| | |
|---|---|
| **Official Protocol Title:** | A Phase 2B, Randomized, Double-Blind, Active-Comparator-Controlled, Dose-Ranging Clinical Trial to Evaluate the Safety, Tolerability, Antiretroviral Activity, and Pharmacokinetics of MK-8591 Given in Combination with Doravirine (DOR) and Lamivudine (3TC) in HIV-1-Infected Treatment-Naïve Adults |
| **NCT number:** | NCT03272347 |
| **Document Date:** | 06-Jul-2020 |

# Title Page

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**Protocol Title:** A Phase 2B, Randomized, Double-Blind, Active-Comparator-Controlled, Dose-Ranging Clinical Trial to Evaluate the Safety, Tolerability, Antiretroviral Activity, and Pharmacokinetics of MK-8591 Given in Combination with Doravirine (DOR) and Lamivudine (3TC) in HIV-1-Infected Treatment-Naïve Adults

**Protocol Number: 011-05**

**Compound Number: MK-8591**

**Sponsor Name and Legal Registered Address:**

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
(hereafter referred to as the Sponsor or Merck)

One Merck Drive
P.O. Box 100
Whitehouse Station, New Jersey, 08889-0100, U.S.A.

**Regulatory Agency Identifying Number(s):**

**IND NUMBER:** 134,036

**EudraCT NUMBER:** 2017-000437-32

**Approval Date: 06 July 2020**

**Sponsor Signatory**

Typed Name:
Title:

Date

**Protocol-specific Sponsor Contact information can be found in the Investigator Trial File Binder (or equivalent).**

**Investigator Signatory**

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.

Typed Name:
Title:

Date

## DOCUMENT HISTORY

| Document | Date of Issue | Overall Rationale |
|---|---|---|
| Amendment 05 | 06-JUL-2020 | At the eDMC meeting review of the Week 96 data, it was determined that no further meetings of the eDMC would be needed and that the study could proceed as planned. The Sponsor therefore has decided to remove the Week 120 interim analysis and to perform data analysis on an annual basis so that the next analysis would occur at Week 144. |
| Amendment 04 | 06-MAR-2020 | The study has been extended for an additional 48 weeks (Part 4: 2-drug Dosing with MK-8591A) to allow participants in Part 3 receiving the selected dose of MK-8591 in combination with DOR QD or MK-1439A in the control group to switch to a 2-drug fixed-dose combination (FDC) of MK-8591/DOR (referred to as MK-8591A) QD in Part 4, and to collect additional safety and efficacy data. MK-8591A will be provided as open-label supplies. Additional site visits have been added at Weeks 148, 156, 168, 180, and 192. |
| Amendment 03 | 10-OCT-2019 | The terminology in the protocol has been updated from "virologic failure" to "clinically significant confirmed viremia," which is consistent with clinical management of participants with HIV-1 and updated US DHHS guidelines. In addition, the study has been extended to allow participants to receive an additional 24 weeks of open-label study treatment, and to collect additional safety and efficacy data. Thus, following Week 120, additional site visits have been added at Week 132 and Week 144. |
| Amendment 02 | 18-JAN-2018 | Revised the safety follow-up period from ~14 days (2 weeks) to ~42 days (6 weeks) after the final dose of study treatment due to updated data which indicated the half-life of MK-8591 in plasma was expected to be between 87 and 128 hours after cessation of dosing for the dose range studied in this study. Therefore, a safety follow-up period of ~42 days allowed for AE/SAE recording and reporting during this time. |
| Amendment 01 | 20-SEP-2017 | Incorporated several regulatory requests and corrected/added several minor items. |
| Original Protocol | 04-AUG-2017 | Not applicable |

## PROTOCOL AMENDMENT SUMMARY OF CHANGES

**Amendment** 05

**Overall Rationale for the Amendment:**

At the eDMC meeting review of the Week 96 data, it was determined that no further meetings of the eDMC would be needed and that the study could proceed as planned. The Sponsor therefore has decided to remove the Week 120 interim analysis and to perform data analysis on an annual basis so that the next analysis would occur at Week 144.

**Summary of Changes Table:**

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 2.1 Schedule of Activities – Screening and Treatment Visits (Parts 1-3) | The note for dispensing study medication using IVRS/IWRS has been updated to clarify medication dispensation for participants who continue to Part 4 of the study. | Updated for clarity. |
| | The note for the study medication diary has been updated to include instructions for participants who agree to continue to Part 4. | Updated to clarify that at Week 144 study medication diaries for Part 4 will be provided to all participants entering Part 4. |
| | Hepatitis screening for participants in Group 4 who plan to switch from MK-1439A to MK-8591A at Week 144 to enter Part 4 has been moved from Week 144 to Week 132. | Hepatitis screening was moved from Week 144 to Week 132 so results will be available for these participants prior to switching to MK-8591A. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 2.2 Schedule of Activities – Treatment Visits (Part 4) | Removed dispensation of study medication at Week 192. | Updated to clarify that no study medication will be dispensed at Week 192. |
| | A note was added to clarify that only the study medication diary will be reviewed at Week 192. | Added for clarity; no study medication diary will be distributed at this visit. |
| 5.1 Overall Design | Text was added to the last paragraph of this section stating no additional eDMC reviews of safety data will occur following the review of the Week 96 interim analysis. | Statement consistent with removal of the Week 120 interim analysis. |
| 9.5.5 DEXA Assessments | Text referencing the Site Imaging Manual has been added at the end of this section. | Added for clarity. |
| 10.1 Statistical Analysis Plan Summary, 10.7 Interim Analyses | The interim analysis at Week 120 was removed. | The Week 96 interim analysis included approximately 18 months of data showing continued virologic suppression for study participants on the 2-drug regimen with MK-8591 + DOR. After the Week 96 eDMC review, the eDMC deemed that further reviews were unnecessary as the study is no longer blinded and the eDMC does not think the safety profile of MK-8591 + DOR will substantially change. Approximately 30 months of data confirming MK-8591 + DOR virologic suppression will be available for the next interim analysis at Week 144. |
| Throughout | Minor typographical and grammatical edits. | To improve clarity, consistency, and/or to align with Merck policy. |

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## LIST OF FIGURES

## 1. Synopsis

**Protocol Title:**

A Phase 2B, Randomized, Double-Blind, Active-Comparator-Controlled, Dose-Ranging Clinical Trial to Evaluate the Safety, Tolerability, Antiretroviral Activity, and Pharmacokinetics of MK-8591 Given in Combination with Doravirine (DOR) and Lamivudine (3TC) in HIV-1-Infected Treatment-Naïve Adults

**Short Title:**

Dose Ranging Trial of MK-8591 Given in Combination with Doravirine (DOR) and Lamivudine (3TC)

**Objectives/Hypotheses and Endpoints:**

There are no hypotheses to be tested in this trial. Objectives refer to the original regimen to which participants were randomized (Groups 1 to 3: 1 of 3 different doses of MK-8591 administered with doravirine [DOR] 100 mg + lamivudine [3TC] 300 mg, or Group 4: MK-1439A [DOR 100 mg + 3TC 300 mg + tenofovir disoproxil fumarate [TDF] 300 mg]), but participants in the MK-8591 treatment groups will be switched in Part 2 to a 2-drug regimen with MK-8591 + DOR after at least 24 weeks on the 3-drug regimen if their human immunodeficiency virus type 1 (HIV-1) RNA is <50 copies/mL. In Part 3, participants in the MK-8591 treatment groups will receive the selected dose of MK-8591 + DOR, and Group 4 will continue to receive MK-1439A. In Part 4, all participants in each group will receive MK-8591A (FDC of MK-8591/DOR).

In HIV-1-infected antiretroviral treatment-naïve adults:

| **Objective/Hypothesis** | **Endpoint** |
|---|---|
| **Primary** | |
| • Objective: To evaluate the antiretroviral activity of different doses of MK-8591 administered with DOR + 3TC compared to MK-1439A, as assessed by the proportion of participants with HIV-1 RNA <50 copies/mL at Week 24 and at Week 48 | • Proportion of participants with HIV-1 RNA <50 copies/mL at Week 24 and Week 48 |
| • Objective: To evaluate the safety and tolerability of different doses of MK-8591 administered with DOR + 3TC compared to MK-1439A | • Number of participants experiencing adverse events (AEs)<br>• Number of participants discontinuing study drug due to AEs |

| **Secondary** | |
|---|---|
| • Objective: To evaluate the sustained antiretroviral suppression in participants on the selected dose of MK-8591 + DOR compared to MK-1439A as assessed by the proportion of participants with HIV-1 RNA <50 copies/mL 24 and 48 weeks after switching to Part 2 | • Proportion of participants with HIV-1 RNA <50 copies/mL 24 and 48 weeks after entering Part 2 |
| • Objective: To evaluate the immunologic effect of different doses of MK-8591 administered with DOR + 3TC compared to MK-1439A at Week 24, Week 48, Week 96, and Week 144 | • Change from baseline in CD4+ T-cell count at Week 24, Week 48, Week 96, and Week 144 |
| • Objective: To evaluate the antiretroviral suppression and immunologic effect of MK-8591A administered during open-label dosing in Part 4 of the trial | • Proportion of participants with HIV-1 RNA <50 copies/mL at Week 192 (48 weeks after entering Part 4)<br>• Change from baseline in CD4+ T-cell count at Week 192 |
| • Objective: To evaluate the safety and tolerability of different doses of MK-8591 administered with DOR compared to MK-1439A 24 weeks after switching to Part 2 | • Number of participants experiencing AEs<br>• Number of participants discontinuing study drug due to AEs |
| • Objective: To evaluate the safety and tolerability of the selected dose of MK-8591 administered with DOR compared to MK-1439A at Week 96 and through study duration. | • Number of participants experiencing AEs<br>• Number of participants discontinuing study drug due to AEs |
| • Objective: To evaluate the safety and tolerability of MK-8591A during open-label dosing in Part 4 of the trial. | • Number of participants experiencing AEs<br>• Number of participants discontinuing study drug due to AEs |

**Overall Design:**

| | |
|---|---|
| Trial Phase | Phase 2b |
| Clinical Indication | Treatment of HIV-1 infection |

| | |
|---|---|
| Population | Treatment-naïve adults with HIV-1 infection |
| Trial Type | Interventional |
| Type of Design | Parallel, active comparator, dose-ranging |
| Type of Control | Active control |
| Trial Blinding | Double-blind |
| Estimated Duration of Trial | The Sponsor estimates that the trial will require approximately 4.3 years from the time the first participant signs the informed consent until the last participant's last study-related phone call or visit. |

**Number of Participants:**

Approximately 120 participants will be enrolled.

**Treatment Groups and Duration:**

| | |
|---|---|
| Treatment Groups | **3-Drug Dose Ranging (Part 1)**<br>Participants will be randomized in a 1:1:1:1 ratio to 1 of 4 treatment groups:<br>**Group 1 (n=30):**<br>MK-8591 (0.25 mg) once daily (QD) +<br>DOR (100 mg) QD +<br>3TC (300 mg) QD +<br>placebo for MK-1439A QD<br>**Group 2 (n=30):**<br>MK-8591 (0.75 mg) QD +<br>DOR (100 mg) QD +<br>3TC (300 mg) QD +<br>placebo for MK-1439A QD<br>**Group 3 (n=30):**<br>MK-8591 (2.25 mg) QD +<br>DOR (100 mg) QD +<br>3TC (300 mg) QD +<br>placebo for MK-1439A QD<br>**Group 4 (n=30):**<br>MK-1439A (DOR 100 mg + 3TC 300 mg + TDF 300 mg) QD +<br>placebo for DOR QD + |

| | |
|---|---|
| | placebo for 3TC QD +<br>placebo for MK-8591 QD<br><br>Groups 1 to 3 will receive 1 of 3 doses of MK-8591 QD administered with DOR QD and 3TC QD (3-drug dose ranging). Group 4 will receive MK-1439A. Matching placebos will be administered in Part 1. Randomization will be stratified by screening HIV-1 RNA level (≤100,000 copies/mL or >100,000 copies/mL). Participants will receive a minimum of 24 weeks of treatment in Part 1. Participants will be eligible to switch to Part 2 at Week 24 if they have not met viral failure criteria (Section 5.4.1.1.1) and the Week 20 HIV-1 RNA result is <50 copies/mL. Participants whose HIV-1 RNA result is ≥50 copies/mL at Week 20 will continue to receive blinded study drug until the HIV-1 RNA result is <50 copies/mL. Participants who do not achieve HIV RNA <50 copies/mL by the Week 48 assessment or have met any of the other viral failure criteria prior to Week 48 will be discontinued from treatment and complete the early discontinuation and end of trial phone and site follow-up visits.<br><br>**2-Drug Dose Ranging/Maintenance (Part 2):**<br><br>Participants in Groups 1 to 3 who were eligible to switch to Part 2 will continue treatment with the dose of MK-8591 QD they were randomized to in Part 1 in combination with DOR QD. In Part 2, 3TC is dropped from the regimen for those in the MK-8591 groups, the dose of MK-8591 remains blinded and DOR is provided in an open-label fashion. Participants in Group 4 will receive open-label MK-1439A QD. Matching placebos are no longer administered to any treatment group in Part 2.<br><br>**Group 1:** MK-8591 (0.25 mg) QD + DOR (100 mg) QD (n~ 30)<br><br>**Group 2:** MK-8591 (0.75 mg) QD + DOR (100 mg) QD (n~ 30)<br><br>**Group 3:** MK-8591 (2.25 mg) QD + DOR (100 mg) QD (n~ 30)<br><br>**Group 4:** MK-1439A QD (n~ 30)<br><br>**2-Drug Selected Dose Maintenance (Part 3):**<br><br>Once the dose of MK-8591 has been selected and communicated to site personnel, participants in Groups 1 to 3 will switch to the selected dose of MK-8591 QD at the |

| | |
|---|---|
| | next scheduled visit and continue treatment in combination with open-label DOR QD. Participants in Group 4 will continue to receive open-label MK-1439A.<br>**Groups 1-3:** MK-8591 (selected dose) QD + DOR (100 mg) QD (n~ 90)<br>**Group 4:** MK-1439A QD (n~ 30)<br>**2-Drug Dosing with MK-8591A (Part 4):**<br>Participants receiving the selected dose of MK-8591 in combination with DOR QD or MK-1439A in the control group in Part 3 will all be switched to the 2-drug FDC of MK-8591A QD in Part 4. MK-8591A will be provided as open-label supplies.<br>**Groups 1-3:** MK-8591A (MK8591 0.75 mg/DOR 100 mg) QD (n ~ 90)<br>**Group 4:** MK-8591A (MK8591 0.75 mg/DOR 100 mg) QD (n ~ 30) |
| Duration of Participation | Each participant enrolled will participate in the trial for approximately 206.5 weeks from the time the participant signs the informed consent form through the final contact. After a screening phase of up to 8.5 (60 days) weeks, participants will receive assigned treatment for approximately 192 weeks. After the end of treatment, each participant will be followed for 6 weeks. |

A list of abbreviations used in this document can be found in Appendix 1.

## 2. Schedule of Activities (SoA)

### 2.1 Schedule of Activities - Screening and Treatment Visits (Parts 1-3)

| Trial Epoch: | *Part 1 3-Drug Dose Ranging* | | | | | | | | *Part 2 2-Drug Dosing Ranging/Maintenance*[1] | | | | | | | | *Part 3 2-Drug Selected Dose Maintenance*[2] | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Number:** | **V1** | **V2** | **V3** | **V4** | **V5** | **V6** | **V7** | **V8** | **V9**[1] | **V10**[1] | **V11**[1] | **V12**[1] | **V13**[1] | **V14**[1] | **V15**[1] | **V16**[1] | **V17**[2] | **V18**[2] | **V19** | **V20** | **V21** | **V22** | **V23** | **V24** | **NOTES** |
| **Treatment Week (W):** | **Screen** | **Randomization (Day 1) (Fasting)**[3] | **W2** | **W4** | **W8** | **W12** | **W16** | **W20** | **W24 (Fasting)**[3] | **W28** | **W32** | **W36 (Fasting)**[3] | **W40** | **W44** | **W48 (Fasting)**[3] | **W52** | **W60** | **W72 (Fasting)**[3] | **W84** | **W96 (Fasting)**[3] | **W108** | **W120 (Fasting)**[3] | **W132** | **W144 (Fasting)**[3] | The expected date of each visit should be calculated using the date of Day 1. |
| **Scheduling Window** | **≤60 days** | **NA** | **± 3 days** | | **± 5 days** | | | | | | | | | | | | **± 7 days** | | | | | | | | To ensure timely study medication resupply. |
| **Administrative and General Procedures** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Informed consent | X | | | | | | | | | | | | | | | | | | | | | X | | X | Obtain consent on or prior to scheduled visit. |
| Informed consent for Future Biomedical Research | X | | | | | | | | | | | | | | | | | | | | | | | | |
| Participant identification card | X | | | | | | | | | | | | | | | | | | | | | | | | |
| Inclusion/exclusion | X | X | | | | | | | | | | | | | | | | | | | | | | | Inclusion/exclusion should be reviewed prior to dose on Day 1 to ensure no changes to participant's eligibility since screening. |
| Medical history | X | | | | | | | | | | | | | | | | | | | | | | | | Includes history of tobacco, alcohol, and illicit drug use. |
| Prior/concomitant medication review | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | Prior to dose on Day 1. |

| Trial Epoch: | *Part 1 3-Drug Dose Ranging* | | | | | | | | *Part 2 2-Drug Dosing Ranging/Maintenance*[1] | | | | | | | | *Part 3 2-Drug Selected Dose Maintenance*[2] | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Number:** | **V1** | **V2** | **V3** | **V4** | **V5** | **V6** | **V7** | **V8** | **V9**[1] | **V10**[1] | **V11**[1] | **V12**[1] | **V13**[1] | **V14**[1] | **V15**[1] | **V16**[1] | **V17**[2] | **V18**[2] | **V19** | **V20** | **V21** | **V22** | **V23** | **V24** | **NOTES** |
| **Treatment Week (W):** | **Screen** | **Randomization (Day 1) (Fasting)**[3] | **W2** | **W4** | **W8** | **W12** | **W16** | **W20** | **W24 (Fasting)**[3] | **W28** | **W32** | **W36 (Fasting)**[3] | **W40** | **W44** | **W48 (Fasting)**[3] | **W52** | **W60** | **W72 (Fasting)**[3] | **W84** | **W96 (Fasting)**[3] | **W108** | **W120 (Fasting)**[3] | **W132** | **W144 (Fasting)**[3] | The expected date of each visit should be calculated using the date of Day 1. |
| **Scheduling Window** | **≤60 days** | **NA** | **± 3 days** | | **± 5 days** | | | | | | | | | | | | **± 7 days** | | | | | | | | To ensure timely study medication resupply. |
| Register trial visit in IVRS/IWRS | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Treatment randomization | | X | | | | | | | | | | | | | | | | | | | | | | | Prior to dose on Day 1. |
| Dispense study medication using IVRS/IWRS | | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | At Week 144, participants in Groups 1-3 who agree to continue to Part 4 will receive MK-8591A (3 bottles of study medication will be dispensed until the next visit at Week 156). Participants in Group 4 who agree to continue to Part 4 and switch from MK-1439A to MK-8591A will be dispensed 1 bottle of study medication until the next visit at Week 148. |

| Trial Epoch: | *Part 1 3-Drug Dose Ranging* | | | | | | | | *Part 2 2-Drug Dosing Ranging/Maintenance*[1] | | | | | | | | *Part 3 2-Drug Selected Dose Maintenance*[2] | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Number:** | **V1** | **V2** | **V3** | **V4** | **V5** | **V6** | **V7** | **V8** | **V9**[1] | **V10**[1] | **V11**[1] | **V12**[1] | **V13**[1] | **V14**[1] | **V15**[1] | **V16**[1] | **V17**[2] | **V18**[2] | **V19** | **V20** | **V21** | **V22** | **V23** | **V24** | **NOTES** |
| **Treatment Week (W):** | **Screen** | **Randomization (Day 1) (Fasting)**[3] | **W2** | **W4** | **W8** | **W12** | **W16** | **W20** | **W24 (Fasting)**[3] | **W28** | **W32** | **W36 (Fasting)**[3] | **W40** | **W44** | **W48 (Fasting)**[3] | **W52** | **W60** | **W72 (Fasting)**[3] | **W84** | **W96 (Fasting)**[3] | **W108** | **W120 (Fasting)**[3] | **W132** | **W144 (Fasting)**[3] | The expected date of each visit should be calculated using the date of Day 1. |
| **Scheduling Window** | **≤60 days** | **NA** | **± 3 days** | | **± 5 days** | | | | | | | | | | | | **± 7 days** | | | | | | | | To ensure timely study medication resupply. |
| Provide & review study medication diary | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | Prior to dose on Day 1. At Week 144, all participants who agree to continue to Part 4 will be provided study medication diaries for Part 4. |
| **Safety Procedures** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Full physical examination | X | | | X | | X | | | X | | | | | | X | | | X | | | | X | X | X | |
| Directed physical examination | | X | X | | X | | X | X | | X | X | X | X | X | | X | X | | X | X | X | | | | Prior to dose on Day 1. |
| Vital signs | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | Prior to dose on Day 1. Include pulse, blood pressure, respiratory rate, and body temperature. |
| Weight | X | | | X | | X | | | X | | | | | | X | | | X | | X | | X | X | X | |
| Height | | X | | | | | | | | | | | | | | | | | | | | | | | |

