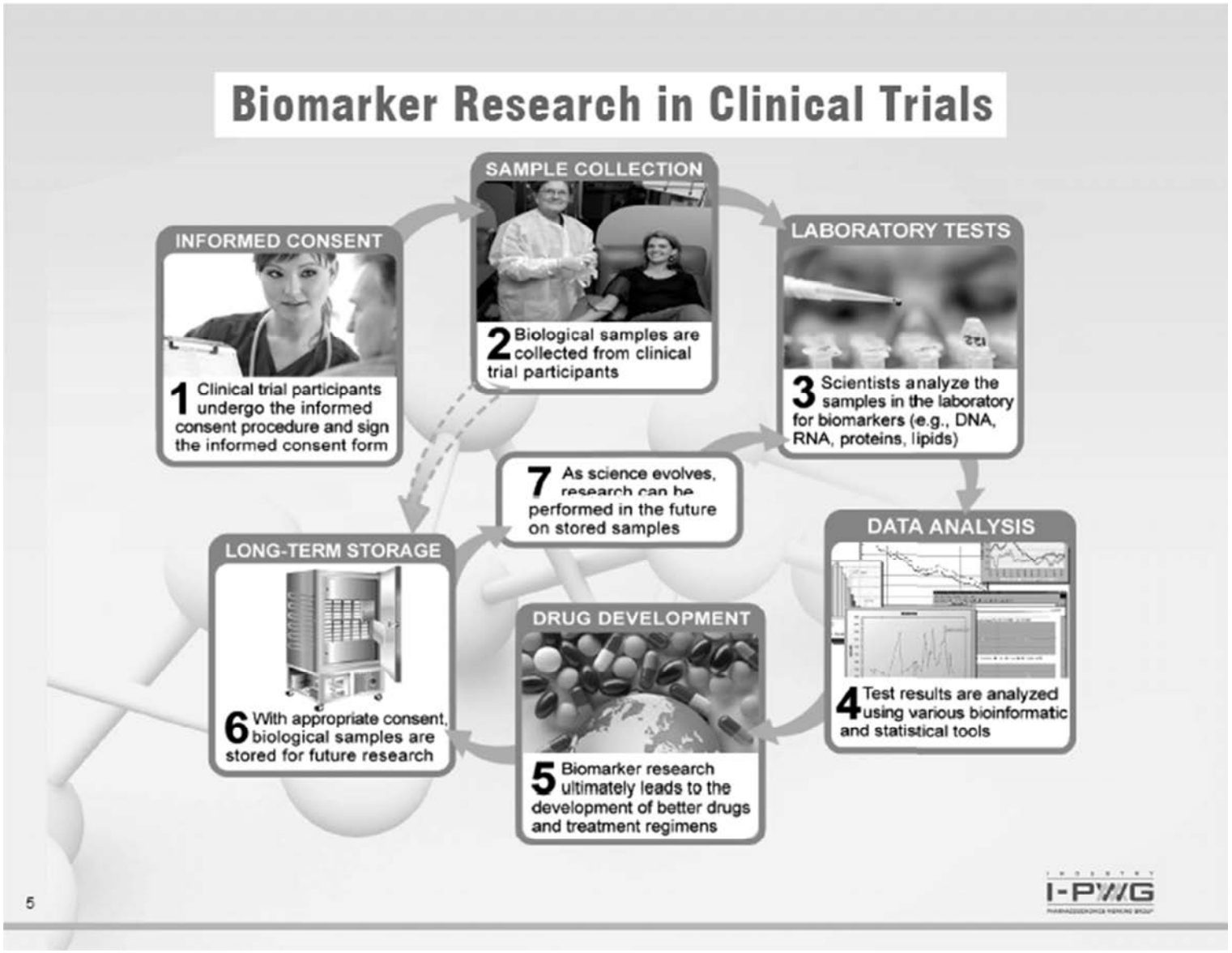
Biomarker Research in Clinical Trials
SAMPLE COLLECTION
2 Biological samples are collected from clinical trial participants
INFORMED CONSENT
1 Clinical trial participants undergo the informed consent procedure and sign the informed consent form
LABORATORY TESTS
3 Scientists analyze the samples in the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