| Trial Epoch: | *Part 1 3-Drug Dose Ranging* | | | | | | | | *Part 2 2-Drug Dosing Ranging/Maintenance*[1] | | | | | | | | *Part 3 2-Drug Selected Dose Maintenance*[2] | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Number:** | **V1** | **V2** | **V3** | **V4** | **V5** | **V6** | **V7** | **V8** | **V9**[1] | **V10**[1] | **V11**[1] | **V12**[1] | **V13**[1] | **V14**[1] | **V15**[1] | **V16**[1] | **V17**[2] | **V18**[2] | **V19** | **V20** | **V21** | **V22** | **V23** | **V24** | **NOTES** |
| **Treatment Week (W):** | **Screen** | **Randomization (Day 1) (Fasting)**[3] | **W2** | **W4** | **W8** | **W12** | **W16** | **W20** | **W24 (Fasting)**[3] | **W28** | **W32** | **W36 (Fasting)**[3] | **W40** | **W44** | **W48 (Fasting)**[3] | **W52** | **W60** | **W72 (Fasting)**[3] | **W84** | **W96 (Fasting)**[3] | **W108** | **W120 (Fasting)**[3] | **W132** | **W144 (Fasting)**[3] | The expected date of each visit should be calculated using the date of Day 1. |
| **Scheduling Window** | **≤60 days** | **NA** | **± 3 days** | | **± 5 days** | | | | | | | | | | | | **± 7 days** | | | | | | | | To ensure timely study medication resupply. |
| 12-lead ECG | | X | | | | | | | X | | | | | | X | | | | | X | | | | | Within 7 days prior to dose on Day 1. Only performed once the participant is confirmed to meet all eligibility criteria. |
| Review adverse events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Birth control confirmation | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Serum pregnancy test | X | | | | | | | | | | | | | | | | | | | | | | | | For women of childbearing potential only. Performed by the central laboratory. |
| Urine pregnancy test | | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | For women of childbearing potential only. Performed by the local laboratory (kits provided) prior to dose on Day 1.Serum pregnancy test must be performed to confirm a positive urine test result. |

| Trial Epoch: | *Part 1 3-Drug Dose Ranging* | | | | | | | | *Part 2 2-Drug Dosing Ranging/Maintenance*[1] | | | | | | | | *Part 3 2-Drug Selected Dose Maintenance*[2] | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Number:** | **V1** | **V2** | **V3** | **V4** | **V5** | **V6** | **V7** | **V8** | **V9**[1] | **V10**[1] | **V11**[1] | **V12**[1] | **V13**[1] | **V14**[1] | **V15**[1] | **V16**[1] | **V17**[2] | **V18**[2] | **V19** | **V20** | **V21** | **V22** | **V23** | **V24** | **NOTES** |
| **Treatment Week (W):** | **Screen** | **Randomization (Day 1) (Fasting)**[3] | **W2** | **W4** | **W8** | **W12** | **W16** | **W20** | **W24 (Fasting)**[3] | **W28** | **W32** | **W36 (Fasting)**[3] | **W40** | **W44** | **W48 (Fasting)**[3] | **W52** | **W60** | **W72 (Fasting)**[3] | **W84** | **W96 (Fasting)**[3] | **W108** | **W120 (Fasting)**[3] | **W132** | **W144 (Fasting)**[3] | The expected date of each visit should be calculated using the date of Day 1. |
| **Scheduling Window** | **≤60 days** | **NA** | **± 3 days** | | **± 5 days** | | | | | | | | | | | | **± 7 days** | | | | | | | | To ensure timely study medication resupply. |
| Hematology | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | Prior to dose on Day 1. See Appendix 2 for list of specific laboratory tests. |
| Chemistry | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | Prior to dose on Day 1. See Appendix 2 for list of specific laboratory tests. |
| Urinalysis | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | Prior to dose on Day 1. See Appendix 2 for list of specific laboratory tests. |
| Hemostatic function test | X | | | | | | | | | | | | | | | | | | | | | | | | See Appendix 2 for list of specific laboratory tests. |
| HIV-1 screen | X | | | | | | | | | | | | | | | | | | | | | | | | See Appendix 2 for list of specific laboratory tests. |

| Trial Epoch: | *Part 1 3-Drug Dose Ranging* | | | | | | | | *Part 2 2-Drug Dosing Ranging/Maintenance*[1] | | | | | | | | *Part 3 2-Drug Selected Dose Maintenance*[2] | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Number:** | **V1** | **V2** | **V3** | **V4** | **V5** | **V6** | **V7** | **V8** | **V9**[1] | **V10**[1] | **V11**[1] | **V12**[1] | **V13**[1] | **V14**[1] | **V15**[1] | **V16**[1] | **V17**[2] | **V18**[2] | **V19** | **V20** | **V21** | **V22** | **V23** | **V24** | **NOTES** |
| **Treatment Week (W):** | **Screen** | **Randomization (Day 1) (Fasting)**[3] | **W2** | **W4** | **W8** | **W12** | **W16** | **W20** | **W24 (Fasting)**[3] | **W28** | **W32** | **W36 (Fasting)**[3] | **W40** | **W44** | **W48 (Fasting)**[3] | **W52** | **W60** | **W72 (Fasting)**[3] | **W84** | **W96 (Fasting)**[3] | **W108** | **W120 (Fasting)**[3] | **W132** | **W144 (Fasting)**[3] | The expected date of each visit should be calculated using the date of Day 1. |
| **Scheduling Window** | **≤60 days** | **NA** | **± 3 days** | | **± 5 days** | | | | | | | | | | | | **± 7 days** | | | | | | | | To ensure timely study medication resupply. |
| Hepatitis screen | X | | | | | | | X | X | X | X | X | X | X | X | X | | | | | | | X | | Post-randomization HBV/HCV sample collected until the participant switches to Part 2. Refer to Sections 8.1 and 9.10.1. See Appendix 2 for list of specific laboratory tests. Week 132 applies only to participants in Group 4 who plan to switch from MK-1439A to MK-8591A in Part 4, at Week 144. |
| DEXA scan | | X | | | | | | | | | | | | | X | | | | | X | | | | X | Prior to dose on Day 1. May occur prior to Day 1 once the participant is confirmed to meet all eligibility criteria. May require additional planning/scheduling. DEXA scans for fat distribution and bone mineral density. |

| Trial Epoch: | *Part 1 3-Drug Dose Ranging* | | | | | | | | *Part 2 2-Drug Dosing Ranging/Maintenance*[1] | | | | | | | | *Part 3 2-Drug Selected Dose Maintenance*[2] | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Number:** | **V1** | **V2** | **V3** | **V4** | **V5** | **V6** | **V7** | **V8** | **V9**[1] | **V10**[1] | **V11**[1] | **V12**[1] | **V13**[1] | **V14**[1] | **V15**[1] | **V16**[1] | **V17**[2] | **V18**[2] | **V19** | **V20** | **V21** | **V22** | **V23** | **V24** | **NOTES** |
| **Treatment Week (W):** | **Screen** | **Randomization (Day 1) (Fasting)**[3] | **W2** | **W4** | **W8** | **W12** | **W16** | **W20** | **W24 (Fasting)**[3] | **W28** | **W32** | **W36 (Fasting)**[3] | **W40** | **W44** | **W48 (Fasting)**[3] | **W52** | **W60** | **W72 (Fasting)**[3] | **W84** | **W96 (Fasting)**[3] | **W108** | **W120 (Fasting)**[3] | **W132** | **W144 (Fasting)**[3] | The expected date of each visit should be calculated using the date of Day 1. |
| **Scheduling Window** | **≤60 days** | **NA** | **± 3 days** | | **± 5 days** | | | | | | | | | | | | **± 7 days** | | | | | | | | To ensure timely study medication resupply. |
| **Efficacy Procedures** | | | | | | | | | | | | | | | | | | | | | | | | | |
| HIV-1 RNA (real time PCR) | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | Prior to dose on Day 1. See Section 2.3 if criteria are met for clinically significant confirmed viremia. |
| CD4+ T-cell count | X | X | | X | X | X | | | X | | | X | | | X | | | X | | X | | X | X | X | Prior to dose on Day 1. |
| Blood (plasma) for viral resistance | X | | | | | | | | | | | | | | | | | | | | | | | | |
| **Exploratory Laboratory Procedures** | | | | | | | | | | | | | | | | | | | | | | | | | |
| HIV-1 RNA single-copy assay | | | | | | | | | X | | | | | | X | | | | | X | | | | X | Only performed if HIV-1 RNA is below the limit of detection of the real time PCR assay. |
| **Biomarkers/FBR/PK/PD** | | | | | | | | | | | | | | | | | | | | | | | | | |
| IL-6 | | X | | | | | | | X | | | | | | X | | | | | X | | | | X | Prior to dose on Day 1. |
| D-dimer | | X | | | | | | | X | | | | | | X | | | | | X | | | | X | Prior to dose on Day 1. |
| Soluble CD163 | | X | | | | | | | X | | | | | | X | | | | | X | | | | X | Prior to dose on Day 1. |
| Urinary analytes | | X | | | | | | | X | | | | | | X | | | | | X | | | | X | Prior to dose on Day 1. See Appendix 2 for list of specific laboratory tests. |

| Trial Epoch: | *Part 1 3-Drug Dose Ranging* | | | | | | | | *Part 2 2-Drug Dosing Ranging/Maintenance*[1] | | | | | | | | *Part 3 2-Drug Selected Dose Maintenance*[2] | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Number:** | **V1** | **V2** | **V3** | **V4** | **V5** | **V6** | **V7** | **V8** | **V9**[1] | **V10**[1] | **V11**[1] | **V12**[1] | **V13**[1] | **V14**[1] | **V15**[1] | **V16**[1] | **V17**[2] | **V18**[2] | **V19** | **V20** | **V21** | **V22** | **V23** | **V24** | **NOTES** |
| **Treatment Week (W):** | **Screen** | **Randomization (Day 1) (Fasting)**[3] | **W2** | **W4** | **W8** | **W12** | **W16** | **W20** | **W24 (Fasting)**[3] | **W28** | **W32** | **W36 (Fasting)**[3] | **W40** | **W44** | **W48 (Fasting)**[3] | **W52** | **W60** | **W72 (Fasting)**[3] | **W84** | **W96 (Fasting)**[3] | **W108** | **W120 (Fasting)**[3] | **W132** | **W144 (Fasting)**[3] | The expected date of each visit should be calculated using the date of Day 1. |
| **Scheduling Window** | **≤60 days** | **NA** | **± 3 days** | | **± 5 days** | | | | | | | | | | | | **± 7 days** | | | | | | | | To ensure timely study medication resupply. |
| Blood for Genetic Analysis | | X | | | | | | | | | | | | | | | | | | | | | | | Collected from randomized participants only; FBR consent is not required to participate in the study. |
| Population PK blood draws | | X | | X | X | X | X | | | | | | | | X | | | | | | | | | | Prior to dose on Day 1. Two samples (pre-dose and between 0.5 and 2 hours post-dose, respectively) will be collected at W4 and W8 for participants who take their dose during the day; for participants who take their dose in the evening, only a post-dose sample will be collected the following day irrespective of time of dose. One sample will be collected at W12, W16, and W48 at any time irrespective of dose. |

| Trial Epoch: | *Part 1 3-Drug Dose Ranging* | | | | | | | | *Part 2 2-Drug Dosing Ranging/Maintenance*[1] | | | | | | | | *Part 3 2-Drug Selected Dose Maintenance*[2] | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Number:** | **V1** | **V2** | **V3** | **V4** | **V5** | **V6** | **V7** | **V8** | **V9**[1] | **V10**[1] | **V11**[1] | **V12**[1] | **V13**[1] | **V14**[1] | **V15**[1] | **V16**[1] | **V17**[2] | **V18**[2] | **V19** | **V20** | **V21** | **V22** | **V23** | **V24** | **NOTES** |
| **Treatment Week (W):** | **Screen** | **Randomization (Day 1) (Fasting)**[3] | **W2** | **W4** | **W8** | **W12** | **W16** | **W20** | **W24 (Fasting)**[3] | **W28** | **W32** | **W36 (Fasting)**[3] | **W40** | **W44** | **W48 (Fasting)**[3] | **W52** | **W60** | **W72 (Fasting)**[3] | **W84** | **W96 (Fasting)**[3] | **W108** | **W120 (Fasting)**[3] | **W132** | **W144 (Fasting)**[3] | The expected date of each visit should be calculated using the date of Day 1. |
| **Scheduling Window** | **≤60 days** | **NA** | **± 3 days** | | **± 5 days** | | | | | | | | | | | | **± 7 days** | | | | | | | | To ensure timely study medication resupply. |
| Blood (plasma) for repeat HIV-1 drug resistance testing or PK as needed | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | At the screening visit, the sample will be used if needed to repeat the HIV-1 drug resistance. At all other visits, the sample will be used to test PK as needed in the event of clinically significant confirmed viremia. |

DEXA=dual-energy x-ray absorptiometry; ECG=electrocardiogram; FBR=Future Biomedical Research; HIV-1=human immunodeficiency virus type 1; IL-6=interleukin-6; IVRS/IWRS=Interactive Voice/Web Response System; PCR=polymerase chain reaction; PD=pharmacodynamic; PK=pharmacokinetic; RNA=ribonucleic acid; V=visit; W=week.

1 After a minimum of 24 weeks of dosing in Part 1, participants who were virologically suppressed at the previous visit (HIV-1 RNA <50 copies/mL) and had not met any viral failure criteria (Section 5.4.1.1.1) were switched to Part 2 (Section 9.10.1). Participants who had not met viral failure criteria, but whose HIV-1 RNA levels were ≥50 copies/mL continued to receive the 3-drug regimen (Part 1) until the HIV-1 RNA is <50 copies/mL. Prior to Amendment 03, participants who met viral failure criteria or participants who did not achieve HIV RNA <50 copies/mL following the Week 48 assessments were to be discontinued from treatment (Section 5.4.1.1.1, Section 8.1, and Section 9.10.1) and complete the early discontinuation and end-of-trial follow-up visits. As of Amendment 03, if a participant has a viral load of ≥50 copies/mL at any time during the study, a Viremia Confirmation visit must be conducted within 2 to 4 weeks of the initial HIV-1 viremia (Sections 2.2 and 5.4.1.1.2); a participant with confirmed HIV-1 virologic rebound will be discontinued from treatment (Section 5.4.1.1.2 and Section 8.1).

2 The transition from Part 2 to Part 3 will most likely occur at Week 60 or beyond. Participants in treatment Groups 1 to 3 will continue on the blinded dose of MK-8591 until dose selection is announced.

3 Fasting for at least 8 hours.

## 2.2 Schedule of Activities - Treatment Visits (Part 4)

| **Trial Epoch:** | ***Part 4 2-Drug Dosing with MK-8591A*** | | | | | |
|---|---|---|---|---|---|---|
| **Visit Number:** | **V25 [1]** | **V26** | **V27** | **V28** | **V29** | **NOTES** |
| **Treatment Week (W):** | **W148** | **W156** | **W168** | **W180** | **W192 (Fasting)[2]** | The expected date of each visit should be calculated using the date of Day 1. |
| **Scheduling Window** | **± 7 days** | | | | | To ensure timely study medication resupply. |
| **Administrative and General Procedures** | | | | | | |
| Concomitant medication review | X | X | X | X | X | |
| Register trial visit in IVRS/IWRS | X | X | X | X | X | |
| Dispense study medication using IVRS/IWRS | X | X | X | X | | |
| Provide & review study medication diary | X | X | X | X | X | At Week 192, review only. |
| Evaluation to receive continued study intervention | | | | | X | See Section 7.8. |
| **Safety Procedures** | | | | | | |
| Full physical examination | | | | | X | |
| Directed physical examination | X | X | X | X | | |
| Vital signs | X | X | X | X | X | Include pulse, blood pressure, respiratory rate, and body temperature. |
| Weight | X | X | X | X | X | |
| Review adverse events | X | X | X | X | X | |
| Birth control confirmation | X | X | X | X | X | |
| Urine pregnancy test | X | X | X | X | X | For women of childbearing potential only. Serum pregnancy test must be performed to confirm a positive urine test result. |
| Hematology | X | X | X | X | X | See Appendix 2 for list of specific laboratory tests. |
| Chemistry | X | X | X | X | X | See Appendix 2 for list of specific laboratory tests. |
| Urinalysis | X | X | X | X | X | See Appendix 2 for list of specific laboratory tests. |
| DEXA scan | | | | | X | May require additional planning/scheduling. DEXA scans for fat distribution and bone mineral density. |

| Trial Epoch: | *Part 4 2-Drug Dosing with MK-8591A* | | | | | |
|---|---|---|---|---|---|---|
| **Visit Number:** | **V25 [1]** | **V26** | **V27** | **V28** | **V29** | **NOTES** |
| **Treatment Week (W):** | **W148** | **W156** | **W168** | **W180** | **W192 (Fasting)[2]** | The expected date of each visit should be calculated using the date of Day 1. |
| **Scheduling Window** | **± 7 days** | | | | | To ensure timely study medication resupply. |
| **Efficacy Procedures** | | | | | | |
| HIV-1 RNA (real time PCR) | X | X | X | X | X | See Section 2.3 if criteria are met for clinically significant confirmed viremia. |
| CD4+ T-cell count | | | X | | X | |
| **Biomarkers/FBR/PK/PD** | | | | | | |
| IL-6 | | | | | X | |
| D-dimer | | | | | X | |
| Soluble CD163 | | | | | X | |
| Urinary analytes | | | | | X | See Appendix 2 for list of specific laboratory tests. |
| Blood (plasma) for repeat HIV-1 drug resistance testing or PK as needed | X | X | X | X | X | The sample will be used to test PK as needed in the event of clinically significant confirmed viremia. |

DEXA=dual-energy x-ray absorptiometry; ECG=electrocardiogram; FBR=Future Biomedical Research; HIV-1=human immunodeficiency virus type 1; IL-6=interleukin-6; IVRS/IWRS=Interactive Voice/Web Response System; PCR=polymerase chain reaction; PD=pharmacodynamic; PK=pharmacokinetic; RNA=ribonucleic acid; V=visit; W=week.

1. V25 (W148) is only applicable to participants in Group 4 who agree to switch from open-label MK-1439A to MK-8591A in Part 4 of the study.
2. Fasting for at least 8 hours.

## 2.3 Schedule of Activities – Viremia Confirmation, Early Discontinuation (D/C), and End of Trial (EOT) Site Follow-Up Visits

| Trial Period | Viremia Confirmation | Early Discontinuation of Treatment | | End of Trial | Notes |
|---|---|---|---|---|---|
| Visit Name: | Viremia Confirmation | Early D/C | EOT Site Follow-Up | EOT Site Follow-Up[a] | |
| Visit Window: | Within 2 to 4 weeks of HIV-1 Viremia (≥50 copies/mL) | NA | ≥42 to ≤49 days after EOT | ≥42 to ≤49 days after EOT | |
| Prior/concomitant medication review | X | X | X | X | |
| Register trial visit in IVRS/IWRS | X | X | | | |
| Provide & review study medication diary | X | X | | | |
| Full physical examination | | X | X | X | |
| Vital signs | | X | X | X | Includes pulse, blood pressure, respiratory rate, and body temperature. |
| 12-lead ECG | | X | | | |
| Review adverse events | X | X | X | X | |
| Birth control confirmation | X | X | X | X | |
| Serum pregnancy test | | X | X | X | For women of childbearing potential only. Performed by the central laboratory. |
| Hematology | | X | X | X | See Appendix 2 for list of specific laboratory tests. |
| Chemistry | | X | X | X | See Appendix 2 for list of specific laboratory tests. |

| Trial Period | Viremia Confirmation | Early Discontinuation of Treatment | | End of Trial | Notes |
|---|---|---|---|---|---|
| **Visit Name:** | **Viremia Confirmation** | **Early D/C** | **EOT Site Follow-Up** | **EOT Site Follow-Up[a]** | |
| **Visit Window:** | **Within 2 to 4 weeks of HIV-1 Viremia (≥50 copies/mL)** | **NA** | **≥42 to ≤49 days after EOT** | **≥42 to ≤49 days after EOT** | |
| Urinalysis | | X | X | X | See Appendix 2 for list of specific laboratory tests. |
| HIV-1 RNA | X | X | X | | |
| CD4+ T-cell count | | X | | | |
| Blood (plasma) for HIV-1 drug resistance | X | X | | | If a HIV-1 drug resistance sample was collected at the viremia confirmation visit, it is not necessary to collect another sample at Early D/C. |
| HIV-1 RNA single-copy assay | | X | | | Only performed if HIV-1 RNA is below the limit of detection of the real time PCR assay |
| IL-6 | | X | | | |
| D-dimer | | X | | | |
| Soluble CD163 | | X | | | |
| Urinary analytes | | X | | | See Appendix 2 for list of specific laboratory tests. |
| Blood (plasma) for repeat HIV-1 drug resistance testing or PK as needed | X | X | X | | |

D/C=discontinuation; ECG=electrocardiogram; EOT=end of treatment; HIV-1=human immunodeficiency virus type 1; IL-6=interleukin-6; IVRS/IWRS=Interactive Voice/Web Response System; PCR=polymerase chain reaction; PK=pharmacokinetic; RNA=ribonucleic acid.

a. The EOT site follow-up visit is only for those participants who will not continue with MK-8591A after the end of the study (Section 7.8).

## 3. Introduction

MK-8591 (also referred to as islatravir) is a novel, potent human immunodeficiency virus type 1 (HIV-1) nucleoside reverse transcriptase translocation inhibitor (NRTTI) being developed for the treatment of HIV-1 infection. MK-8591 is an inactive nucleoside that is converted to the pharmacologically active triphosphate form via endogenous intracellular kinases. MK-8591 is the first member of a new class of antiretroviral agents, known as NRTTIs, which block HIV reverse transcriptase by a novel dual mechanism of action. In contrast to all NRTIs used for the treatment of HIV infection, which lack a 3'-OH to block incorporation of incoming nucleotide, MK-8591 retains a 3' OH. It acts through multiple mechanisms, including both immediate chain termination by inhibition of translocation and delayed chain termination prevents nucleotide excision (a significant mechanism of NRTI drug resistance) from occurring [Michailidis E 2014]. MK-8591 is highly differentiated from other HIV-1 treatments based on its high potency, long half-life, favorable drug resistance profile, and broad pharmacologic distribution.

Doravirine (DOR, MK-1439) is a novel non-nucleoside reverse transcriptase inhibitor (NNRTI) in Phase 3 development for the treatment of HIV-1. DOR is differentiated from other NNRTIs by its activity against prevalent mutations that confer resistance to other NNRTIs, low potential for drug-drug interactions (DDIs), promising efficacy, low likelihood of selection for viral resistance in vivo, and good tolerability.

Lamivudine (3TC) is a well-tolerated NRTI and is approved for treatment of HIV in combination with other antiretroviral agents.

### 3.1 Study Rationale

The currently preferred recommendation for first-line treatment of HIV-1 infection in treatment-naïve patients includes 3 drugs from 2 different classes. Although a 3-drug regimen has been the standard of care in HIV-1 infection, there are increasing lines of evidence that a 2-drug regimen (depending on the 2 drugs combined) may work as well, and therefore, have the potential to simplify the treatment regimen. A 2-drug regimen could mean a smaller pill burden, fewer DDIs, and a lesser likelihood of safety or tolerability issues compared to the addition of a third drug into the regimen. Current antiretroviral agents have known safety and tolerability issues, which can be improved upon. Specific NRTIs have been associated with lactic acidosis, loss of bone mineral density (BMD), renal toxicity, and hypersensitivity reactions. Specific NNRTIs have been associated with adverse central nervous system events, rash, lipid abnormalities, decreased efficacy in patients with high viral load, and significant DDIs. A need exists for new antiretroviral NRTI and NNRTI agents like MK-8591 and DOR that possess a high barrier to viral resistance with an improved safety and tolerability profile and are convenient to take.

This trial will be broken into 4 parts: 1) 3-drug dose ranging treatment initiation, 2) 2-drug dose ranging maintenance of Part 1 participants, 3) 2-drug maintenance with the selected dose of MK-8591, and 4) 2-drug dosing with MK-8591A. This trial design allows for dose ranging of MK-8591 in the traditional setting of 3 antiretroviral agents followed by evaluation of MK-8591 in the setting of a 2-drug regimen.

## 3.2 Background

Refer to the Investigator's Brochures (IB) for detailed background information on MK-8591 and DOR as single entities, MK-8591A as an FDC, and MK-1439A.

### 3.2.1 Pharmaceutical and Therapeutic Background

Human immunodeficiency virus type 1 infection, which causes acquired immune deficiency syndrome (AIDS) and for many years was associated with substantial morbidity and mortality, has now become a chronic disease that can be controlled through lifelong combination antiretroviral therapy (ART). Currently, there are more than 30 individual drugs and FDC regimens available for the treatment of HIV-1 infection. These agents belong to 6 distinct mechanistic classes: NRTIs, NNRTIs, protease inhibitors (PIs), fusion inhibitors, co–receptor antagonists, and integrase strand transfer inhibitors (InSTIs). Successful combinations of antiretroviral medications generally utilize 3 agents from at least 2 different mechanistic classes. The goal of ART is to suppress HIV-1 to undetectable levels so that immune function is preserved or restored. Yet, while ART can delay disease progression and death, as well as reduce the risk of HIV-1 transmission, it does not cure the infection. As a result, lifelong treatment must be maintained, which may lead to therapy fatigue and noncompliance, specifically if treatment regimen adherence is difficult (e.g., pill burden, frequency of treatment). Lifelong treatment may also be associated with intolerable adverse effects. These factors can potentially lead to treatment failures with the possible development of drug-resistant virus [AIDS info 2016].

The ART regimen for a treatment-naïve HIV-1-infected patient generally consists of a 3-drug approach containing 2 NRTIs plus a drug from the PI, NNRTI, or InSTI class. As shown in clinical trials and by retrospective evaluation of cohorts of participants in clinical care, this strategy for initial treatment has resulted in HIV-1 RNA suppression and CD4+ T-cell count increases in most participants [Moore, R. D. 2011] [Gill, V. S., et al 2010] [Lee, F. J., et al 2014]. However, significant concerns remain regarding toxicities of some widely used antiretroviral agents, including decline in BMD, hepatic and renal effects, neuropsychiatric toxicities, gastrointestinal toxicities such as diarrhea associated with multiple PIs, and serum lipid abnormalities associated with multiple mechanistic classes. Therefore, new agents that offer high potency, distinct resistance profiles, dosing convenience, and favorable safety and tolerability profiles are needed.

MK-8591 is a specific HIV-1 NRTTI with demonstrated properties of high potency, long half-life, a strong resistance profile, and broad pharmacologic distribution. At the lowest proposed dose to be used in this trial, 0.25 mg, the inhibitory quotient (IQ; lowest concentration reached by a drug before the next dose is administered [$C_{trough}$]/half-maximal inhibitory concentration [$IC_{50}$]) at the projected steady-state peripheral blood mononuclear cell (PBMC) MK-8591-triphosphate (TP) levels are ~70× for wild-type HIV-1 (0.007 pmol/$10^6$ cells), and are ≥14 × the in vitro intracellular $IC_{50}$ for relevant mutant viruses (such as those with RT M184V). These IQs were investigated in P009 in the 0.25 mg panel (daily dosing of MK-8591 for 28 days; see details in Section 3.2.3). On average, the MK-8591-TP IQ for wild-type virus at steady state was 119x and for relevant mutants was 23x. These IQs greatly exceed those achieved by tenofovir alafenamide (TAF) and 3TC, both of which exhibit IQs of ~3 × for wild-type virus at steady state. The high IQ projected

at the lowest proposed dose of MK-8591 for wild-type and NRTI-resistant HIV-1 variants make it a strong candidate to substitute for a more traditional backbone comprised of 2 NRTIs, each with substantially lower IQs. In preclinical studies, MK-8591 exhibited a superior resistance profile compared to lamivudine and azidothymidine (zidovudine), demonstrated no inhibitory activity against human DNA polymerases, and demonstrated an acceptable safety and tolerability profile. It is not expected that MK-8591 will be a victim or perpetrator of drug interactions.

MK-8591 has been evaluated in 3 completed Phase 1 trials (Section 3.2.2) and 2 ongoing Phase 1 trials (Section 3.2.3). MK-8591-001, MK-8591-002, and MK-8591-005 are complete. MK-8591-001 was a double-blind, randomized, placebo-controlled, single-rising dose trial that evaluated the safety and PK of an oral suspension of MK-8591 (doses 5 to 400 mg) in healthy adults. MK-8591-002 was a double-blind, randomized, placebo-controlled trial that evaluated the safety and PK of once weekly, multiple doses of MK-8591 (10 mg, 30 mg, and 100 mg) administered as oral capsules to healthy adults. MK-8591-005 was an open-label, fixed-sequence, 2-period study that assessed the 2-way interaction of MK-8591 and dolutegravir or tenofovir disoproxil fumarate (TDF). On the basis of unblinded data from MK-8591-001, MK-8591-002, and MK-8591-005, MK-8591 is considered generally well tolerated.

While the current paradigm for HIV treatment is a 3-drug regimen, simplified, 2-drug regimens have been sought after for many years, both for therapy initiation as well as part of induction-maintenance strategies. In this study, MK-8591 will be studied initially in a 3-drug regimen in combination with DOR and 3TC (Part 1). Dose ranging of MK-8591 will then continue in the setting of a 2-drug regimen in participants who are virologically suppressed (Part 2). A selected dose of MK-8591 will be chosen for Part 3 following 48 weeks of total treatment (3-drug and 2-drug regimens combined). It is anticipated that administration of MK-8591 in combination with a second ART (2-drug regimen) in HIV-1-infected participants will result in HIV-1 suppression and increases in CD4+ T-cell counts similar to those seen with a traditional 3-drug regimen.

DOR is an NNRTI that, like MK-8591, can be administered once daily (QD), is highly potent, and has a favorable viral resistance profile. In the completed Phase 2b clinical trial of DOR, response rates (defined as the percentage of participants with HIV-1 RNA <40 copies/mL) were numerically higher in the DOR group (71.4%) than the comparator (efavirenz) group (64.3%), and DOR was generally well tolerated in Phase 1 and Phase 2b.

The extensive DDI analysis of DOR to date has demonstrated only the interaction with cytochrome P450 (CYP)3A4 inhibitors and inducers, which was predicted based on the in vitro studies. As MK-8591 in vitro was not observed to inhibit or induce CYP3A4, it is not anticipated to affect the PK of DOR. MK-8591 has not demonstrated significant DDI in the 2 DDI studies to date. An examination of potential DDIs between MK-8591 and dolutegravir or TDF demonstrated no meaningful interaction, and the DDI study between MK-8591 and levonorgestrel/ethinyl estradiol also demonstrated no DDI. The elimination of MK-8591 is anticipated to be balanced between renal filtration and adenosine deaminase-mediated metabolism. Thus, MK-8591 is unlikely to be a victim of drug interactions mediated by CYP or transporter inhibitors. DOR has not been tested as an inhibitor of adenosine deaminase. However, considering the important role of adenosine deaminase in

endogenous nucleotide metabolism and hematopoietic development, the lack of hematologic findings in the chronic toxicity studies and in the Phase 2 and Phase 3 studies to date suggests DOR is not likely to inhibit this enzyme, and thus, the potential for an interaction with MK-8591 through this pathway is low.

In Part 4, MK-8591A, the FDC of MK-8591 (0.75 mg) and DOR (100 mg) will be administered open-label as a single tablet QD. MK-8591 and DOR represent 2 distinct classes of antiretrovirals that inhibit reverse transcription by different mechanisms. Based on the profiles of each of these drugs and data available to-date, the combination MK-8591/DOR is expected to be safe, well-tolerated, and highly efficacious, with a high barrier to resistance. The combination has demonstrated additive antiretroviral activity in vitro and has suppressed emergence of resistance at clinically-relevant concentrations.

The comparator in this trial through Week 144 is MK-1439A, an FDC of DOR 100 mg + 3TC 300 mg + TDF 300 mg. The 300 mg doses of 3TC and TDF, used either as single entities or as part of an FDC, are the standard doses of these 2 commercially-available and commonly-used NRTIs. The 3-drug regimen of MK-1439A is currently approved for the treatment of HIV-1 infection in adults. Refer to Section 5.4.2 and the approved labeling for additional information.

### 3.2.2 Completed Preclinical and Clinical Trials

A 1-month daily oral combination toxicity study in rats was completed to support the clinical co-administration of MK-8591/DOR. In this study, MK-8591 and DOR were evaluated either alone or in combination at clinically relevant dose levels. There were no antemortem, clinical pathology, ophthalmic, or postmortem (gross, organ weight, or histopathology) test article-related findings with either MK-8591 or DOR when evaluated alone or in combination at up to the highest dose levels evaluated. MK-8591 and DOR systemic (AUC) exposures achieved in this study at these no-observed effect levels exceeded those expected clinically at projected therapeutic dose levels (Exposure Multiples [EM] of ~ 15X[a] and ~ 4X[b], respectively). This MK-8591/DOR combination toxicity study in rats together with the nonclinical safety packages for MK-8591 and DOR alone support the continued clinical development of combined dose of MK-8591 and DOR.

Refer to the MK-8591 and DOR IBs for additional information on completed preclinical and clinical trials of MK-8591, DOR, and MK-1439A.

a. EM for MK-8591 was calculated using the estimated steady state human exposure over 24 hours, $AUC_{0\text{-}24\ hr}$ (0.21 μM·hr), at the highest anticipated Phase 2 once-daily dose of 2.25 mg.

b. EM for DOR (MK-1439) was calculated based on a PK/PD analysis from Part 1 of the MK-1439 Phase 2b study (PN007), where the expected therapeutic 100-mg once-daily clinical dose results in an $AUC_{0\text{-}24hr}$ of 37 μM•hr at steady state.

Protocol MK-8591-003 was a trial to evaluate the antiretroviral activity of single-dose MK-8591 in HIV-1-infected participants. MK-8591 was administered to treatment-naïve HIV-1-positive adults at single doses of 0.5 mg, 1 mg, 2 mg, 10 mg, and 30 mg. Viral load reduction data showed a greater than 1.0 log drop in HIV-1 RNA on average at all doses tested. No viral load rebound was observed through 7 to 10 days of follow-up after administration of the single doses of MK-8591. Additionally, 2 Phase 1 trials are complete (MK-8591-009 and MK-8591-010). P009 was a multiple-dose study to assess the safety and

PK of QD MK-8591 administration in healthy adult subjects, and P010 evaluated the potential interaction of MK-8591 with DOR in healthy adult subjects. Results are as follows:

- P009 investigated MK-8591 QD dosing for 28 days at 0.25 mg and 0.75 mg and for 42-days at 5 mg. It was observed that the apparent terminal half-life of MK-8591 in plasma was longer than observed in weekly dosing studies (87–230 hours with QD dosing compared to 50-60 hours with weekly dosing). The longer observed half-life for MK-8591 in plasma is possibly due to the conversion of the active triphosphate (MK-8591-TP) back to MK-8591 (parent) and subsequent diffusion of MK-8591 into plasma. A 42-day post last dose follow-up period was employed for the 5-mg panel in P009 with no notable observations.
- P010 investigated QD MK-8591 dosing for 14 days at 2.25 mg alone and in combination with DOR. No interaction was noted between MK-8591 and DOR. An apparent terminal half-life of 128 hours was noted for MK-8591.

Examination of these data indicates that the half-life of MK-8591 in plasma is expected to be between 87 and 128 hours after cessation of dosing for the dose range to be studied in P011. As such, a safety follow-up period of 42 days will be used and will allow for AE/SAE recording and reporting during this time.

### 3.2.3 Ongoing Clinical Trials

There are 4 planned Phase 3 trials evaluating MK-8591A in participants who are virologically suppressed, heavily treatment experienced, and treatment naïve (MK-8591A-017/-018, MK-8591A-019, and MK-8591A-020, respectively). There are 3 ongoing Phase 3 trials of DOR or MK-1439A: MK-1439-018, MK-1439A-021, and MK-1439A-024. MK-1439-018 is an ongoing Phase 3, multicenter, double-blind, randomized, active comparator-controlled clinical trial in treatment-naïve HIV-1-infected adult participants to evaluate the safety and efficacy of DOR 100 mg QD versus ritonavir-boosted darunavir (DRV + r; DRV 800 mg QD plus ritonavir [r] 100 mg QD), each in combination with 2 NRTIs (emtricitabine [FTC]/TDF or abacavir/3TC). The primary efficacy endpoint (Week 48) of the 96-week base study has been achieved; the 96-week open-label extension is ongoing. A total of 769 participants were randomized and have completed 48 weeks of dosing. The primary analysis at Week 48 demonstrated that DOR was non-inferior to DRV + r at Week 48, the primary time point for analysis, with 83.8% (321/383) and 79.9% (306/383) of participants, respectively, achieving HIV-1 RNA <50 copies/mL (difference 3.9%, 95% confidence interval [CI] -1.6, 9.4). This finding was supported by the Week 96 efficacy results. In the subgroup of participants with baseline HIV-1 RNA >100,000 copies/mL, 81.0% (64/79) of DOR recipients and 76.4% (55/72) of DRV + r recipients achieved HIV-1 RNA <50 copies/mL at Week 48. Only 1 of 383 (<1%) participants in the DOR treatment group developed phenotypic and genotypic resistance to DOR (RT V106I, H221Y, and F227C; >90-fold increased $IC_{50}$) by Week 48. The results of the primary efficacy analysis at Week 48 were supported by the Week 96 results. No participants in the DRV + r group developed genotypic or phenotypic resistance. DOR was generally safe and well tolerated. Refer to the DOR IB for additional information.

MK-1439A-021 is a multicenter, double-blind, randomized, active comparator-controlled clinical trial to evaluate the safety and efficacy of MK-1439A QD versus efavirenz 600 mg/FTC 200 mg/TDF 300 mg (EFV/FTC/TDF) QD in treatment-naïve HIV-1-infected participants. The 96-week base study has completed, and the open-label extension is continuing. The primary analysis at Week 48 demonstrated that MK-1439A was non-inferior to EFV/FTC/TDF with 84.3% (307/364) and 80.8% (294/364), respectively, achieving HIV-1 RNA <50 copies/mL (difference 3.5%, 95 CI -2.0, 9.0). In the subgroup of participants with baseline HIV-1 RNA >100,000 copies/mL, 81.2% (56/69) of MK-1439A and 80.8% (59/73) of EFV/FTC/TDF recipients achieved HIV-1 RNA <50 copies/mL at Week 48. The results of the primary efficacy analysis at Week 48 were supported by the Week 96 results. A primary safety endpoint was the proportion of subjects with neuropsychiatric adverse events (AEs) through Week 48 in the pre-specified categories of 1) dizziness, 2) sleep disorders/disturbances, and 3) altered sensorium. MK-1439A was superior to EFV/FTC/TDF with having a significantly lower proportion of subjects with neuropsychiatric events in the 3 pre-specified categories by Week 48. In addition, it was demonstrated that MK-1439A had a statistically significant lower increase from baseline than EFV/FTC/TDF on fasting LDL-C cholesterol (mg/dL) and fasting non-HDL-C cholesterol (mg/dL).

MK-1439A-024 is an on-going open-label trial of MK-1439A in participants who are virologically suppressed on a PI-, NNRTI-, or elvitegravir-based regimen and are switched to MK-1439A. The 48-week base study has completed, and the open-label extension is ongoing. Results showed that an immediate switch to MK-1439A on Study Day 1 was noninferior to continuation of a ritonavir- or cobicistat-boosted PI-based or cobicistat-boosted EVG-based or NNRTI-based regimen for 24 weeks. As part of the study, the effect of an immediate switch to MK-1439A on Study Day 1 on fasting LDL-C and fasting HDL-C compared with the effect noted on these lipids among participants who continued on a ritonavir-boosted, PI-based regimen for 24 weeks was evaluated. Results showed that an immediate switch to MK-1439A on Study Day 1 demonstrated superior fasting LDL-C and fasting non-HDL-C profiles relative to the profiles observed among participants in the DSG; for both serum lipid parameters, the effect was statistically significant ($p < 0.0001$).

### 3.2.4 Information on Other Trial-Related Therapy

The standard marketed QD dose of 3TC was selected for inclusion in this study as the second NRTI in the MK-8591 treatment groups in Part 1 because of its demonstrated efficacy and safety in numerous treatment-naïve and treatment-experienced HIV-1 trials conducted over many years, and because of its extensive real world use. Preclinical data with MK-8591 also demonstrated that MK-8591 had additive antiviral activity with 3TC in vitro with no evidence of antagonism (refer to the MK-8591 IB).

## 3.3 Benefit/Risk Assessment

It cannot be guaranteed that participants in clinical trials will directly benefit from treatment during participation as clinical trials are designed to provide information about the safety and effectiveness of an investigational medicine. Participants in this study will be closely monitored for viremia (Section 5.4.1.1.2). In the event a participant fails, he/she will continue to have multiple alternative treatment options.

MK-8591 is a promising new NRTTI for the treatment of HIV-1 infection. It is a potent inhibitor of HIV-1 replication in vitro and is active against both wild-type virus and most common NRTI-resistant variants at concentrations achieved with QD dosing. MK-8591 is not expected to have many of the safety concerns associated with other NRTIs. In addition, MK-8591 is not expected to have major DDIs that would limit its utility in clinical practice. Therefore, MK-8591 could represent a valuable addition to the HIV-1 treatment paradigm for treatment-naïve patients in both 3-drug and 2-drug treatment regimens. Additional details regarding specific benefits and risks for participants in this clinical trial may be found in the accompanying MK-8591 IB and informed consent documents.

DOR is a potent NNRTI for treatment of HIV-1 infection. It is a potent inhibitor of HIV-1 replication in vitro and is active against both wild-type virus and most common NNRTI-resistant variants at concentrations achieved with QD dosing. DOR displays excellent potency against wild-type virus with an $IC_{50}$ of 12 nM in the presence of 100% normal human serum. Preclinical studies also indicate a favorable in vitro resistance profile that is distinct from other NNRTIs, with an $IC_{50}$ of 21 nM, 31 nM, and 55 nM against mutants containing the most frequently transmitted NNRTI-resistant mutations in RT, K103N, Y181C and G190A, respectively, under the same conditions. The preclinical toxicity profile of DOR is also favorable. Clinical pharmacology studies indicate that DOR can be dosed QD, without regard to food, and DOR is not a metabolic inducer or inhibitor, reducing the likelihood of significant DDI. Additional details regarding specific benefits and risks for participants participating in this clinical trial may be found in the accompanying DOR IB and informed consent documents.