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

## 9. Return of Research Results to Study Participants

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

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

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

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

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

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

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

## 10. Benefits and Risks Associated with Biomarker Research

**Benefits**

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

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

**Risks**

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

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

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

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

## 11. Privacy, Confidentiality, and Patient Rights

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

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

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

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

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

## 12.Where to Get More Information?

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

## 13. What is I-PWG?

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

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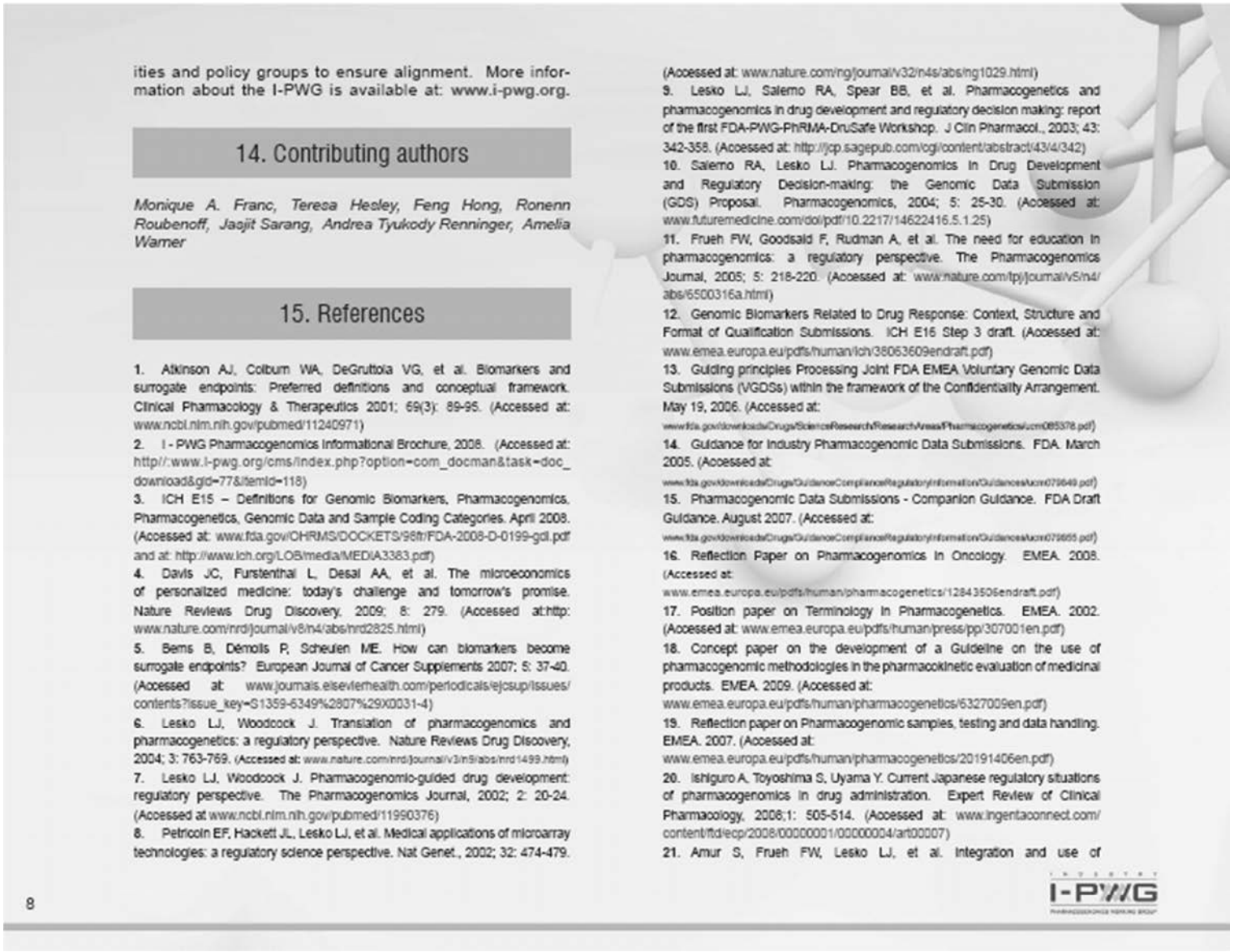

ities and policy groups to ensure alignment. More information about the I-PWG is available at: www.i-pwg.org.

## 14. Contributing authors

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

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## 12.4 Algorithm for Assessing Out-of-Range Laboratory Values

For all laboratory values obtained at prestudy (screening) visit and/or pre-dose evaluation:

A. If all protocol-specified laboratory values are normal, the subject may enter the study. If a protocol specified laboratory value is outside of the parameter(s) outlined in the inclusion/exclusion criteria (including a repeat if performed), the subject will be excluded from the study.

B. If ≥1 protocol-specified laboratory value not specified in the inclusion/exclusion criteria is outside the normal range, the following choices are available:

   1. The subject may be excluded from the study;

   2. The subject may be included in the study if the abnormal value(s) is not clinically significant (NCS) (the investigator must annotate the laboratory value "NCS" on the laboratory safety test source document).

   3. The subject may be included in the study if the abnormality is consistent with a preexisting medical condition which is not excluded per protocol (e.g., elevated eosinophil count in a subject with asthma or seasonal allergies) the medical condition should be annotated on the laboratory report or

   4. The abnormal test may be repeated (refer to items a. and b. below for continuation of algorithm for repeated values)

      a. If the repeat test value is within the normal range, the subject may enter the study.

      b. If the repeat test value is still abnormal, the study investigator will evaluate the potential subject with a complete history and physical examination, looking especially for diseases that could result in the abnormal laboratory value in question. If such diseases can be ruled out, and if the abnormal laboratory value is not clinically relevant, then the subject may enter the study.

If there is any clinical uncertainty regarding the significance of an abnormal value, the subject will be excluded from the study.

## 12.5 12-Lead ECG Abnormality Criteria

| 12-Lead Electrocardiogram Abnormality Criteria | | |
|---|---|---|
| | **Screen Failure Criteria** | **Potentially Significant Post-Randomization Findings (clarification on action to take)** |
| **RHYTHM** | | |
| Sinus Tachycardia | > 110 bpm | HR >110 bpm and HR increase of ≥ 25 bpm from baseline and |
| Sinus Bradycardia | < 40 bpm | HR < 40 bpm and HR decrease of ≥ 5 bpm from baseline |
| Sinus Pause/Arrest | > 2.0 seconds | > 2.0 seconds |
| Atrial premature complex | > 1 beat | ≥ 3 beats |
| Ventricular premature complex | All | ≥ 3 beats |
| Ectopic Atrial Rhythm | None | None |
| Junctional Rhythm | Junctional Rhythm with HR < 40 bpm | Junctional Rhythm with HR < 40 bpm |
| Idioventricular Rhythm | All | All |
| Atrial Fibrillation | All | All |
| Atrial Flutter | All | All |
| Supraventricular Tachycardia | All | All |
| Ventricular Tachycardia | All | All |
| **AXIS** | | |
| Left Axis Deviation | RBBB with Left Anterior Hemiblock (LAHB) | New onset LAHB |
| Right Axis Deviation | RBBB with Left Posterior Hemiblock (LPHB) | New onset LPHB |
| **CONDUCTION** | | |
| 1st degree A-V Block | PR ≥ 230 ms | PR ≥ 230 ms + increase of > 15 ms; or PR increase of > 25% |
| 2nd degree A-V Block | Mobitz Type II | Mobitz Type II |
| 3rd degree A-V Block | All | All |
| LBBB | All | All |
| RBBB | RBBB with LAHB/LPHB as defined above | New onset RBBB (not including intermittent or rate-related) |
| Incomplete Right BBB (ICRBBB) (QRS<120 ms) | No exclusion | Nothing |
| Short PR/ Preexcitation syndrome | Delta wave + PR < 120 ms | Delta wave + PR < 120 ms |
| Other Intra-ventricular Conduction Delay | QRS ≥ 130 ms | QRS ≥ 130 ms + increase of ≥ 10 ms |