## 4. Objectives/Hypotheses and Endpoints

There are no hypotheses to be tested in this trial. Objectives refer to the original regimen to which participants were randomized (Groups 1 to 3: 1 of 3 different doses of MK-8591 administered with DOR + 3TC, or Group 4: MK-1439A), but participants in the MK-8591 treatment groups will be switched in Part 2 to a 2-drug regimen with MK-8591 + DOR after at least 24 weeks on the 3-drug regimen if their HIV-1 RNA is <50 copies/mL. In Part 3, participants in the MK-8591 treatment groups will receive the selected dose of MK-8591 + DOR, and Group 4 will continue to receive MK-1439A. In Part 4, all participants in each group will receive MK-8591A (FDC of MK-8591/DOR).

In HIV-1-infected antiretroviral treatment-naïve adults:

| Objective | Endpoint |
|---|---|
| **Primary** | |
| • Objective: To evaluate the antiretroviral activity of different doses of MK-8591 administered with DOR + 3TC compared to MK-1439A, as assessed by the proportion of participants with HIV-1 RNA <50 copies/mL at Week 24 and at Week 48 | • Proportion of participants with HIV-1 RNA <50 copies/mL at Week 24 and Week 48 |

| Objective | Endpoint |
|---|---|
| • Objective: To evaluate the safety and tolerability of different doses of MK-8591 administered with DOR + 3TC compared to MK-1439A | • Number of participants experiencing AEs<br>• Number of participants discontinuing study drug due to AEs |
| **Secondary** | |
| • Objective: To evaluate the sustained antiretroviral suppression in participants on the selected dose of MK-8591 + DOR compared to MK-1439A as assessed by the proportion of participants with HIV-1 RNA <50 copies/mL 24 and 48 weeks after switching to Part 2 | • Proportion of participants with HIV-1 RNA <50 copies/mL 24 and 48 weeks after entering Part 2 |
| • Objective: To evaluate the immunologic effect of different doses of MK-8591 administered with DOR + 3TC compared to MK-1439A at Week 24, Week 48, Week 96, and Week 144 | • Change from baseline in CD4+ T-cell count at Week 24, Week 48, Week 96, and Week 144 |
| • Objective: To evaluate the antiretroviral suppression and immunologic effect of MK-8591A administered during open-label dosing in Part 4 of the trial | • Proportion of participants with HIV-1 RNA <50 copies/mL at Week 192 (48 weeks after entering Part 4)<br>• Change from baseline in CD4+ T-cell count at Week 192 |
| • Objective: To evaluate the safety and tolerability of different doses of MK-8591 administered with DOR compared to MK-1439A 24 weeks after switching to Part 2 | • Number of participants experiencing AEs<br>• Number of participants discontinuing study drug due to AEs |
| • Objective: To evaluate the safety and tolerability of the selected dose of MK-8591 administered with DOR compared to MK-1439A at Week 96 and through study duration. | • Number of participants experiencing AEs<br>• Number of participants discontinuing study drug due to AEs |
| • Objective: To evaluate the safety and tolerability of MK-8591A during open-label dosing in Part 4 of the trial. | • Number of participants experiencing AEs<br>• Number of participants discontinuing study drug due to AEs |

| Objective | Endpoint |
|---|---|
| **Tertiary/Exploratory** | |
| • Objective: To evaluate the antiretroviral activity of different doses of MK-8591 administered with DOR + 3TC compared to MK-1439A as assessed by different HIV-1 RNA thresholds and different time points | • Proportion of participants with HIV-1 RNA <50 copies/mL at Week 96 and Week 144 and <40 copies/mL at Week 24, Week 48, Week 96, and Week 144 |
| • Objective: To explore the antiretroviral activity of different doses of MK-8591 administered with DOR + 3TC compared to MK-1439A | • Time to Loss of Virologic Response<br>• Proportion of participants achieving an HIV-1 RNA level below the limit of detection of a single-copy assay at Week 24, Week 48, Week 96, and Week 144 |
| • Objective: To assess the development of HIV-1 drug resistance to MK-8591 administered with DOR + 3TC in participants who have protocol-defined virologic failure (prior to Amendment 03) or clinically significant confirmed viremia (as of Amendment 03) | • Frequency and type of viral genotypic and phenotypic resistance to study treatment |
| • Objective: To evaluate the effects of MK-8591 administered with DOR + 3TC on body fat distribution and bone loss | • Percentage and absolute change from baseline in peripheral fat and trunk fat at Week 48, Week 96, Week 144, and Week 192<br>• Change from baseline in body mass index at Week 48, Week 96, Week 144, and Week 192<br>• Percentage change from baseline in spine BMD and hip BMD at Week 48, Week 96, Week 144, and Week 192 |
| • Objective: To evaluate the PK of MK-8591 | • PK values such as AUC, $C_{max}$ and $C_{24}$ |
| • Objective: To explore the impact of MK-8591 administered with DOR + 3TC on laboratory markers | • Blood levels of IL-6, sCD163, d-dimer, and urine levels of albumin, protein, beta-2microglobulin/creatinine ratio and retinol binding protein/creatinine ratio |

| Objective | Endpoint |
|---|---|
| • Objective: To explore the relationship between genetic variation and response to the treatment(s) administered, and mechanisms of disease. Variation across the human genome may be analyzed for association with clinical data collected in this study. | • Germline genetic variation |

3TC=lamivudine; AE=adverse event; AUC=area under the curve; BMD=bone mass density; $C_{24}$=concentration at 24 hours; $C_{max}$=maximum serum concentration; DOR=doravirine; HIV-1=human immunodeficiency virus type 1; IL-6=interleukin-6; PK=pharmacokinetics; RNA=ribonucleic acid

## 5. Study Design

### 5.1 Overall Design

This randomized, active-controlled, multicenter, blinded trial will evaluate the safety, tolerability, antiretroviral activity, and PK of 3 doses of MK-8591 (also referred to as islatravir) QD given in combination with DOR QD and 3TC QD (Part 1 only) to antiretroviral treatment-naïve adult participants with HIV-1 infection. This is a 4-part trial: 1) dose ranging as part of a 3-drug regimen in Part 1 (double-blind with in-house blinding), 2) 2-drug dose ranging maintenance in Part 2 (site blinded to dose of MK-8591), 3) maintenance with the selected dose of MK-8591 or MK-1439A in Part 3 (open-label), and 4) dosing with MK-8591A in Part 4 (open-label).

In Part 1, participants will be randomized in a 1:1:1:1 ratio to receive one of 4 study treatments QD, as follows:

- Group 1: MK-8591 0.25 mg + DOR 100 mg + 3TC 300 mg + placebo for MK-1439A (n=30)
- Group 2: MK-8591 0.75 mg + DOR 100 mg + 3TC 300 mg + placebo for MK-1439A (n=30)
- Group 3: MK-8591 2.25 mg + DOR 100 mg + 3TC 300 mg + placebo for MK-1439A (n=30)
- Group 4: MK-1439A + placebo for DOR + placebo for 3TC + placebo for MK-8591 (n=30)

Randomization will be stratified by screening HIV-1 RNA level (≤100,000 copies/mL or >100,000 copies/mL). Participants will receive at least 24 weeks of treatment in Part 1. An interim analysis will be performed by the Sponsor on the accrued data through Week 24 to assess the safety and efficacy objectives for the 3-drug regimen. Sponsor personnel will be unblinded to treatment group assignments. The results of this analysis will be shared with an external Data Monitoring Committee (eDMC); however, they will not be shared with the investigators. Participants may be switched to Part 2 starting at Week 24 depending on the HIV-1 RNA results from the previous visit. Participants in Part 1 must be virologically

suppressed (i.e., have not met viral failure criteria [Section 5.4.1.1.1] and have HIV RNA <50 copies/mL), to move to Part 2 (Section 9.10). Participants who have not achieved HIV-1 RNA <50 copies/mL by Week 20 and have not met viral failure criteria (Section 5.4.1.1.1) will continue to receive study medication in Part 1 (3-drug double blind) until their HIV-1 RNA is <50 copies/mL. Prior to Amendment 03, participants who met viral failure criteria (Section 5.4.1.1.1) or who were not virologically suppressed following the Week 48 assessments were to be discontinued from treatment and complete the early discontinuation and end of trial follow-up visits (Section 9.10 and Section 8.1). As of Amendment 03, if a participant has a viral load of ≥50 copies/mL at any time during the study, a Viremia Confirmation visit must be conducted within 2 to 4 weeks of the initial HIV-1 viremia (Section 2.3 and Section 5.4.1.1.2); a participant with confirmed HIV-1 virologic rebound will be discontinued from treatment (Section 5.4.1.1.2 and Section 8.1). Participants who met the protocol-defined virologic failure criteria in Part 1 were communicated to the unblinded statistician. If 3 or more participants (10% or more out of 30 expected participants) in any treatment group are observed to have virologic failure by the unblinded statistician, this will be reported to the eDMC. The eDMC may recommend dropping a treatment group on the basis of this criterion.

In Part 2, participants in Groups 1 to 3 will receive the 2-drug regimen of MK-8591 QD given in combination with open-label DOR QD. Participants will continue to receive the dose of MK-8591 to which they were randomized, and 3TC will be dropped from the regimen. The dose of MK-8591 will remain blinded. Participants in Group 4 will continue to receive MK-1439A QD. DOR (Groups 1 to 3) and MK-1439A (control group) will be provided as open-label supply and matching placebos will no longer be administered. The total duration of treatment for individual participants in Part 2 will be dependent upon the time point at which the participant is switched to Part 2 and is anticipated to be ~20 to 48 weeks. A second interim analysis will be conducted when all participants have reached Week 48. This analysis will include participants who have completed at least 24 weeks in Part 1 (3-drug regimen) and participants who have been in Part 2 for various durations of time (0–24 weeks). Dose selection of MK-8591 will occur following the second interim analysis. The primary efficacy endpoint is the proportion of participants achieving HIV-1 RNA <50 copies/mL. The primary safety endpoint is the proportion of participants with certain clinical and laboratory AEs. The detailed results of the Week 48 interim analysis will be shared with an eDMC. The selected MK-8591 dose will be communicated to both the eDMC and the investigators. It is expected that dose selection will be communicated at Week 60 or beyond.

Once the dose of MK-8591 has been selected and communicated to the sites, participants receiving MK-8591 will be switched to the selected dose given in combination with DOR QD (Part 3). Both MK-8591 and DOR will be provided in an open-label fashion. Participants in the control group will continue to receive open-label MK-1439A. An interim analysis will be conducted when all participants have reached Week 96; detailed results of the Week 96 interim analysis will be shared with the eDMC.

Participants in Part 3 receiving the selected dose of MK-8591 in combination with DOR QD or MK-1439A in the control group will all be switched to the 2-drug FDC tablet of MK-8591A QD in Part 4. MK-8591A will be provided as open-label supplies.

Blood samples will be collected to assess antiretroviral, safety, and immunologic endpoints. Additional blood samples will be collected from all participants to support the evaluation of MK-8591 population PK as described in Section 9.6. Participants will have dual-energy x-ray absorptiometry (DEXA) scans to evaluate body fat distribution and BMD as described in Section 9.5.5.

As of Amendment 03, participants with clinically significant confirmed viremia (as described in Section 5.4.1.1.2) during the trial will return to the site for repeat HIV-1 RNA testing within 2 to 4 weeks of HIV-1 viremia (≥50 copies/mL) at a viremia confirmation visit. If viremia is confirmed and the HIV-1 RNA results meet the criteria for testing specified in Section 10.4.1, a plasma sample will be sent to the central laboratory for resistance testing (Section 9.2.4). Participants with confirmed HIV-1 virologic rebound (Section 5.4.1.1.2) will be discontinued from treatment and will complete the early discontinuation and end of trial follow-up visits (Section 8.1).

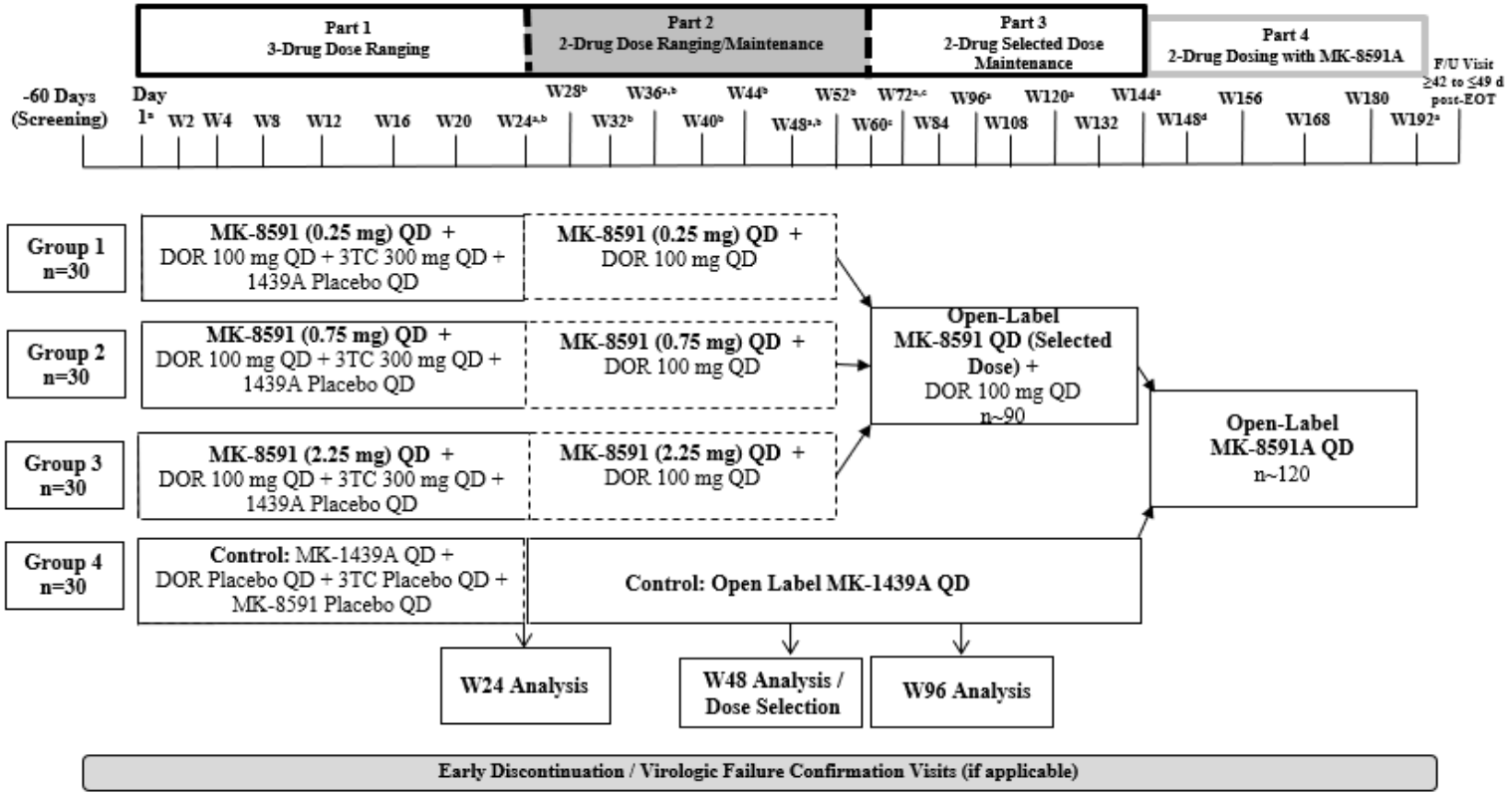
The safety of the participants in this trial will also be monitored during the trial by an eDMC that will provide an ongoing review of the efficacy and safety data with periodic reviews to occur approximately every 4 to 6 months, on an ad hoc basis as needed, or as specified in the DMC charter. The eDMC will recommend steps to ensure the safety of study participants and the integrity of the trial. To guarantee the unrestricted performance of its task, the eDMC will receive study data from an external independent statistician for the ongoing periodic reviews. Details regarding the ongoing periodic reviews by the eDMC will be described in a charter document. Following eDMC review of the Week 96 interim analysis, no additional eDMC reviews will occur.

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial SoA - Section 2. Details of each procedure are provided in Section 9 – Study Assessments and Procedures.

### 5.1.1 Study Diagram

The trial design is depicted in Figure 1.

Figure 1 Study Diagram




DOR=doravirine; 3TC=lamivudine; MK-1439A=DOR 100 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg; MK-8591A=MK-8591 0.75 mg/ DOR 100 mg; F/U=follow-up; QD=once daily; W=week.

a. Fasting for at least 8 hours.
b. After a minimum of 24 weeks of dosing in Part 1, participants who are virologically suppressed at the previous visit (HIV-1 RNA <50 copies/ml) and have not met any viral failure criteria (Section 5.4.1.1.1) will switch to Part 2 (Section 9.11.1). Participants who have not met viral failure criteria, but whose HIV-1 RNA levels are ≥50 copies/ml will continue to receive the 3-drug regimen (Part 1) until the HIV-1 RNA is <50 copies/mL. Participants who have met viral failure criteria or participants who do not achieve HIV RNA <50 copies/mL following the Week 48 assessments will be discontinued from treatment (Section 5.4.1.1.1, Section 8.1 and Section 9.11.1) and complete the early discontinuation and end of trial follow-up visits.
c. The transition from Part 2 to Part 3 will most likely occur at Week 60 or beyond. Participants in treatment Groups 1 to 3 will continue on the blinded dose of MK-8591 until dose selection is announced.
d. W148 is only applicable to participants in Group 4 who agree to switch from open-label MK-1439A to MK-8591A in Part 4 of the study.

## 5.2 Number of Participants

Approximately 120 participants will be randomized, as described in Section 10.6.

## 5.3 Beginning and End of Study Definition

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

### 5.3.1 Clinical Criteria for Early Trial Termination

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

1. The eDMC recommends termination of the trial and the Executive Oversight Committee (EOC) agrees per Appendix 3, or as stated in the DMC charter
2. Incidence or severity of adverse drug reactions in this or other trials suggest a potential health hazard to participants
3. Plans to modify or discontinue the development of the trial drugs

### 5.3.2 Clinical Criteria for Termination of a Treatment Group(s)

Participants who meet the protocol-defined virologic failure criteria (Section 5.4.1.1.1) in Part 1 will be communicated to the unblinded statistician. If 3 or more participants (10% or more out of 30 expected participants) in any treatment group are observed to have virologic failure by the unblinded statistician, this will be reported to the eDMC. The eDMC may recommend dropping a treatment group on the basis of this criterion. In the event a decision is made to terminate a treatment group, the disposition of the participants in that arm will be determined after consultation with the eDMC.

A treatment group may also be discontinued at the request of a regulatory agency.

## 5.4 Scientific Rationale for Study Design

This trial will be conducted in HIV-1–infected treatment-naïve participants and different doses of a new NRTTI, MK-8591, and a new NNRTI, DOR will be evaluated. Only participants with no evidence of baseline HIV resistance mutations to any approved HIV-1 RT inhibitor, protease inhibitor, or integrase inhibitor will be allowed to enroll. This is to ensure that an effective antiviral regimen can be constructed for a participant who may experience virologic failure and resistance to both classes of NRTIs and NNRTIs.

A 3-drug combination, in which the ART regimen generally consists of 2 NRTIs plus 1 drug from the NNRTI, protease inhibitor, or integrase inhibitor class, is the current standard of care for HIV-1–infected treatment-naïve adults. In Part 1 of this trial, the 3 different dose levels of the NRTTI, MK-8591, will be given in combination with 2 other HIV-1 ART: DOR (an NNRTI) and lamivudine (an NRTI). Thus, Part 1 of this trial is designed to assess MK-8591 in the setting of a standard 3-drug regimen.

Part 2 and Part 3 of this trial is designed to assess the ability of the different doses of MK-8591 and the selected dose of MK-8591, respectively, given in combination with DOR to maintain HIV-1 RNA suppression following at least 24 weeks of treatment with the 3-drug regimen. Similar clinical trials have assessed the utility of a 2-drug maintenance regimen after an initial 3-drug treatment regimen.

Part 4 of this trial is designed to assess the ability of the selected dose of MK-8591 in combination with DOR in the FDC of MK-8591A to maintain HIV-1 RNA suppression. Participants who received MK-1439A (Group 4) and consent to continue in Part 4 will be switched to MK-8591A in order to: (1) generate safety and efficacy data in virologically-suppressed participants who switch to MK-8591A, and (2) provide access to treatment with investigational MK-8591A through study duration and after completing the study, until MK-8591A becomes commercially available (Section 7.8).

Follow-up through 1-year of age for infants born to participants who become pregnant while receiving study intervention provides the ability to monitor growth and development as well as potential adverse effects that may be associated with prenatal drug exposure. Growth parameters (ie, length, weight, and head circumference) within normal range at approximately 1-year of age are key noninvasive indicators that a serious congenital malformation caused by in utero drug exposure is unlikely.

### 5.4.1 Rationale for Endpoints

#### 5.4.1.1 Efficacy Endpoints

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

At the Week 48 time point, it is expected that the majority of participants will have had 24 weeks of treatment on the 3-drug regimen and 24 weeks of treatment on the 2-drug regimen. However, it is possible that some participants may take longer to meet the criterion to switch to the 2-drug regimen and may have received treatment for more than 24 weeks on the 3-drug regimen and less than 24 weeks on the 2-drug regimen at Week 48. It is also possible that some participants may have received treatment on the 3-drug regimen for all 48 weeks.