| 12-Lead Electrocardiogram Abnormality Criteria | | |
|---|---|---|
| | **Screen Failure Criteria** | **Potentially Significant Post-Randomization Findings (clarification on action to take)** |
| **QTc (B or F)** | | |
| Male | QTc ≥ 470 ms | QTc ≥ 500 ms or increase of ≥ 60 ms from baseline |
| Female | QTc ≥ 480 ms | QTc ≥ 500 ms or increase of ≥ 60 ms from baseline |
| **HYPERTROPHY** | | |
| Atrial abnormalities | Definite evidence of P mitrale or P pulmonale | Definite evidence of P mitrale or P pulmonale |
| Ventricular abnormalities | Voltage criteria for LVH plus Strain Pattern | Voltage criteria for LVH plus Strain Pattern |
| **MYOCARDIAL INFARCTION** | | |
| Acute or Recent | All | All |
| Old | All | All |
| **ST/T MORPHOLOGY** | | |
| ST elevation suggestive of Myocardial Injury | In 2 or more contiguous leads | In 2 or more contiguous leads |
| ST depression suggestive of Myocardial Ischaemia | In 2 or more contiguous leads | In 2 or more contiguous leads |
| T-wave Inversions suggestive of Myocardial Ischaemia | In 2 or more contiguous leads | In 2 or more contiguous leads |
| Non-specific ST-T changes (In 2 or more leads) | No exclusion | In 2 or more contiguous leads |
| **PACEMAKER** | All | All |
| Baseline is defined as Predose Day 1<br>ms=milliseconds, mm=millimeter | | |

## 12.6 Blood Samples for MK-8591 Assay – Procedures for Collection, Handling, Storage and Shipping of Plasma PK Samples

**Supplies and Equipment**

1. Plastic Lavender Topped Vacutainers Containing K2EDTA as the anticoagulant. Capable of holding 4 mL of whole blood.
2. 3.6 mL NUNC Internal Thread Round Bottom Cryotubes (NUNC Part #366524).
   ***Note**: If 3.6 mL NUNC cryotubes are unavailable 4.5 mL NUNC cryotubes may be substituted if permission is granted by the analytical supervisor based on the proper functioning of the automated liquid handling system. This applies to the duration of the study as tube sizes should not be interchanged though out the course of a study. (4.5mL Cryotube NUNC Part #363452)*
3. Disposable Plastic Pipettes. Suitable for delivering volumes between 1.5 mL and 3 mL.
4. Refrigerated Centrifuge. Capable of rotating between 1000-1300 RCF (x g) at between 4°C to 10°C for 10 minutes. Note that RCF varies according to the centrifuge rotor radius. The formula for computing RCF from rotation speed and centrifuge radius is RCF = $11.2r(RPM/1000)^2$, where r is rotor radius, in cm, and RPM is the rotations per minute setting of the centrifuge. A typical refrigerated centrifuge (GH-3.8 model from Beckman) yields 1150 RCF at 2500 RPM, for example.
5. -20C Sample Storage Freezer.

**Collection of Blood**

For specific time points of sample collection, please refer to the Study Flow Chart.

**Sample Labeling**

1. Whole Blood Samples. Vacutainers containing whole blood should be labeled (non-barcoded) as appropriate.
2. Plasma Samples. NUNC tubes containing plasma samples should be labeled with the pre-printed barcoded labels with the allocation number, day, date and time (hours post-dose) provided by the Sponsor. Labels should be placed on the NUNC tubes toward the top 30% of the tube in order for the level of plasma in the tube to be viewed. Only **one (1)** layer of label should be placed on the tube (not 2). This is critical for the proper functioning of the automated liquid handling station.

**Procedure**

1. Draw approximately 4 mL whole blood into plastic (PET) vacutainer containing K2EDTA as the anticoagulant and invert 6 times. The vacutainer should be labeled as appropriate (see above).
2. Immediately after collection, the blood containing tubes should be placed on ice and centrifuged within 30 minutes at between 1000-1300 RCF (x g) at between 4°C to

10°C for 10 minutes. Note that RCF varies according to the centrifuge rotor radius. The formula for computing RCF from rotation speed and centrifuge radius is RCF = 11.2r(RPM/1000)$^2$, where r is rotor radius, in cm, and RPM is the rotations per minute setting of the centrifuge. If the samples cannot be centrifuged immediately, the tubes should be kept on ice and centrifuged within 30 minutes of collection.
*Note: Be sure to account for rotor size variations by adjusting the revolutions per minute (RPM) for the specific centrifuge to yield between 1000-1300 RCF (xg) as noted in the Supplies and Equipment section.*

3. Immediately after separation of the whole blood, carefully transfer the plasma **(at least 1.5 - 2.0 mL)** using a plastic pipette into a 3.6 mL internally-threaded NUNC cryotube identified with pre-printed barcoded labels (see above) and store at -20C until transfer to Merck on DRY ICE.
   ***Note:*** *In the event that the whole blood samples can not be processed immediately the samples should be kept on ice. No more than 60 minutes should elapse between blood draw and the freezing of plasma samples.*

**Sample Shipping**

It is the responsibility of the primary investigator to ensure that all staff personnel who will be handling, packaging, and/or shipping clinical specimens act in conformance with International Air Transport Association (IATA) regulations relating to the handling and shipping of hazardous goods.

1. All shipments will be made in freezer boxes containing at least 10 kg DRY ICE.

2. Please include a sample inventory with each shipment.

3. Samples should be sent at intervals to be determined by the Sponsor and the investigator. Shipments should be sent on MONDAY or TUESDAY to assure receipt by Friday.

4. Samples should be shipped to:

   PPD
   MRL, Division or Merck & Co., Inc.
   770 Sumneytown Pike
   Building No. 75B, LAB 1210
   West Point, PA USA 19486
   Telephone: PPD
   Fax: PPD

***Note:*** *Sample storage for this study is -20C.*

## 12.7 Urine Sample for MK-8591 – Procedures for Collection, Handling, Storage and Shipment of Urine PK Samples

### Introduction

Adding Tween 20 in the urine collection procedure is required. The suggested amount of Tween 20 added should make a final concentration of 0.2 % of Tween 20 in urine. Tween 20 must be added to the original urine collection container before an aliquot is removed for analysis. Any sample transfers from the original sample container prior to the addition of Tween 20 must be avoided in that loss of drug and metabolite may occur. Urine weights, rather than volumes, are determined in order to eliminate the need to pour the sample into a graduated cylinder before the addition of the surfactant.

### Supplies and Equipment

1. Nalgene Series 2105 Wide Mouth Bottles: These bottles are to be used for the actual urine collection, and are available in sizes ranging from 250 to 1000 mL. Thus, the bottle size may be varied depending on the length of the collection interval. The bottles are available in the United States from Fisher Scientific. Their catalog numbers are as follows:

   250 mL bottle: #02-893B
   500 mL bottle: #02-893C
   1000 mL bottle: #02-893D

   A list of Nalgene distributors for countries outside of the U.S. may be found on the World Wide Web at PPD

2. 10% Tween 20 solution (1 L bottle) : Bio-Rad (PPD, www.bio-rad.com), catalog # 161-0781, currently (2007 pricing) $26 per bottle in the US, but available through Bio-Rad worldwide.