Secondary measurements for efficacy include HIV-1 RNA <50 copies/mL and change from baseline in CD4+ T-cell counts. Exploratory efficacy measurements include HIV-1 RNA <40 copies/mL at different time points, time to loss of virologic response (TLOVR), HIV-1 RNA level below the limit of detection of a single-copy assay, and HIV-1 drug resistance for participants who meet protocol-defined virologic failure criteria (prior to Amendment 03, Section 5.4.1.1.1) or clinically significant confirmed viremia (as of Amendment 03, Section 5.4.1.1.2) and whose virus can be amplified.

#### 5.4.1.1.1 Virologic Failure Criteria

Prior to Amendment 03, protocol-defined virologic failure for this study was defined as 1 of the following:

1. Confirmed (i.e., 2 consecutive measurements at least 1 week apart) HIV-1 RNA ≥50 copies/mL after initial response of HIV-1 RNA <50 copies/mL **at any time during the study**; OR
2. Confirmed (i.e., 2 consecutive measurements at least 1 week apart) HIV-1 RNA >1 log increase from the HIV-1 RNA nadir after a >1 log decrease in HIV-1 RNA from baseline at any time during the study; OR
3. Confirmed (i.e., 2 consecutive measurements at least 1 week apart) HIV-1 RNA ≥200 copies/mL at any time from Week 24 through Week 48; OR
4. Confirmed (i.e., 2 consecutive measurements at least 1 week apart) HIV-1 RNA ≥50 copies/mL at Week 48

Prior to Amendment 03, participants were to be discontinued from treatment and complete the early discontinuation and end of trial phone and site follow-up visits, regardless of compliance to study therapy if they met the protocol-defined virologic failure criteria (See Section 8.1).

In addition to the 4- to 6-month review of safety and efficacy data, participants who met the protocol-defined virologic failure criteria in Part 1 were communicated to the unblinded statistician. If 3 or more participants in any treatment group were observed by the unblinded statistician to have virologic failure, this was to be reported to the eDMC. The eDMC was to convene to review unblinded data and could recommend dropping a treatment group on the basis of this criterion.

#### 5.4.1.1.2 Definition of Clinically Significant Confirmed Viremia

Beginning with Amendment 03, for the purpose of managing participants in this study, clinically significant confirmed viremia is defined as:

- **Virologic Rebound**: Two consecutive (2 to 4 weeks apart) occurrences of HIV-1 RNA ≥200 copies/mL after achieving HIV-1 RNA <50 copies/mL at any time during the study.

There is currently no global standard for definition of patients with low-level viremia (viral load ≥50 and <200 copies/mL), and the predictive implication of such low-level viremia is uncertain [Vandenhende, M. A., et al 2015] [Charpentier, C., et al 2014]. The US DHHS guidelines currently define virologic failure as confirmed HIV RNA ≥200 copies/mL and do not recommend that low-level viremia (detectable HIV RNA <200 copies/mL) automatically result in treatment modification or more frequent virologic monitoring [Panel on Antiretroviral Guidelines for Adults and Adolescents 2018]. Participants with HIV-1 RNA between 50 and 200 copies/mL have a lower risk of developing resistance compared to those with HIV-1 RNA >200 copies/mL and should continue on their current regimen, with HIV-1 RNA levels monitored as outlined in Section 9.2.2.

An HIV-1 RNA level of ≥50 copies/mL must be confirmed and requires further management as described in Section 9.2.2.

#### 5.4.1.2 Safety Endpoints

The primary safety endpoints are the number of participants experiencing AEs and the number of participants discontinuing study drug due to AEs. Safety evaluations will include physical examinations (including vital signs) and laboratory tests (hematology, chemistry and urinalysis) performed per the Schedule of Activities (SoA) in Section 2. Adverse events will be evaluated at each visit and assessed according to the guidelines in Section 9.3 and Appendix 2A. Participants may be asked to return for unscheduled visits in order to perform additional safety monitoring.

This trial will also explore the impact of MK-8591 + DOR + 3TC in Part 1, MK-8591 + DOR in Part 2 and Part 3, and MK-8591A in Part 4 on fat distribution and BMD (i.e., DEXA), inflammatory and urinary markers, including blood levels of the pro-inflammatory cytokine interleukin-6 (IL-6), D-dimer, soluble CD163, and urine levels of the analytes urine albumin, urine protein, retinol binding protein/creatinine ratio, and beta-2-microglobulin/creatinine ratio (Section 9.5.5, Section 9.9.1). DEXA scans will be performed and blood/urine samples will be collected from all participants as indicated in the SoA (Section 2).

#### 5.4.1.3 Pharmacokinetic Endpoints

The sparse PK data will be used for a population PK model. Plasma samples will be collected as indicated in the SoA (Section 2) and Section 9.6.

#### 5.4.1.4 Pharmacodynamic Endpoints

There are no pharmacodynamics endpoints in this trial.

#### 5.4.1.5 Planned Exploratory Biomarker Research

##### 5.4.1.5.1 Planned Genetic Analysis

Genetic variation may impact a participant's response to therapy, susceptibility to, and severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a sample will be collected for DNA analysis from consenting participants.

DNA samples will be used for research related to the study treatment(s), the disease under study and related diseases. They may also be used to develop tests/assays including diagnostic tests related to the disease under study, related diseases and study drug(s). Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome [or analysis of the entire genome] (as appropriate).

DNA samples will be analyzed for variation across the entire genome. Analyses may be conducted if it is hypothesized that this may help further understand the clinical data.

The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to understand study disease or related conditions.

#### 5.4.1.6 Future Biomedical Research

The Sponsor will conduct Future Biomedical Research on DNA specimens consented for future biomedical research during this clinical trial.

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 participants. The objective of collecting/retaining specimens for Future Biomedical Research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that participants receive the correct dose of the correct drug/vaccine at the correct time. The details of Future Biomedical Research are presented in Appendix 6 – Collection and Management of Specimens for Future Biomedical Research.

### 5.4.2 Rationale for The Use of Comparator/Placebo

The comparator for this trial is MK-1439A, the FDC of DOR 100 mg/3TC 300 mg/TDF 300 mg. DOR is a novel NNRTI being studied for the treatment of HIV-1 infection. It is a potent inhibitor of HIV-1 replication in vitro and is active against both wild-type virus and the most common NNRTI-resistant variants at concentrations achieved with QD dosing. The available long-term (beyond Week 48) data from a Phase 2 trial (MK-1439A-007) in treatment-naïve HIV-infected participants and Week 48 Phase 3 data from MK-1439 PN018 and MK-1439A PN021 trials demonstrate that DOR in combination with FTC/TDF and 3TC/TDF has a favorable safety and tolerability profile and potent efficacy. The use of MK-1439A will allow direct comparison of MK-8591 to 3TC/TDF in the 2 drug maintenance parts of the study. Refer to the DOR IB for additional information.

## 5.5 Justification for Dose

Three doses of MK-8591 will be evaluated in this trial: 0.25 mg, 0.75 mg, and 2.25 mg. A dose of MK-8591 will be selected after analysis of 48 weeks of dosing in Parts 1 and 2. Participants will be switched to the selected dose in Part 3 (administered with DOR as single entities) and Part 4 (administered with DOR as an FDC) and will complete the remaining treatment duration with that dose (Section 5.1).

The 0.25 mg dose is expected, based on population PK modeling, to achieve target PK values, specifically concentration after 24 hours ($C_{24}$) of 0.05 pmol/$10^6$ cells of the active MK-8591-TP in peripheral blood mononuclear cells (PBMCs) after 1 dose. A $C_{24}$ of 0.05 pmol/$10^6$ cells is 5-fold over the in vitro intracellular $IC_{50}$, providing an ample margin over wild-type virus. The $C_{24}$ of MK-8591-TP was investigated in P009 (daily dosing of 0.25 mg MK-8591 for 28 days) and found, on average, to be 0.115 pmol/$10^6$ cells (16-fold over the in vitro intracellular $IC_{50}$). While the HIV-1 RT M184V resistance substitution can decrease MK-8591 susceptibility up to 5-fold in cell culture, at a 0.25 mg QD dose of MK-8591, this substitution will be covered after 1 dose. Other substitutions with higher fold shifts will be covered within three 0.25 mg doses (72 hours) of MK-8591. In comparison, TAF, TDF, and 3TC at steady state (240 hours) achieve intracellular tenofovir diphosphate or 3TC-TP

concentrations that are only ~4-fold, ~3-fold, and less than 1-fold, respectively, over the in vitro wild-type $IC_{50}$. The additional MK-8591 doses of 0.75 mg and 2.25 mg will permit exploration of the safety and efficacy of MK 8591 with increased exposure and have been chosen to minimize overlap of the exposures between doses. Based on Phase 1 safety, PK, Phase 1b efficacy, and viral dynamic simulations, all doses selected for this trial should be well tolerated, safe, and confer adequate antiviral effect.

The maximum MK-8591 daily dose studied in this trial is 2.25 mg.

## 6. Study Population

Male and female participants with HIV-1 infection who are naïve to antiretroviral therapy and 18 years of age or older will be enrolled in this trial.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

### 6.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

**Type of Participant and Disease Characteristics**

1. Has HIV-1 infection as determined by a positive enzyme-linked immunosorbent assay and a screening plasma HIV-1 RNA (completed by the central laboratory) ≥1000 copies/mL within 60 days of the treatment phase of the study.
2. Has a screening CD4+ T-cell count ≥200 cells/$mm^3$ (completed by the central laboratory) within 60 days prior to the treatment phase of this study.
3. Is naïve to ART.

   Note: Naïve is defined as having received no (0 days) ART therapy for the treatment of active HIV-1 infection including prevention of mother-to-child transmission.
4. Has the following laboratory values (completed by the central laboratory) within 60 days prior to the treatment phase of this study:
   a) International normalized ratio ≤1.2
   b) Urine protein is within normal limits (no more than trace protein by urine dipstick)
   c) Hemoglobin ≥9.0 g/dL if female or ≥10.0 g/dL if male
   d) Absolute neutrophil count ≥1000/$mm^3$
   e) Platelet count ≥100,000/$mm^3$
   f) Total serum bilirubin ≤the upper limit of normal (ULN)
   g) Alkaline phosphatase <1.5 × ULN
   h) Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) <1.5 × ULN

Note: A single repeat of a laboratory screening test will be allowed for test results that are unexpected based on documented prior laboratory results, but the repeat test results must be available within the 60-day screening window.

5. Has a calculated creatinine clearance ($Cl_{cr}$) ≥50 mL/min within 60 days prior to the treatment phase of this study , based on the following Cockcroft-Gault equations:

   - If male

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

   - If female

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

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

**Demographics**

7. Is a male or female at least 18 years of age on the day informed consent is signed.
8. A female participant is eligible to participate if she is not pregnant (see Appendix 5), not breastfeeding, and at least one of the following conditions applies:
   a.) Not a woman of childbearing potential (WOCBP) as defined in Appendix 5
   OR
   b.) A WOCBP who agrees to follow the contraceptive guidance in Appendix 5 during the treatment period and for at least 6 weeks (corresponding to time needed to eliminate any study treatments (MK-8591, DOR, or 3TC) or MK-1439A after the last dose of study treatment.
9. All participants, male and female, agree to use barrier methods of contraception when engaged in any sexual activity during treatment and for 6 weeks following treatment.

**Informed Consent**

10. The participant (or legally acceptable representative, if applicable) provides written informed consent for the trial. The participant (or legally acceptable representative, if applicable) may also provide consent for Future Biomedical Research. However, the participant may enroll in the main trial without consenting to Future Biomedical Research.

## 6.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

**Medical Conditions**

1. Has a history or current evidence of any condition, therapy, laboratory abnormality or other circumstance that might, in the opinion of the investigator, confound the results of the study or interfere with the participant's participation for the full duration of the study, such that it is not in the best interest of the participant to participate.
2. Is, at the time of signing informed consent, a user of recreational or illicit drugs or has had a history of drug or alcohol abuse or dependence that may interfere with trial participation. The nature and potential clinical context of the participant's illicit drug use, in relation to their exclusion from this trial, will be at the discretion of the investigator.
3. Has significant hypersensitivity or other contraindication to any of the components of the study drugs as determined by the investigator.
4. Has a history of malignancy ≤5 years prior to signing informed consent except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer.
5. Is female and is expecting to donate eggs at any time during the study (donation of sperm should follow local guidelines for HIV-positive individuals).

   **Note**: Investigators should provide appropriate guidance to female participants regarding egg donation after completion of the study treatment. Consistent with the recommendations for contraceptive use, it is recommended that all female participants refrain from egg donation for 6 weeks following their last dose of study treatment.
6. Is breastfeeding or expecting to conceive.
7. A WOCBP who has a positive urine pregnancy test on Day 1 before the first dose of study treatment. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

**Prior/Concomitant Therapy**

8. Has been treated for a viral infection other than HIV-1, such as hepatitis B, with an agent that is active against HIV-1, including, but not limited to, the following: adefovir, TDF, TAF, entecavir, FTC, or 3TC.
9. Has used systemic immunosuppressive therapy or immune modulators within 30 days prior to treatment in this study or is anticipated to need them during the course of the study.

   **Note:** Time limited courses of corticosteroids (e.g., for asthma exacerbation) will be allowed.

10. Requires or is anticipated to require any of the following prohibited medications:
    - Carbamazepine
    - Phenobarbital
    - Phenytoin
    - Rifabutin
    - Rifampin
    - Herbal remedies
    - St. John's Wort
    - Modafinil
    - Bosentan
    - Nafcillin
    - Pentostatin

**Prior/Concurrent Clinical Study Experience**

11. Is currently participating in or has participated in an interventional clinical trial with an investigational compound or device within 30 days of signing informed consent to participate in this current trial.

**Diagnostic assessments**

12. Has a documented or known virologic resistance to any approved HIV-1 reverse transcriptase inhibitor, protease inhibitor, integrase inhibitor, or any study drug, as demonstrated by any the following resistance substitutions (according to the 2017 IAS-USA drug resistance mutations list [Wensing, A. M., et al 2017]):
    a. NRTI resistance substitutions: RT M41L, K65E/N/R, D67N, T69Insert, K70E/R, L74V, V75I, F77L, Y115F, F116Y, Q151M, M184I/V, L210W, T215F/Y, K219E/Q. This list includes all resistance substitutions that may also impact study drugs MK-8591, 3TC, or TDF.
    b. NNRTI resistance substitutions: RT L100I, K101E/P, K103N/S, V106A/I/M, V108I, E138A/G/K/Q/R, V179L, Y181C/I/V, Y188C/H/L, G190A/S, H221Y, P225H, F227C/L/V, M230I/L, L234I, P236L, or Y318F. This list includes all resistance substitutions that may also impact study drug DOR.
    c. Protease inhibitor resistance substitutions: Protease D30N, V32I, M46I/L, I47A/V, G48V, I50L/V, I54L/M, Q58E, T74P, L76V, V82A/F/L/S/T, N83D, I84V, N88S, orL90M
    d. Integrase inhibitor resistance substitutions: Integrase T66I, E92Q, F121Y, 143C/H/R, S147G, Q148H/K/R, or N155H.

       Note: This exclusionary list is for the purpose of this study and includes major (or primary) resistance substitutions but not substitutions that are minor and found as naturally occurring polymorphisms.

13. Has active hepatitis C virus (HCV) coinfection (defined as detectable HCV RNA) or HBV co-infection (defined as hepatitis B surface antigen [HBsAg]-positive) (completed by the central laboratory). Participants with prior/inactive HCV infection (defined as undetectable HCV RNA) or past HBV infection (defined as HBsAg-negative and positive for antibody against HBsAg) may be enrolled
14. Has a current (active) diagnosis of acute hepatitis due to any cause.

**Other Exclusions**

15. Has previously been randomized in a study and received MK-8591, DOR, MK-1439A, or 3TC.
16. Is or has an immediate family member (eg, spouse, parent/legal guardian, sibling or child) who is investigational site or sponsor staff directly involved with this trial.

## 6.3 Lifestyle Restrictions

No restrictions are required.

### 6.3.1 Meals and Dietary Restrictions

Study medications may be administered without regard to meals (Section 7.5).

### 6.3.2 Caffeine, Alcohol, and Tobacco

Participants should be questioned about their estimated daily intake of alcohol and about substance abuse during the screening evaluation of eligibility. Any participant who in the opinion of the investigator has an excessive intake of any of these substances which might interfere with participation in the trial must be excluded from the study.

### 6.3.3 Activity

It is recommended that participants abstain from strenuous exercise (e.g., beginning new weight lifting, running, bicycling, regimens, etc.) for 24 hours before each blood collection for clinical laboratory tests to minimize abnormal results due to physical exertion. Abstinence from strenuous exercise should be documented by the participant in the study diary or by the site in another source document.

## 6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any adverse events or serious adverse events (SAE) meeting reporting requirements as outlined in the entry guidelines.

### 6.5 Participant Replacement Strategy

A participant who discontinues from study treatment or withdraws from the trial will not be replaced.

## 7. Treatments

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Clinical supplies [study treatment(s) provided by the Sponsor] will be packaged to support enrollment as required. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

### 7.1 Treatments Administered

The study treatments to be used in this trial are outlined below in Table 1.

Table 1 Study Treatments

| Study Treatment Name: | MK-8591 | Placebo for MK-8591 | DOR (MK-1439) | Placebo for DOR (MK-1439) | 3TC | Placebo for 3TC | MK-1439A | Placebo for MK-1439A | MK-8591A |
|---|---|---|---|---|---|---|---|---|---|
| **Dosage Formulation:** | Capsule | Capsule | Tablet | Tablet | Tablet | Tablet | Tablet | Tablet | Tablet |
| **Unit Dose Strength(s):** | 0.25 mg<br>0.75 mg<br>2.25 mg | 0 mg | 100 mg | 0 mg | 300 mg | 0 mg | DOR 100 mg + 3TC 300 mg + TDF 300 mg | 0 mg | 0.75 mg/ 100 mg |
| **Dosage Level(s):** | QD | QD | QD | QD | QD | QD | QD | QD | QD |
| **Route of Administration:** | Oral | Oral | Oral | Oral | Oral | Oral | Oral | Oral | Oral |
| **Sourcing:** | Central | Central | Central or Local | Central | Central | Central | Central or Local | Central | Central |

3TC=lamivudine; DOR=doravirine; MK-1439A=doravirine 100 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg; MK-8591A=MK-8591 0.75 mg/DOR 100 mg; QD=once daily; TDF=tenofovir disoproxil fumarate.

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

All supplies indicated in Table 1 will be provided per the 'Sourcing' row depending upon local country operational requirements. Every attempt should be made to source these supplies from a single lot/batch number. The trial site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

Refer to Section 9.1.8 for details regarding administration of the study treatment.

## 7.2 Dose Modification (Escalation/Titration/Other)

No dose modification of MK-8591 (or placebo), DOR (or placebo), 3TC (or placebo), MK-1439A (or placebo), or MK-8591A is allowed during the trial, beyond the protocol specified switch to open-label study medication.

Decisions to temporarily withhold study treatment because of an AE will be reviewed on a case-by-case basis by the investigator. Interruptions from the protocol-specified treatment plan that are expected to be 7 days or longer require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

**The investigator should consider temporarily withholding study treatment if the severity of the AE is Grade 3 or above and/or if clinically indicated.** Guidelines for grading the severity of laboratory AEs for the purposes of participant care are based on Division of Acquired Immunodeficiency Syndrome (DAIDS) Criteria for Grading Severity of Adverse Events (Appendix 2A). **The decision to interrupt study treatment should take into account the participant's baseline laboratory values and any concomitant medication or comorbidities that could be contributory.** At the discretion of the investigator, study treatment may generally be reinitiated when AEs resolve (i.e., laboratory parameters return to near normal or baseline values). See Appendix 4 for instructions if a rechallenge is planned for an AE that was serious and which may have been caused by the study medication or poses a significant risk to the participant.

If there is a recurrence of the AE after re-initiation of study treatment, consideration should be given to permanently discontinuing all study treatment. In general, when an AE occurs which requires interruption of study treatment, all study medications should be interrupted to avoid having a participant receive suboptimal therapy, which may predispose them to the development of drug resistance. In general, all study medications should be restarted concomitantly at full dose.

## 7.3 Method of Treatment Assignment

Treatment allocation/randomization will occur centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). There are 4 study treatment arms. Participants will be assigned randomly in a 1:1:1:1 ratio to the treatment groups as shown below.

Group 1: MK-8591 (0.25 mg) + DOR (100 mg) + 3TC (300 mg) QD + placebo for MK-1439A
Group 2: MK-8591 (0.75 mg) + DOR (100 mg) + 3TC (300 mg) QD + placebo for MK-1439A
Group 3: MK-8591 (2.25 mg) + DOR (100 mg) + 3TC (300 mg) QD + placebo for MK-1439A
Group 4: MK-1439A QD + placebo for DOR + placebo for 3TC + placebo for MK-8591

As described in Section 5.1 and Section 9.10, after at least 24 weeks of treatment on the 3-drug regimen all participants who are virologically suppressed and have not met viral failure

criteria (Section 5.4.1.1.1), will be switched to Part 2. In Part 2, the doses of MK-8591 will remain blinded, DOR and MK-1439A will be provided as open-label supplies and the 3TC will be dropped. Participants will be assigned study medication via Interactive Voice/Web Response System (IVRS/IWRS) as follows:

Group 1: MK-8591 (0.25 mg) + DOR (100 mg)
Group 2: MK-8591 (0.75 mg) + DOR (100 mg)
Group 3: MK-8591 (2.25 mg) + DOR (100 mg)
Group 4: MK-1439A QD

After all participants have received 48 weeks of study therapy (Part 1 + Part 2), a dose of MK-8591 will be selected. Following dose selection and site notification (Week 60 or beyond), participants in Groups 1 to 3 will be switched to the selected dose of MK-8591 administered with DOR provided as open-label supplies in Part 3. Participants in Group 4 will continue to receive open-label MK-1439A. Participants will be assigned study medication via IVRS/IWRS as follows:

Groups 1 to 3: MK-8591 selected dose + DOR (100 mg)
Group 4: MK-1439A QD

In Part 4, all participants will receive open-label MK-8591A.

### 7.3.1 Stratification

Treatment allocation/randomization will be stratified according to the following factors:

- Screening HIV-1 RNA level (≤100,000 copies/mL or >100,000 copies/mL).

## 7.4 Blinding

In Part 1 of the trial, a double-blinding technique with in-house blinding will be used for MK-8591, DOR, 3TC, and MK-1439A. The participant, the investigator, and Sponsor personnel or delegate(s) who are involved in the study treatment administration or clinical evaluation of the participants will be unaware of the group assignments. During the double-blind portion of the trial, all active drug treatments will be packaged identically relative to their matching placebos.

In Part 2, when participants are switched to the 2-drug dose-ranging/maintenance regimen (Section 5.1 and Section 9.10), the dose of MK-8591 will remain blinded, however, the DOR (Groups 1 to 3) and MK-1439A (Group 4) will be provided as open-label supplies; matching placebos will not be administered.

Once the MK-8591 dose is selected and sites are notified (Part 3), all study treatments will be provided as open-label supplies. Matching placebos will not be administered (Section 9.1.8.1). In Part 4, MK-8591A will be provided as open-label supplies.

See Section 9.1.10 for a description of the method of unblinding a participant during the trial, should such action be warranted.

## 7.5 Preparation/Handling/Storage/Accountability

### 7.5.1 Dose Preparation

The rationale for selection of doses to be used in this trial is provided in Section 3.2. There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each participant.

### 7.5.2 Handling, Storage and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

For all trial sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

The trial site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

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

## 7.6 Treatment Compliance

Study Medication Diary Cards completed by the participants will be used to document drug compliance. Study medication diary cards will be provided to the participants at the visits specified in the SoA (Section 2). The investigator/study coordinator will be responsible for entering the identification number (allocation number), visit number, next visit date, and indicating if the visit is fasting or a PK visit (if applicable) before giving the diary card to the participant. Participants will be instructed to record dates/times and the number of tablets or capsules of study drug taken on the diary card daily and return the completed diary at each visit. Only the participant should enter information onto the diary card. At visits when used/unused study medications are returned, site personnel must verify the accuracy of the dosing diary by comparing entries with amounts of returned study medication. If a discrepancy is noted, investigator/study coordinator must discuss the discrepancy with the

participant, and the explanation must be documented. Only the participant shall make any changes to the entries on the diary card. The investigator/study coordinator will be responsible for transferring the appropriate information from the diary card onto the appropriate case report form.

Interruptions from the protocol specified treatment plan for ≥7 days require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

## 7.7 Concomitant Therapy

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

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

- The medications and/or substances below are prohibited in this study because they are moderate or potent broad inducers of CYP3A4 and their co-administration with DOR could possibly result in reduced drug levels of DOR, or they have the potential for additional DDIs.

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

  - Carbamazepine
  - Phenobarbital
  - Phenytoin
  - Rifabutin
  - Rifampin
  - Herbal remedies
  - St. John’s Wort
  - Modafinil
  - Bosentan
  - Nafcillin
  - Enzalutamide
  - Mitotane
  - Oxcarbazepine

- Rifapentine

- The following medication is prohibited as it is a known adenosine deaminase inhibitor which may increase MK-8591 levels:
  - Pentostatin
- Investigational agents are not permitted. Investigational agents must be discontinued 30 days prior to receiving study therapy.
- Concomitant use of immune therapy agents, immune modulators, or other immunosuppressive therapy is not allowed within 30 days prior to treatment or during the course of the study with the following exceptions:
  - Short courses of corticosteroids (e.g., as for asthma exacerbation)
  - If a participant develops a malignancy (e.g., lymphoma) after randomization, the participant may receive chemotherapy and remain in the study if, in the opinion of the investigator, the benefits outweigh the risks. Depending on the type of chemotherapy, study medication may need to be interrupted until completion of the chemotherapy.
- Treatment for participants with newly diagnosed HCV should be deferred until study completion when possible. Treatment options are dependent upon which part of the trial a participant is in:
  - For participants in Part 1 and those receiving MK-8591 in the dose-ranging arms in Part 2: Participants who require treatment must be discontinued from treatment and complete the early discontinuation and end of trial phone and site follow-up visits.
  - For participants in Group 4 (open-label MK-1439A) in Part 2 and all participants in Part 3 and in Part 4: A consultation with the Sponsor Clinical Director is required for participants who require treatment during this part of the trial. After consultation, participants may be allowed to receive treatment and remain in the study if, in the opinion of the investigator, the benefits outweigh the risks.
- Other antiretroviral therapies beyond those described in the study (MK-8591, DOR, 3TC, MK-1439A, or MK-8591A) are not permitted during the course of the study.

### 7.7.1 Rescue Medications & Supportive Care

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

## 7.8 Treatment After the End of the Study

Provided that development of MK-8591 is continuing, there will be a mechanism for all participants who are virologically suppressed to receive treatment with MK-8591A, after completing the study and without interruption, until it becomes commercially available.

Participants eligible for this mechanism will be those who have completed the last scheduled study visit, who are considered by the investigator to have derived benefit from study

participation (regardless of treatment group assigned) and for whom further treatment with MK-8591 + DOR is considered clinically appropriate.

### 7.9 Clinical Supplies Disclosure

In Part 1, all study supplies will be double-blinded; therefore, the participant, the trial site personnel, the Sponsor and/or designee will be blinded. In Part 2, DOR and MK-1439A will be provided as open-label supplies; the doses of MK-8591 will be blinded. In Parts 3 and 4, the trial is open-label; therefore, the participant, the trial site personnel, the Sponsor and/or designee are not blinded. Study treatment (name, strength or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

The emergency unblinding call center will use the treatment/randomization schedule for the trial to unblind participants and to unmask study treatment identity. The emergency unblinding call center should only be used in cases of emergency (see Section 9.1.10). In the event that the emergency unblinding call center is not available for a given site in this trial, the central electronic treatment allocation/randomization system (IVRS/IWRS) should be used in order to unblind participants and to unmask study treatment identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

See Section 9.1.10, Participant Blinding/Unblinding, for a description of the method of unblinding a participant during the trial, should such action be warranted.

## 8. Discontinuation/Withdrawal Criteria

### 8.1 Discontinuation of Study Treatment

Discontinuation of study treatment does not represent withdrawal from the study.

As certain data on clinical events beyond study treatment discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study treatment. Therefore, all participants who discontinue study treatment prior to completion of the protocol-specified treatment period will still continue to participate in the study as specified in the SoA (Section 2) by participating in the Early Discontinuation and End of Trial Site Follow-Up visit.

Participants may discontinue study treatment at any time for any reason or be dropped from the study treatment at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study treatment by the investigator or the Sponsor if study treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study treatment discontinuation are provided in Section 9.1.9.

A participant must be discontinued from study treatment for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study treatment.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or sponsor, placed the participant at unnecessary risk from continued administration of study treatment.

- The participant has a confirmed positive serum pregnancy test (See Section 9.3.6).

  **Note**: Infants born to participants who become pregnant while receiving study intervention will have follow-up data collected up to approximately 1 year after birth (See Section 9.5.6).

- The participant experiences a severe skin or hypersensitivity reaction.
- The participant has a $Cl_{cr}$ of <50 mL/min based on the Cockcroft-Gault equation (Section 6.1, #5):

  **Note:** Creatinine clearance should be confirmed by repeat analysis prior to discontinuing treatment.

- The participant has been diagnosed with HBV infection.
- Prior to Amendment 03, the participant has met 1 of the virologic failure criteria (Section 5.4.1.1.1).
- As of Amendment 03, the participant has confirmed HIV-1 virologic rebound as defined in Section 5.4.1.1.2.
- Participants in Part 1 or participants in the MK-8591 dose-ranging groups in Part 2 who are newly diagnosed with HCV and require treatment. See Section 7.7 for instruction regarding participants in other treatment groups or parts of the trial.

NOTE: Participants who are discontinued from study treatment should be switched as soon as possible to another ART regimen, which will not be provided by the Sponsor, in order to avoid potential exposure to MK-8591 monotherapy due to the long half-life of MK-8591.

For participants who are discontinued from study treatment but continue to be monitored in the trial, see the Early Discontinuation and End of Trial Site Follow-up visits, as outlined in the SoA (Section 2) for those procedures to be completed at each specified visit.

Discontinuation from study treatment is "permanent." Once a participant is discontinued, he/she shall not be allowed to restart study treatment.

## 8.2 Withdrawal from the Study

A participant must be withdrawn from the study if the participant or participant's legally acceptable representative withdraws consent from the study.

If a participant withdraws from the study, they will no longer receive study treatment or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from Future Biomedical Research are outlined in Section 9.1.9. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 8.3.

### 8.3 Lost to Follow Up

If a participant fails to return to the clinic for a required study visit and/or if the site is unable to contact the participant, the following procedures are to be performed:

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, phone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.
- Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The amount of missing data for the participant will be managed via the pre-specified data handling and analysis guidelines.

## 9. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed approximately 867 mL.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

### 9.1 Administrative and General Procedures

#### 9.1.1 Informed Consent

The investigator or qualified designee must obtain documented consent from each potential participant or each participant's legally acceptable representative prior to participating in a clinical trial or Future Biomedical Research. If there are changes to the participant's status during the trial (eg, health or age of majority requirements), the investigator or qualified designee must ensure the appropriate consent is in place.

#### 9.1.1.1 General Informed Consent

Consent must be documented by the participant's dated signature or by the participant'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 participant before participation in the trial.

The initial ICF, any subsequent revised written ICF and any written information provided to the participant must receive the IRB/IEC's approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant'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 participant's dated signature or by the participant'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/IEC requirements, applicable laws and regulations and Sponsor requirements.

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

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

#### 9.1.1.3 Consent for Infant Safety Follow-up

Depending on applicable laws and regulations, a separate informed consent may be required for participation in the infant safety follow-up period (Section 9.5.6). If a separate consent is required, the investigator or medically qualified designee will explain the infant safety follow-up consent to the participant, answer all questions, and obtain written informed consent before collecting any data related to the infant follow-up. A copy of the informed consent will be given to the participant.

### 9.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the participant qualifies for the trial. Refer to Appendix 2 for list of specific laboratory tests.

### 9.1.3 Participant Identification Card

All participants will be given a Participant 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 participant with a Participant Identification Card

immediately after the participant provides written informed consent. At the time of treatment allocation/randomization, site personnel will add the treatment/randomization number to the Participant Identification Card.

The participant identification card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about study treatment in emergency situations where the investigator is not available.

### 9.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. The medical history should include information pertaining to the diagnosis of HIV-1 infection and AIDS (if applicable) and the year diagnosed. In addition, the participants' history of smoking should be obtained and recorded on the appropriate electronic case report form (eCRF) as relevant for calculating cardiovascular risk.

### 9.1.5 Prior and Concomitant Medications Review

#### 9.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use and record prior medication taken by the participant within 30 days before Screening and during the screening period.

#### 9.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the trial once randomization has occurred.

### 9.1.6 Assignment of Screening Number

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

### 9.1.7 Assignment of Treatment/Randomization Number

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

A single participant cannot be assigned more than 1 treatment/randomization number.

### 9.1.8 Treatment Administration

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

#### 9.1.8.1 Timing of Dose Administration

All study medications should be administered QD at approximately the same time each day without regard to food. The tablets from each container should be taken together (Section 7.5.1).

In Part 1, all participants will take 1 tablet from each of 4 containers, A, B, C and D, QD.

In Part 2, participants in Groups 1 to 3 will take 1 tablet each from Containers E and F QD, participants in Group 4 will take 1 tablet from Container G QD.

In Part 3, participants in Groups 1 to 3 will take 1 tablet each from Containers H and F QD, and participants in Group 4 will continue to take 1 tablet from Container G QD.

Study medication will be provided as per Table 2.

If a participant misses a dose of any of the study drugs, the following guidance should be followed:

- If it is ≤12 hours before the next dose, the missed dose should be skipped and the normal dosing schedule resumed. The subject should not double the next dose in order to compensate for what has been missed
- If it is >12 hours before the next dose, the missed dose should be taken and the normal dosing schedule resumed

Table 2 Study Medication Labeling

| Container Label | Medication Label | Blinding |
|---|---|---|
| **Part 1 – Double Blind** | | |
| **All Groups** | | |
| A | MK-8591 0.25 mg, 0.75 mg, or 2.25 mg or placebo | Blinded |
| B[1] | MK-1439 100 mg or placebo | Blinded |
| C | Lamivudine 300 mg or placebo | Blinded |
| D | MK-1439A (MK-1439 100 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg) or placebo | Blinded |
| **Part 2 – Site Blinded to MK-8591 Dose** | | |
| **Groups 1 -3** | | |
| E | MK-8591 0.25 mg, 0.75 mg, or 2.25 mg | Dose blinded |
| F[1] | MK-1439 100 mg | Open-label |
| **Group 4** | | |
| G | MK-1439A (MK-1439 100 mg/ lamivudine 300 mg/ tenofovir disoproxil fumarate 300 mg) | Open-label |

| Container Label | Medication Label | Blinding |
|---|---|---|
| **Part 3 – Open-label** | | |
| **Groups 1 – 3** | | |
| H | MK-8591 Selected dose (0.25 mg, 0.75 mg, or 2.25 mg) | Open-label |
| F[1, 2] | MK-1439 100 mg | Open-label |
| **Group 4** | | |
| G[2] | MK-1439A (MK-1439 100 mg/ lamivudine 300 mg/ tenofovir disoproxil fumarate 300 mg) | Open-label |
| **Part 4 – Open-label** | | |
| **Groups 1 – 4** | | |
| J | MK-8591A (MK-8591 0.75 mg/DOR 100 mg) | Open-label |
| [1] Tablets must be kept in the original container prior to taking study medication.<br>[2] If locally sourced, container labels F and G will not apply. | | |

Centrally sourced study medication containers will contain enough study drug for 35 days while locally sourced study medication containers will contain enough study drug for 30 days. All study medication should be dispensed 1 container for each 4-week visit interval.

### 9.1.9 Withdrawal/Discontinuation

Participants who discontinue study treatment prior to completion of the treatment period should be encouraged to continue to be followed for all remaining study visits.

When a participant withdraws from participation in the trial, all applicable activities scheduled for the Early Discontinuation Visit should be performed at the time of withdrawal. Any adverse events which are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 9.3 - Adverse Events.

#### 9.1.9.1 Withdrawal From Future Biomedical Research

Participants may withdraw their consent for Future Biomedical Research. Participants 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). Subsequently, the participant's consent for Future Biomedical Research will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the participant of completion of withdrawal. Any analyses in progress at the time of request for withdrawal 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 (eg, 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

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

### 9.1.10 Participant Blinding/Unblinding

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

For emergency situations where the investigator or delegate needs to identify the drug used by a participant and/or the dosage administered, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or delegate the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the sponsor. Prior to contacting the emergency unblinding call center to request unblinding of a participant's treatment assignment, the investigator or delegate must enter the intensity of the adverse events observed, the relation to study drug, the reason thereof, etc., in the medical chart etc.

Participants whose treatment assignment has been unblinded by the investigator/delegate and/or non-study treating physician should continue to be monitored in the trial.

Additionally, the investigator must go into the IVRS system and perform the unblind in the IVRS system to update drug disposition. In the event that the emergency unblinding call center is not available for a given site in this trial, IVRS/IWRS should be used for emergency unblinding in the event that this is required for participant safety.

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

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

As noted, Part 1 is double-blind (operating under in-house blinding procedures) in which the participant enrolled; the trial investigator, study center personnel, and the Sponsor are blinded to which study drugs, MK-8591, DOR, 3TC, and MK-1439A, are received. In Part 2, DOR and MK-1439A will be provided as open-label supplies, the dose of MK-8591 will continue to be blinded. In Parts 3 and 4, all study medications will be provided and dispensed as open-label supplies. Matching placebos will no longer be provided/dispensed in Parts 2 - 4.

### 9.1.11 Calibration of Equipment

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

Documentation of equipment calibration must be retained as source documentation at the study site.

## 9.2 Efficacy Assessments

The primary efficacy measurement is HIV-1 RNA. Additional blood samples will be collected as indicated in the SoA (Section 2) to explore single-copy HIV-1 RNA. Additional efficacy measurements include CD4+ T-cell counts and viral resistance testing. Blood will be collected to evaluate CD4+ T-cell counts and viral resistance as indicated in the SoA (Section 2).

### 9.2.1 HIV-1 RNA

Plasma HIV-1 RNA quantification will be performed at the central laboratory using a real time polymerase chain reaction (PCR) assay with a lower limit of detection of 40 copies/mL. Exploratory measurements of HIV-1 RNA will be assessed at certain time points. The single-copy HIV-1 RNA assay will only be performed at the visits specified in the SoA (Section 2) when the HIV-RNA is below the lower limit of detection for the HIV-1 RNA assay.

### 9.2.2 Management of Study Participants with Viremia

When viremia (HIV-1 RNA ≥50 copies/mL) is detected (Section 5.4.1.1.2), the investigator should query the participant regarding adherence to study therapy, intercurrent illness, or recent immunization. All cases of viremia must be confirmed, and the participant should continue to take the full assigned dosage of study medication while awaiting confirmation.

#### 9.2.2.1 Viremia Confirmation

Confirmation of viremia requires 2 consecutive plasma HIV-1 RNA results of ≥50 copies/mL (Section 5.4.1.1.2) with the second sample collected at a "Viremia Confirmation" visit at least 2 weeks but not more than 4 weeks from the date of the initial sample. This timeframe may be extended if study medication is interrupted for 1 of the following circumstances:

- Intercurrent illness: redraw 2 to 4 weeks following resolution of the illness, during which time the participant should continue to receive the assigned dosage of study medication(s) without interruption;
- Immunization: redraw at least 4 weeks following any immunization, during which time the participant should continue to receive the assigned dosage of study medication(s) without interruption;
- Toxicity management, noncompliance, or other reason: redraw 2 to 4 weeks following resuming the assigned dosage of study medication(s).

#### 9.2.2.2 Participants With Clinically Significant Confirmed Viremia (≥200 copies/mL)

Study participants with confirmed HIV-1 RNA of ≥200 copies/mL will be assessed for development of viral drug resistance (Section 9.2.4) and discontinuation from study intervention (Section 8.1). Once it is determined that study intervention discontinuation is

appropriate, Early Discontinuation and End of Treatment visit procedures should be completed (Section 2.3 and Section 9.10.4) and the participant managed by the investigator per local standard-of-care.

#### 9.2.2.3 Participants With Low-Level Viremia (≥50 and <200 copies/mL)

Study participants with confirmed HIV-1 RNA of ≥50 and <200 copies/mL should continue study medication and all regularly scheduled study visits during which HIV-1 RNA levels will be monitored per the SoA (approximately every 3 months). Additional visits may be conducted to monitor HIV-1 RNA levels more frequently than every 3 months, if appropriate, after discussion with the Sponsor.

Investigators should use their clinical judgment regarding the most appropriate clinical management of participants, if more stringent local guidelines apply, and may contact the Sponsor's Clinical Director to discuss questions on clinical management of individual participants.

### 9.2.3 CD4+ T-cell Counts

CD4+ T-cell counts (absolute and percentage) will be performed at the central laboratory.

### 9.2.4 Viral Resistance Testing

Participants with HIV-1 RNA ≥200 copies/mL at any time during the study will be assessed for development of viral drug resistance.

Blood samples will be collected for phenotypic and genotypic HIV-1 drug resistance testing to determine resistance to MK-8591, DOR, 3TC, and TDF per the SoA (Section 2). An extra sample of blood is being collected at the screening visit, which may be used in the event the first sample is not evaluable and needs to be repeated. Resistance testing will be performed by the central laboratory.

## 9.3 Adverse Events, Serious Adverse Events and Other Reportable Safety Events

The definitions of an adverse event (AE) or serious adverse event (SAE), as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE and other reportable safety event reports can be found in Appendix 4.

AE, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator, who is a qualified physician, and any designees are responsible for detecting, assessing, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AE, SAEs and other reportable safety events for outcome according to Section 9.3.3.

### 9.3.1 Time Period and Frequency for Collecting AE, SAE and Other Reportable Safety Event Information

All AEs, SAEs and other reportable safety events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event cause the participant to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

From the time of treatment allocation/randomization through 42 days following cessation of treatment, all AEs, SAEs and other reportable safety events must be reported by the investigator.

Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified in the previous paragraph must be reported immediately to the Sponsor if the event is considered to be drug-related.

For infants born to participants who become pregnant while receiving study intervention and consent to infant follow-up, SAEs occurring (in these infants) from the time of birth through 1-year of age must be reported by the investigator to the Sponsor within 24 hours of learning of the event.

Investigators are not obligated to actively seek AE or SAE or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.

All initial and follow-up AEs, SAEs and other reportable safety events will be recorded and reported to the sponsor or designee within the timeframes as indicated in Table 3.

Table 3 Reporting Time Periods and Timeframes for Adverse Events and Other Reportable Safety Events

| Type of Event | Reporting Time Period: Consent to Randomization/ Allocation | Reporting Time Period: Randomization/ Allocation through Protocol-Specified Follow-up Period | Reporting Time Period: After the Protocol Specified Follow-up Period | Timeframe to Report Event and Follow-up Information to SPONSOR: |
|---|---|---|---|---|
| **Serious Adverse Event (SAE)** | Report if:<br>- due to protocol-specified intervention<br>- causes exclusion<br>- subject is receiving placebo run-in or other run-in treatment | Report all | Report if:<br>- drug/vaccine related.<br>(Follow ongoing to outcome.) | Within 24 hours of learning of event |
| **Non-Serious Adverse Event (NSAE)** | Report if:<br>- due to protocol-specified intervention<br>- causes exclusion<br>- subject is receiving placebo run-in or other run-in treatment | Report all | Not required | Per data entry guidelines |
| **Overdose** | Report if:<br>- receiving placebo run-in or other run-in medication | Report all | Not required | Within 5 days of learning of event |
| **Event of Clinical Interest (require regulatory reporting)** | Report if:<br>- due to intervention<br>- causes exclusion | Report<br>- Potential DILI<br>- Require regulatory reporting | Not required | Within 24 hours of learning of event |
| **Event of Clinical Interest (Do not require regulatory reporting)** | Report if:<br>- due to intervention<br>- causes exclusion | Report<br>- non-DILI ECIs and those not requiring regulatory reporting | Not required | Within 5 days of learning of event |
| **Cancer** | Report if:<br>- due to intervention<br>- causes exclusion | Report all | Not required | Within 5 days of learning of event |
| **Pregnancy/ Lactation Exposure** | Report if:<br>- due to intervention<br>- causes exclusion | Report all | Previously reported – Follow to completion/termination; report outcome | Within 24 hours of learning of event |

### 9.3.2 Method of Detecting AE, SAE and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AE and/or SAE and other reportable safety events. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

### 9.3.3 Follow-up of AE, SAE and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AE, SAE and other reportable safety events including pregnancy and exposure during breastfeeding, ECI, Cancer and Overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). In addition, the investigator will make every attempt to follow all non-serious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 4.

### 9.3.4 Regulatory Reporting Requirements for SAE

- Prompt notification (within 24 hours) by the investigator to the sponsor of SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, i.e., per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAE) from the sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

### 9.3.5 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

This section is not applicable to the trial.

### 9.3.6 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered adverse events, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee) that occurs during the trial are reportable to the Sponsor.

All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole,

blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

For infants born to participants who become pregnant while receiving study intervention and consent to infant follow-up, SAEs occurring (in these infants) from the time of birth through 1-year of age must be reported by the investigator to the Sponsor within 24 hours of learning of the event.

### 9.3.7 Events of Clinical Interest (ECI)

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

Events of clinical interest for this trial include:

1. 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).

## 9.4 Treatment of Overdose

In this trial, an overdose is any dose greater than 2× the protocol-specified dose(s) in a calendar day of MK-8591, DOR, 3TC, MK-1439A, or MK-8591A.

No specific information is available on the treatment of overdose.

Decisions regarding dose interruptions will be made by the investigator in consultation with the Merck Clinical Director or designee based on the clinical evaluation of the participant. No dose modification of MK-8591, DOR, 3TC, MK-1439A, or MK-8591A is allowed during the trial (Section 7.2).

## 9.5 Safety

One of the primary endpoints of this trial is to evaluate the safety and tolerability of the different doses of MK-8591 + DOR. Details regarding specific safety procedures/assessments to be performed in this trial are provided below.

Participants should be in a fasted state (at least 8 hours) for collection of the blood samples for safety assessment at Day 1 and at Weeks 24, 36, 48, 72, 96, 120, 144, and 192.

The approximate blood volumes drawn/collected by assessment can be found in Appendix 2.

Planned time points for all safety assessments are provided in the SoA.

### 9.5.1 Physical Examinations

The complete physical examination will be conducted as per institutional standard. The full physical examination will include examination of body systems (including, but not limited to, general appearance, skin, neck, eyes, ears, nose, throat, breast, lungs, heart, abdomen, back, lymph nodes, extremities, and nervous system).

The directed physical examination will be conducted as per institutional standard, sign- and symptom-directed, and based on the participant's condition and circumstances. The investigator should note any changes in the participant's condition (body systems) since the last examination. This does not preclude examination of any of the body systems as clinically indicated.

Weight and height will be measured at the visits specified in SoA (Section 2).

Investigators should pay special attention to clinical signs related to previous serious illnesses.

### 9.5.2 Vital Signs

Vital signs will include temperature, pulse, respiratory rate, and systolic and diastolic blood pressure. The participant should be in a rested state for 10 minutes prior to measurement. Any lying position during rest and measurement (eg, supine, semi-supine, semi-recumbent) is acceptable.

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

### 9.5.3 Electrocardiograms

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 participants may need to remove their bra. Participants should be in a rested state for 10 minutes prior to measurement. Any lying position during rest and measurement (eg, supine, semi-supine, semi-recumbent) is acceptable.

The correction formula to be used for the corrected QT interval is Fridericia.

Procedures for printing, archiving, and review of ECGs will be specified by the central laboratory vendor.

### 9.5.4 Clinical Safety Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).
- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 42 days after the last dose of study treatment, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

### 9.5.5 DEXA Assessments

Decreases in BMD and lipodystrophy have been reported in HIV-1-infected patients taking ART [AIDS info 2017], particularly with the use of certain NRTIs. Lipodystrophy includes the buildup of body fat and the loss of body fat.

An assessment of BMD as well as peripheral and visceral fat will be conducted by utilizing DEXA scans per the SoA (Section 2) to assess if these changes are seen with the use of the different doses of MK-8591 and considered in context of historical data for other agents. Only those participants who are confirmed eligible to be randomized will undergo total body DEXA scans for BMD of the spine and hip as well as peripheral fat and trunk fat. Dual-energy x-ray absorptiometry images will be evaluated by a central imaging reader.

If a subject fractures the hip being examined during the study, no further DEXA scans of either hip will be required.

Refer to the Site Imaging Manual for additional details regarding DEXA procedures, including participant preparation instructions to be considered prior to DEXA imaging.

### 9.5.6 Infant Safety Follow-up Assessments

Infants, born to participants who become pregnant while receiving study intervention and consent to infant follow-up, will have safety follow-up through approximately 1-year of age as outlined in Table 4. This infant safety follow-up data may be collected by phone call. Length, weight, and head circumference measurements will be collected at birth and at 1-year of age. Infant SAEs, including congenital anomalies identifiable on physical examination at birth or shortly after birth, will be collected as per Section 9.3.1.

Table 4 Infant Safety Follow-up: Data Collection Through 1-Year of Age

| **Study Period** | **Infant Safety Follow-up** | |
|---|---|---|
| **Scheduled Day** | At Birth | 1-Year After Birth[1] |
| **Data Collection Window** | +90 days | +90 days |
| **Administrative and Safety Procedures** | | |
| Informed Consent (if applicable)[2] | X | |
| Review Pregnancy Outcome[3] | X | |
| Length | X | X |
| Weight | X | X |
| Head Circumference | X | X |
| Review Infant Serious Adverse Events[4] | X ---------- X | |

[1] If a participant withdraws from the study, data from 1-Year After Birth should be collected at the time of withdrawal.
[2] Depending on applicable laws and regulations, a separate informed consent may be required (Section 9.1.1.3).
[3] Collect and report pregnancy outcome (health of infant), per Section 9.3.6.
[4] Collect SAEs, including any congenital anomalies, per Section 9.3.1.

## 9.6 Pharmacokinetics

Population PK samples will be collected from all participants as outlined in Table 5. The exact time the dose of study medication was taken prior to the sample collection will be recorded on the appropriate eCRF. The type of meal (i.e., no, light, medium, or full) consumed 2 hours before or 2 hours after the dose of study medication, as per the sampling time point outlined in Table 5, will also be recorded on the appropriate eCRF. The type of meal is defined as follows:

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

Table 5 Timing for Collection of Population Pharmacokinetics Samples

| Study Day/Week | Time Relative to Container "A" Dose (MK-8591 or placebo) |
|---|---|
| Day 1 | Sample to be collected predose |
| Week 4 | Sample to be collected predose and within 0.5 and 2 hours postdose* |
| Week 8 | Sample to be collected predose and within 0.5 and 2 hours postdose* |
| Week 12 | Sample to be collected irrespective of time of dose (time of last dose and time of PK sample collection must be documented) |
| Week 16 | Sample to be collected irrespective of time of dose (time of last dose and time of PK sample collection must be documented) |
| Week 48 | Sample to be collected irrespective of time of dose (time of last dose and time of PK sample collection must be documented) |

PK = pharmacokinetic

* For participants who take their dose during the day, samples should be collected predose and postdose. For participants who take their medication in the evening, only a post-dose sample should be collected the following day irrespective of time of dose (time of last dose and time of PK sample collection must be documented).

Venous blood samples will be collected for measurement of MK-8591. Sample collection, storage and shipment instructions for samples will be provided in the operations/laboratory manual.

## 9.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study

## 9.8 Future Biomedical Research Sample Collection

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

- DNA for Future Biomedical Research

Refer to Section 9.8 for further description of the Future Biomedical Research sample.

## 9.9 Biomarkers

### 9.9.1 Laboratory Markers Associated with Clinical Outcome

Interleukin-6, D-dimer, and soluble CD163 have been shown to be predictive of the risk for both short- and long-term mortality [Baker, J. V., et al 2011] [Knudsen, T. B., et al 2016] [Wang, H., et al 2016]. The causes of persistent inflammation and thrombotic activity in HIV-1-infected patients remain the subject of debate and ongoing research. Blood samples will be collected to evaluate the inflammatory and thrombotic response as measured by the following laboratory markers as indicated in the SoA (Section 2):

- Interleukin-6
- D-dimer
- Soluble CD163

Decreases in renal function have been noted with the use of certain NRTIs. Urine samples will be collected to evaluate renal function as measured by the following urinary analytes and calculations:

- Albumin
- Protein
- Beta-2-microglobulin/creatinine ratio
- Retinol binding protein/creatinine ratio

### 9.9.2 Planned Genetic Analysis Sample Collection

The "Blood for Genetic Analysis" sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at the site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for FBR if the participant signs the informed consent for FBR. If the planned genetic analysis is not approved, but FBR is approved and informed consent for FBR is given, this sample will be collected for the purpose of FBR.

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

## 9.10 Visit Requirements

Visit requirements are outlined in Section 2 – Schedule of Activities (SoA). Specific procedure-related details are provided above in Section 9 – Study Assessments and Procedures.

### 9.10.1 Switch from Part 1 (3-drug Dose Ranging) to Part 2

After 24 weeks of dosing in Part 1, participants who are virologically suppressed (i.e., HIV-1 RNA <50 copies/mL) at the Week 20 visit and have not met any viral failure criteria (Section 5.4.1.1.1) will switch to Part 2 of the trial at Week 24 after other visit procedures

have been completed. Participants who have met the viral failure criteria (Section 5.4.1.1.1) will not be eligible to continue to Part 2 and should be discontinued from treatment and complete the early discontinuation and end of trial phone and site follow-up visits. In Part 2, the 3TC and/or matching placebos will be dropped from the regimen and participants will be unblinded as to whether they are receiving 1 of the MK-8591 doses or the control, MK-1439A. The doses of MK-8591 will remain blinded, but the DOR and MK-1439A will be provided in an open-label fashion. Upon confirmation of eligibility, site personnel will contact the IVRS/IWRS in order to dispense the supplies.

Participants who have HIV-1 RNA levels ≥50 copies/mL at Week 20 will continue to receive the 3-drug regimen (Part 1) until the HIV-1 RNA is <50 copies/mL and they have not met any of the viral failure criteria (Section 5.4.1.1.1). The participant will then switch to the 2-drug regimen or open-label MK-1439A in Part 2 of the trial at the next visit after all other visit procedures have been completed as outlined in Table 6.

Table 6 Guidelines for Switching to Part 2 Beginning at the Week 24 Visit

| Treatment Week (Visit) | Prior Treatment Week (Visit) | HIV-1 RNA Result from Prior Treatment Week | Action |
|---|---|---|---|
| Week 24 (Visit 9) | Week 20 (Visit 8) | <50 copies/mL | Switch to Part 2 at Week 24 |
| | | ≥50 copies/mL | Continue with 3-drug regimen |
| Week 28 (Visit 10) | Week 24 (Visit 9) | <50 copies/mL | Switch to Part 2 at Week 28 |
| | | ≥50 and <200 copies/mL[1] | Continue with 3-drug regimen |
| Week 32 (Visit 11) | Week 28 (Visit 10) | <50 copies/mL | Switch to Part 2 at Week 32 |
| | | ≥50 and <200 copies/mL[1] | Continue with 3-drug regimen |
| Week 36 (Visit 12) | Week 32 (Visit 11) | <50 copies/mL | Switch to Part 2 at Week 36 |
| | | ≥50 and <200 copies/mL[1] | Continue with 3-drug regimen |
| Week 40 (Visit 13) | Week 36 (Visit 12) | <50 copies/mL | Switch to Part 2 at Week 40 |
| | | ≥50 and <200 copies/mL[1] | Continue with 3-drug regimen |
| Week 44 (Visit 14) | Week 40 (Visit 13) | <50 copies/mL | Switch to Part 2 at Week 44 |
| | | ≥50 and <200 copies/mL[1] | Continue with 3-drug regimen |
| Week 48 (Visit 15) | Week 44 (Visit 14) | <50 copies/mL | Switch to Part 2 at Week 48 |
| | | ≥50 and <200 copies/mL[1] | Continue with 3-drug regimen |
| | Week 48 (Visit 15) | <50 copies/mL | Switch to Part 2 at Week 52 |
| | | ≥50 copies/mL | Conduct Viral Failure Confirmation visit >7 days and ≤14 days from Week 48:<br>• Switch to Part 2 at Week 52 if <50 copies/mL, or<br>• Discontinue treatment if ≥50 copies/mL |

HIV-1 = human immunodeficiency virus type 1; RNA = ribonucleic acid
[1] If the HIV-1 RNA result obtained at the Week 24 visit through the Week 44 visit is ≥200 copies/mL, a viral failure confirmation visit is required to be conducted as noted in Section 9.10.4 and Section 2. If HIV-1 RNA is confirmed ≥200 copies/mL, the participant should be discontinued from treatment and complete the early discontinuation and end of trial phone and site follow-up visits (Section 5.4.1.1.1).

For participants who have continued to receive study medication in Part 1 through Week 48, the HIV-1 RNA results from Week 48 should be reviewed immediately upon receipt. If the Week 48 HIV-1 RNA results are ≥50 copies/mL, per Section 2 and Section 5.4.1.1.1, the participant should continue the Part 1 regimen and a virologic failure confirmation visit should be conducted within 7 to 14 days (e.g., no greater than Week 50). If the HIV-1 results from the viral failure confirmation visit are <50 copies/mL, the participant should return at Week 52 and be switched to Part 2. If the results from the viral failure confirmation visit are ≥50 copies/mL, the participant may not be switched and should be discontinued from treatment and complete the early discontinuation and end of trial phone and site follow up visits (Section 8.1).

In addition to the routine sample collections noted in the SoA (Section 2.1), blood should be collected for a hepatitis screen (HBV surface antigen and HCV antibody/HCV RNA per Appendix 2) beginning at Week 20. This screen will be performed only for subjects with HIV-1 RNA <50 copies/mL (those participants eligible to switch to Part 2). The hepatitis screen blood sample should continue to be collected at the Treatment Week Visits until a participant is transitioned from Part 1 to Part 2 or discontinued. If the results indicate that the participant is positive for HBV infection, the participant should be discontinued from study treatment (Section 8.1, Section 2.3). If the participant is positive for HCV and treatment for HCV is required, see Section 8.1 regarding discontinuation of study treatment.

### 9.10.2 Transition from Part 2 to Part 3

Once the MK-8591 dose selection has occurred and has been communicated by the Sponsor, participants who are receiving MK-8591 will be switched to the selected dose (provided as open-label supplies) at the next visit. Participants in the control group will continue to receive open-label MK-1439A. Site personnel will contact the IVR/IWR in order to dispense the open-label supplies as well as conduct all other assessments noted for the visit in the SoA (Section 2).

### 9.10.3 Transition from Part 3 to Part 4

Participants will be reconsented on or before the scheduled Week 144 visit, prior to performing any Part 4 procedures as per the SoA (Section 2). All participants (those receiving the selected dose of MK-8591 in combination with DOR [Groups 1-3] or MK-1439A in the control group [Group 4]) who consent to continue in Part 4 will be switched to MK-8591A (provided as open-label supplies) at the Week 144 visit. Site personnel will contact the IVRS/IWRS in order to dispense the open-label supplies as well as conduct all other assessments noted for the visit in the SoA (Section 2).

Participants who received MK-1439A in the control group (Group 4) and do not consent to continue in Part 4 will complete Week 144 and subsequent Day 42 post-study visit. These participants will be converted to a locally approved antiretroviral regimen at the discretion of the investigator.

### 9.10.4 Viremia Confirmation Visit

Prior to Amendment 03, if a participant met the criteria for viral failure (Section 5.4.1.1.1), the viral failure confirmation visit was to be conducted within 7 to 14 days (cannot be conducted <7 days) as outlined in the SoA (Section 2).

As of Amendment 03, if a participant has a viral load of ≥50 copies/mL at any time during the study, a Viremia Confirmation visit must be conducted within 2 to 4 weeks of the initial HIV-1 viremia (Sections 2.3 and 5.4.1.1.2).

If a scheduled visit is to occur within the timeframe that a participant would return for a viremia confirmation visit, the assessments for the scheduled visit should be conducted and the viral resistance sample from the viremia confirmation visit must be collected. Refer to Section 8.1 for the discontinuation of study treatment criteria.

### 9.10.5 End of Treatment Follow-up Visit

Participants in all Groups who discontinue study medication at any time prior to the Week 192 visit will have an End of Treatment safety follow-up visit in-clinic approximately 42 days after the last dose of study intervention. Assessments for this visit are outlined in Section 2.3.