3. Top loading digital balance with a capacity of at least 2500 g.

4. Set of pipettes suitable for delivering volumes between 0.25 mL and 20 mL .

5. 4.5 mL NUNC cryotube vials (NUNC #363452 or Fisher #12-565-173N)

### Procedure

1. Prior to use, the urine collection bottles, together with their caps, should be weighed on a digital balance. The bottle weights should then be recorded.

2. During the sample collection interval, instruct the subject to void directly into the pre-weighed collection bottle.

3. At times when they are not in use, the collection bottles may be stored at 4°C.

4. At the end of the collection interval determine and record the weight of the capped collection bottle containing the urine specimen.

5. Subtract the weight of the empty bottle from the weight of the bottle containing the specimen in order to determine the weight of the specimen.

6. Record the weight of the specimen.

7. Calculate the volume of 10% Tween 20 solution that needs to be added to the specimen. The volume (mL) of surfactant solution that needs to be added to the sample is calculated by multiplying the weight of the specimen in grams by 0.02. For example, a specimen weighing 500 grams requires 10 mL of surfactant solution to be added to it.

8. Add the calculated volume of surfactant solution to the specimen. The volume of surfactant solution added to the specimen should also be recorded.

   *Note that if urine collection volumes exceed 1 L for any given interval, separate additions of Tween 20 (to each container within a collection interval) are to be completed as described above, and the separate collections are to be combined after the solutions are mixed thoroughly.*

9. Cap the specimen bottle and shake the sample well in order to ensure that all container surfaces have been exposed to the surfactant treated sample.

10. Transfer a 3 mL aliquot of the surfactant treated specimen to a pre-labeled 4.5 mL NUNC tube.

11. The sample aliquots should be frozen at -20$^{o}$C prior to shipment on dry ice to Merck Research Laboratories.

## 12.8 Approximate Blood Collected by Trial Visit and by Sample Types

### Blood Collection for Panels A-C:

| All Panels | Pre-trial | Treatment Period | Post-trial | Total Collections | mL Per Collection | Total mL/ Test |
|---|---|---|---|---|---|---|
| Laboratory safety tests | 2 | 6 | 1 | 9 | 12 | 108 |
| HIV/Hepatitis Screen (at the discretion of the investigator) | 1 | 0 | 0 | 1 | 5 | 5 |
| FSH* | 1 | 0 | 0 | 1 | 5 | 5 |
| Blood for Future Biomedical Research | 0 | 1 | 0 | 1 | 8.5 | 8.5 |
| Blood for PBMC | 0 | 14 | 0 | 14 | 16 | 224 |
| Blood for MK-8591 | 0 | 24 | 0 | 24 | 4 | 96 |
| | | | | | Total Blood Volume Per Male Subject [a] | 441.5 mL |
| | | | | | Total Maximum Blood Volume Per Female Subject [a] | 446.5 mL |

* for postmenopausal women only.
[a] If additional pharmacokinetic/pharmacodynamics and/or safety analysis is necessary, an additional 50 mL may be obtained.

### Blood Collection for Panels D-E:

| All Panels | Pre-trial | Treatment Period | Post-trial | Total Collections | mL Per Collection | Total mL/ Test |
|---|---|---|---|---|---|---|
| Laboratory safety tests | 2 | 4 | 1 | 7 | 12 | 84 |
| HIV/Hepatitis Screen (at the discretion of the investigator) | 1 | 0 | 0 | 1 | 5 | 5 |
| FSH* | 1 | 0 | 0 | 1 | 5 | 5 |
| Blood for Future Biomedical Research | 0 | 1 | 0 | 1 | 8.5 | 8.5 |
| Blood for PBMC | 0 | 14 | 0 | 14 | 16 | 224 |
| Blood for MK-8591 | 0 | 23 | 0 | 23 | 4 | 92 |
| | | | | | Total Blood Volume Per Male Subject [a] | 413.5 mL |
| | | | | | Total Maximum Blood Volume Per Female Subject [a] | 418.5mL |

* for postmenopausal women only.
[a] If additional pharmacokinetic/pharmacodynamics and/or safety analysis is necessary, an additional 50 mL may be obtained.

## 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 | |