## 10. Statistical Analysis Plan

This section outlines the statistical analysis strategy and procedures for the trial. Changes to analyses made after the protocol has been finalized will be documented in a supplemental Statistical Analysis Plan (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

### 10.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 10.2 to 10.12.

| | |
|---|---|
| **Study Design Overview** | A Phase 2B, Randomized, Double-Blind, Active-Comparator-Controlled, Dose-Ranging Clinical Trial to Evaluate the Safety, Tolerability, Antiretroviral Activity, and Pharmacokinetics of MK-8591 Given in Combination with Doravirine (DOR) and Lamivudine (3TC) in HIV-1-Infected Treatment-Naïve Adults |

| | |
|---|---|
| **Treatment Assignment** | In Part 1, ~ 120 participants will be randomized in a 1:1:1:1 ratio to receive 1 of 3 doses of MK-8591 (0.25 mg, 0.75 mg, or 2.25 mg) given in combination with DOR and 3TC (and placebo for MK-1439A), or MK-1439A (and placebo for MK-8591 + placebo for DOR + placebo for 3TC). Participants will be stratified by screening HIV-1 RNA value (≤100,000 or >100,000 copies/mL).<br>After at least 24 weeks in Part 1, participants who were on 1 of the MK-8591 + DOR + 3TC treatment groups and are virologically suppressed (<50 copies/mL) will be switched to the 2-drug regimen of MK-8591 + DOR, where MK-8591 will be at the same dose to which the participant was randomized. Participants who were on MK-1439A will remain on this same regimen, but MK-1439A will be provided in an open-label fashion in Part 2. The participants and investigators will remain blinded to the dose of MK-8591. Sponsor personnel will be unblinded to all treatment assignments at Week 24 to assess the safety and efficacy objectives for the 3-drug regimen.<br>When participants have reached Week 48 in the study, regardless of length of time on Part 2, analyses for dose selection of MK-8591 will be conducted by the Sponsor. Once a dose is selected, all participants on the MK-8591 treatment groups will continue in the trial (Part 3, open-label) on the selected dose of MK-8591 + DOR, while participants on MK-1439A will remain on this regimen. In Part 4, all participants will be switched to open-label MK-8591A. |
| **Analysis Populations** | Efficacy: Treatment Full Analysis Set (FAS)<br>Safety: All Participants as Treated (APaT) |
| **Primary Endpoint(s)** | 1. Proportion of participants with HIV-1 RNA <50 copies/mL at Week 24 and at Week 48<br>2. Number of participants experiencing AEs, and discontinuing study drug due to AEs |
| **Key Secondary Endpoints** | 1. Proportion of participants on the selected dose of MK-8591 with HIV-1 RNA <50 copies/mL 24 and 48 weeks after switching to the 2-drug regimen<br>2. Change from baseline in CD4+ T-cell count at Week 24, Week 48, Week 96, and Week 144 |
| **Statistical Methods for Key Efficacy/Immunogenicity/ Pharmacokinetic Analyses** | The primary objective will be assessed using 2-sided 95% CIs for the difference between treatment groups in the proportion of participants (MK-8591 treatment group minus MK-1439A) achieving HIV-1 RNA <50 copies/mL at Week 24 and at Week 48. At Week 48, the participants in the MK-8591 treatment groups could have varying durations on the 3-drug regimen (MK-8591 + DOR + 3TC) and on the 2-drug regimen (MK-8591 + DOR), but it is expected that the majority will enter Part 2 at Week 24. The CIs will be based on stratum-adjusted Mantel-Haenszel method [Mantel, N. and Haenszel, W. 1959] with the difference weighted by the harmonic mean of the sample size per treatment group for each stratum. |
| **Statistical Methods for Key Safety Analyses** | Point estimates and 95% CIs will be provided using the Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985] for the difference between treatment groups in the proportion of participants (MK-8591 treatment group minus MK-1439A) in the broad AE categories consisting of the percentage of participants with any AE, with a drug-related AE, with an SAE, with an AE that is both drug-related and serious, and who discontinued due to an AE. |

| | |
|---|---|
| **Interim Analyses** | When all participants have reached Week 24 or have discontinued prior to this, analyses will be performed by the Sponsor to assess safety and efficacy objectives for the 3-drug regimen. When all participants have reached Week 48 or have discontinued prior to this, Sponsor personnel will conduct dose selection analyses. Throughout the trial, an external unblinded statistician will perform analyses for periodic safety reviews by an eDMC, as well as ad hoc reviews as needed. Details are provided in Section 10.7.<br>• Week 24 interim analysis (to be conducted by the Sponsor and results shared with the eDMC) to assess the safety and efficacy objectives for the 3-drug regimen<br>• Week 48 dose selection analyses (to be conducted by the Sponsor and results shared with the eDMC)<br>• Week 96 interim analysis to be conducted by the Sponsor and results shared with the eDMC<br>• Periodic safety reviews (eDMC reviews) to be performed every 4 to 6 months or as specified in the DMC charter<br>• Participants who meet the protocol-defined virologic failure criteria in Part 1 (Section 5.4.1.1.1) will be communicated to the unblinded statistician. If 3 or more participants (10% or more out of 30 expected participants) in any treatment group are observed to have virologic failure by the unblinded statistician, this will be reported to the eDMC. The eDMC may recommend dropping a treatment group on the basis of this criterion. |
| **Multiplicity** | No multiplicity adjustment is planned in this Phase 2B trial. |
| **Sample Size and Power** | The planned sample size is 120 participants. With 30 participants in each treatment group, the trial has 80% power to obtain a 2-sided 95% CI for the treatment difference in the proportions of participants achieving HIV-1 RNA <50 copies/mL that would exclude a ≥33.0% treatment difference when the true proportions are, in fact, equal to 85% in each treatment group. This power statement applies to the 3 treatment differences corresponding to the difference between each specific MK-8591 treatment group and the MK-1439A control group, at both Week 24 and Week 48. Detailed information is in Section 10.9.1. |

## 10.2 Responsibility for Analyses/In-House Blinding

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

Part 1 of this trial will be conducted as a double-blind trial under in-house blinding procedures. Participants on the MK-8591 treatment groups who meet criteria for moving into Part 2 of the trial after at least 24 weeks in Part 1 will switch to the 2-drug regimen (MK-8591 + DOR), where the dose of MK-8591 will be at the same dose to which the participant was randomized in Part 1. The participants and investigators will remain blinded to the dose of MK-8591. Participants randomized to MK-1439A in Part 1 who meet criteria for moving into Part 2 will remain on MK-1439A, which will now be provided in an open-label fashion. When all participants have reached Week 24 or discontinued prior to this, Sponsor personnel will be unblinded to treatment assignment, including the dose of MK-8591, to assess safety

and efficacy objectives for the 3-drug regimen. However, the participants and investigators will remain blinded with respect to the dose of MK-8591 in Part 2.

When all participants have reached Week 48 or discontinued prior to this, analyses will be performed by Sponsor personnel to select a dose for MK-8591. Following dose selection, participants previously on 1 of the MK-8591 dose groups will be switched to the selected dose of MK-8591 + DOR (Part 3). In Part 3, all study treatment will be provided in an open-label fashion and participants will be given either open-label MK-8591 at the selected dose and DOR or MK-1439A at their next scheduled visit.

The detailed results of the Week 24, Week 48, and Week 96 analyses will be shared with the eDMC; the selected MK-8591 dose will be communicated to the sites.

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

Interim analyses are described in Section 10.7. Treatment-level results of periodic safety analyses to be reviewed by the eDMC will be provided by an external unblinded statistician. Moreover, the unblinded statistician will be informed of participants who meet the protocol-defined virologic failure criteria in Part 1 (Section 5.4.1.1.1), and if 3 or more participants in any treatment group are observed to have virologic failure by the unblinded statistician, this will be reported to the eDMC. The eDMC may make recommendations for discontinuation of the trial or for modifications to the trial to the EOC of the Sponsor. If the eDMC recommends modifications to the design of the protocol or discontinuation of the trial, the EOC may be unblinded (if prior to unblinding) to results at the treatment level in order to act on these recommendations. Limited additional Sponsor personnel may also be unblinded to the treatment level results assessed by the eDMC, if required, in order to act on the recommendations of the eDMC. The extent to which individuals are unblinded with respect to results of the periodic safety analyses will be documented by the unblinded statistician. Additional logistical details will be provided in the DMC Charter. Key aspects of the interim analyses are described in Section 10.7.

The unblinded statistician will not be involved in any discussions regarding modifications to the protocol, statistical methods, identification of protocol deviations, or data validation efforts.

## 10.3 Hypotheses/Estimation

There are no hypotheses to be tested in this trial. Objectives of the trial are stated in Section 4.

## 10.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated for within- and between-treatment differences are listed below. Details in this section apply to all Parts in the trial.

### 10.4.1 Efficacy/Pharmacokinetic Endpoints

#### 10.4.1.1 Efficacy Endpoints

An initial description of efficacy measures is provided in Section 4.

Proportions of Participants with Virologic Responses

A real time PCR assay with a reliable lower limit of quantification of 40 copies/mL will be used to measure the HIV-1 RNA level in blood samples obtained at each visit. The primary objectives will be assessed based upon the proportions of participants achieving HIV-1 RNA <50 copies/mL at Week 24 and at Week 48.

At the Week 48 time point, it is expected that the majority of participants will have had 24 weeks of treatment on the 3-drug regimen and 24 weeks of treatment on the 2-drug regimen. However, it is possible that some participants may take longer to meet the criterion to switch to the 2-drug regimen and may have received treatment for more than 24 weeks on the 3-drug regimen and less than 24 weeks on the 2-drug regimen at Week 48. It is also possible that some participants may have received treatment on the 3-drug regimen for all 48 weeks.

For the secondary objective that will be assessed on the basis of the proportion of participants achieving HIV-1 RNA <50 copies/mL 24 and 48 weeks after switching to the 2-drug regimen, the participants may have varying durations of time in the trial. It is expected that the majority of the participants will switch to Part 2 at Week 24, so 24 weeks after the switch will be Week 48. However, some participants may switch as late as Week 48, so 24 weeks after the switch could be as late as Week 72 in terms of time in the trial. Likewise, 48 weeks after switching is expected to be Week 72 for most participants but could be as late as Week 96 for some participants.

Change from Baseline in CD4+ T-cell Count

Change from baseline in CD4+ T-cell count will be estimated at each time point at which CD4+ T-cell count is collected, with a key interest at Week 24 and Week 48.

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

Time to Loss Of Virologic Response (TLOVR)

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

Protocol-defined Virologic Failure (PDVF) (prior to Amendment 03) and Clinically Significant Confirmed Viremia (as of Amendment 03)

Participants with PDVF as defined in Section 5.4.1.1.1 and with clinically significant confirmed viremia as defined in Section 5.4.1.1.2 will be identified and summarized for each treatment group.

Resistance

Participants with PDVF (prior to Amendment 03, Section 5.4.1.1.1), participants with clinically significant confirmed viremia (as of Amendment 03, Section 5.4.1.1.2), and those who discontinue for any reason, who have blood samples available and potentially amplifiable (HIV-1 RNA ≥200 copies/mL) for resistance testing, will be assessed for resistance to study drugs. Resistance data from these participants will be summarized.

#### 10.4.1.2 Pharmacokinetic Endpoints

A population PK model will be developed utilizing the sparse PK data and PK data from Phase 2 studies in order to assess individual exposure to MK-8591 (AUC, $C_{max}$, and $C_{24}$, if feasible) and to predict MK-8591 triphosphate concentrations in PBMCs.

### 10.4.2 Safety Endpoints

An initial description of safety measures is provided in Section 4.

Adverse Events

The following AEs will be summarized: 1) participants with at least 1 AE; 2) participants with at least 1 drug-related AE; 3) participants with at least 1 SAE; 4) participants with at least 1 serious and drug-related AE; and 5) participants who discontinued due to an AE.

Predefined Limits of Change in Laboratory Parameters

For the summaries of laboratory tests, participants must have both a baseline and post-randomization on-treatment measurement to be included. Participants' laboratory values (based on their most abnormal laboratory test values, in the direction of interest, while on study treatment) will be classified as to whether or not they fall outside of the pre-defined limit of change (PDLC) and are worse in grade (i.e., more abnormal in the direction of interest) than at baseline. The criteria are adapted from DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, November 2014, Version 2.0 (Appendix 2A). A listing of the participants who meet the criteria will also be provided.

## 10.5 Analysis Populations

Details in this section apply across all Parts of the trial.

### 10.5.1 Efficacy Analysis Populations

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

- Receive at least 1 dose of study treatment

- Have baseline data for those analyses that require baseline data

Participants will be included in the treatment group to which they are randomized for the analyses of efficacy data using the FAS population. Details on the approach to handling missing data are provided in Section 10.6.

### 10.5.2 Safety Analysis Population

The All Participants as Treated (APaT) population will be used for the analysis of safety data in this trial. The APaT population consists of all randomized participants who received at least 1 dose of study treatment. Participants will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the APaT population. For most participants, this will be the treatment group to which they are randomized. Participants who take incorrect study treatment for the entire treatment period will be included in the treatment group corresponding to the study treatment actually received.

At least 1 laboratory or vital sign measurement obtained subsequent to at least 1 dose of study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

Details on the approach to handling missing data for safety analyses are provided in Section 10.6.

## 10.6 Statistical Methods

This trial will use an estimation approach to provide data on antiviral activity and general tolerability of the MK-8591 treatment groups.

Results from Part 1 will be used to determine if a participant meets the criterion (virologic suppression) to enter Part 2 of the trial. If the participant was on 1 of the MK-8591 treatment groups and enters Part 2, the participant will be switched to a 2-drug regimen. Participants on MK-1439A will remain on this regimen in Part 2 but will be on open-label medication. When all participants have reached Week 24 or have discontinued prior to this, Sponsor personnel will be unblinded to treatment assignment to assess safety and efficacy objectives for the 3-drug regimen.

When all participants have reached Week 48 or discontinued prior to this, the Sponsor will perform analyses to select a dose of MK-8591. Participants randomized to the other doses of MK-8591 will be switched to the selected dose of MK-8591 + DOR following dose selection in Part 3. Participants in the MK-1439A group will remain in that regimen. In Part 4, all participants will be switched to open-label MK-8591A.

Statistical inference for safety analyses are described in Section 10.6.2. Nominal p-values may be computed but should be interpreted with caution due to potential issues of multiplicity, sample size, etc. Unless otherwise stated, all statistical assessments will be conducted at the $\alpha$=0.05 (2-sided) level.

### 10.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the primary and secondary objectives. Methods related to exploratory objectives will be described in the sSAP.

Time Window

Table 7 lists the definition of time windows and the target relative day for the scheduled visits for the trial that will be used for all analyses by time point. The measurement closest to the target date within a window will be used for analyses at a specific time point. Results from additional time points beyond Week 96 may be summarized, and day-range rules will follow the same pattern where the ranges start and end at the mid-points between target days.

Table 7 Definitions of Study Time Points

| Treatment Phase | Treatment Period | Visit | Day-Range Rules | Target Day[a] |
|---|---|---|---|---|
| Pretreatment | Baseline | Day 1 | ≤1 | 1 |
| Treatment | Double-blind with in-house blinding to dose of MK-8591 | Week 2 | ≥2 and ≤21 | 15 |
| | | Week 4 | ≥22 and ≤42 | 29 |
| | | Week 8 | ≥43 and ≤70 | 57 |
| | | Week 12 | ≥71 and ≤98 | 85 |
| | | Week 16 | ≥99 and ≤126 | 113 |
| | | Week 20 | ≥127 and ≤154 | 141 |
| | | Week 24 | ≥155 and ≤182 | 169 |
| | Site Blind to MK-8591 dose, MK-1439A open-label, and without in-house blinding to dose of MK-8591[b] | Week 28 | ≥183 and ≤210 | 197 |
| | | Week 32 | ≥211 and ≤238 | 225 |
| | | Week 36 | ≥239 and ≤266 | 253 |
| | | Week 40 | ≥267 and ≤294 | 281 |
| | | Week 44 | ≥295 and ≤322 | 309 |
| | | Week 48 | ≥323 and ≤350 | 337 |
| | | Week 52 | ≥351 and ≤406 | 365 |
| | Open-label[c] | Week 60 | ≥407 and ≤462 | 421 |
| | | Week 72 | ≥463 and ≤546 | 505 |
| | | Week 84 | ≥547 and ≤630 | 589 |
| | | Week 96 | ≥631 and ≤714 | 673 |
| | | Week 108 | ≥715 and ≤798 | 757 |
| | | Week 120 | ≥799 and ≤882 | 841 |
| | | Week 132 | ≥883 and ≤966 | 925 |
| | | Week 144 | ≥967 and ≤1022 | 1009 |
| | MK-8591A FDC[d] | Week 148 | ≥1023 and ≤1064 | 1037 |
| | | Week 156 | ≥1065 and ≤1134 | 1093 |
| | | Week 168 | ≥1135 and ≤1218 | 1177 |
| | | Week 180 | ≥1219 and ≤1302 | 1261 |
| | | Week 192 | ≥1303 and ≤1351 | 1345 |

DOR=doravirine; FDC=fixed-dose combination.

[a] Relative days and target days are counted from the first day of study medication.
[b] After entering Part 2, participants will be switched to 2-drug MK-8591 + DOR maintenance (dose of MK-8591 blinded) or control (MK-1439A) provided in an open-label fashion.
[c] After MK-8591 dose selection, participants will be switched to the selected dose (open-label) at their next scheduled visit which may occur at different time points during this time period.
[d] MK-8591A administered during open-label dosing in Part 4 of the trial.

Missing Values

There are 3 types of missing values:

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

Two approaches will be used to handle missing values (Table 8). The primary approach for the analysis of the proportion of participants achieving HIV-1 RNA <50 copies/mL is the Non-Completer=Failure (NC=F) approach as defined by the FDA "snapshot" approach [Food and Drug Administration 2013]. Under this approach, only those participants who 1) are on study assigned treatment; 2) have HIV-1 RNA measurement(s) within the time window specified in Table 7; and 3) have the measurement closest to the target date of the time point <50 copies/mL, can be classified as virologic success at that time point. The other participants, either with HIV-1 RNA measurement of ≥50 copies/mL or no virologic data within the time window due to intermittent missing or premature discontinuation regardless of reasons, will be considered as treatment failures in the analyses of the proportion of participants achieving HIV-1 RNA <50 copies/mL at that time point.

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

These approaches will also be used for the secondary analyses of the proportion of participants achieving HIV-1 RNA <50 copies/mL 24 and 48 weeks after switching to the 2-drug regimen. Participants who were discontinued for virologic failure and did not switch to the 2-drug regimen will be considered treatment failures in these analyses. Moreover, to assess the continued viral suppression of participants who were able to switch to the 2-drug regimen, separate analyses will also be conducted at these time points only on participants who were able to be switched. Participants who were not eligible to be switched would not be included in these additional analyses.

Table 8 Summary of the Two Approaches to Handle Missing Values

| Approaches | Intermittent Missing | Non-intermittent Missing Not Related to Treatment | | Non-intermittent Missing Related to Treatment | |
|---|---|---|---|---|---|
| | | Success at Study Therapy Discontinuation | Failure at Study Therapy Discontinuation | Study Therapy Discontinuation Due to Clinical/Laboratory Adverse event | Study Therapy Discontinuation Due to Lack of Efficacy |
| OF | Excluded | Excluded | Failures | Excluded | Failures |
| NC=F | Failures | Failures | Failures | Failures | Failures |

NC=F = Non-Completer=Failure; OF = Observed Failure

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

In this estimation study, the treatment difference in the proportion of participants achieving HIV-1 RNA <50 copies/mL (MK-8591 treatment group minus MK-1439A) and the associated 2-sided 95% CIs will be calculated using the stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of the sample size per treatment group for each stratum. These will be provided for each dose of MK-8591, and for each time point of interest, with primary interest in Week 24 and Week 48.

The NC=F approach as defined by FDA "snapshot" approach will be used as the primary approach to analysis with respect to the proportion of participants with virologic response (HIV-1 RNA <50 copies/mL) [Food and Drug Administration 2013]. All participants with missing data will be treated as failures regardless of the reason.

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

A sensitivity analysis will be performed using the OF approach under which participants with non-intermittent missing data who prematurely discontinued assigned treatment due to lack of efficacy are considered as failures at time points thereafter.

For the secondary endpoints of the proportion of participants achieving HIV-1 RNA <50 copies/mL 24 and 48 weeks after switching to the 2-drug regimen, results of participants from all 4 treatment groups will be reported on the basis of their original randomized groups, but the focus for the MK-8591 dose groups will be on participants who were on the selected dose throughout the trial. Since most participants are expected to switch to the 2-drug regimen at Week 24, it is anticipated that most participants will be at Week 48 and Week 72 in the trial when they reach 24 and 48 weeks in the 2-drug regimen, respectively. However, some participants may have switched after Week 24, and will be in the trial longer than others when they reach 24 and 48 weeks in the 2-drug regimen.

Change from Baseline in CD4+ T-cell Count

Change from baseline in CD4+ T-cell count will be summarized by treatment group at each time point at which CD4+ T-cell count is collected, with a key interest at Week 48. The treatment difference in changes from baseline in CD4+ T-cell count at each time point will be estimated (MK-8591 treatment group minus MK-1439A). However, these estimates will not be evaluated based on an absolute criterion for similarity. The clinical interpretation of the treatment difference is dependent upon the absolute value at baseline, and the magnitude and direction of the changes in CD4+ T-cell counts seen in each treatment group.

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

Table 9 summarizes the key efficacy analyses of the trial. The strategy to address multiplicity issues with regard to multiple treatment comparisons, multiple efficacy endpoints, multiple time points, and interim analyses is described in Section 10.7 and Section 10.8.

Table 9 Analysis Strategy for Key Efficacy Variables

| Endpoint/Variable (Description, Time Point) | Primary vs. Supportive Approach | Statistical Method | Analysis Population | Missing Data Approach |
|---|---|---|---|---|
| **Primary:** | | | | |
| Proportion of participants with HIV-1 RNA <50 copies/mL at Week 24 and at Week 48 | P | Stratum-adjusted Mantel-Haenszel[a] | FAS | NC=F |
| Proportion of participants with HIV-1 RNA <50 copies/mL at Week 24 and at Week 48 | S | Stratum-adjusted Mantel-Haenszel[a] | FAS | OF |
| **Secondary:** | | | | |
| Proportion of participants with HIV-1 RNA <50 copies/mL 24 and 48 weeks after starting Part 2 | P | Stratum-adjusted Mantel-Haenszel[a] | FAS | NC=F |
| Change from baseline in CD4+ T-cell counts at Week 24,Week 48, Week 96, Week 144, Week 168 and Week 192 | P | Descriptive statistics[b] | FAS | OF assuming baseline carried forward |

CI=confidence interval; FAS=Full Analysis Set; HIV-1=human immunodeficiency virus Type 1 NC=F=Non-Completer=Failure; OF=Observed Failure; P=Primary approach; RNA=ribonucleic acid; S=Secondary approach; TLOVR=time to loss of virologic response

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

b Mean and two-sided 95% CI.

### 10.6.2 Statistical Methods for Safety Analyses

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

The analysis of safety results will follow a tiered approach (Table 10). The tiers differ with respect to the analyses that will be performed. Safety parameters or AEs of special interest that are identified a priori as "Tier 1" safety endpoints will be subject to inferential testing for statistical significance with p-values and 2-sided 95% CIs provided for between-group comparisons. Other safety parameters will be considered Tier 2 or Tier 3. Tier 2 parameters will be assessed using point estimates and 95% CIs for between-group comparisons; only point estimates will be provided by treatment group for Tier 3 safety parameters.

There are no a priori clinical events of concern that have been identified; therefore, there are no events defined as Tier 1 in this trial. The broad categories consisting of the percentage of participants with any AE, with a drug-related AE, with an SAE, with an AE that is both drug-related and serious, and who discontinued due to an AE will be considered Tier 2 endpoints. The 95% CIs will be provided for treatment differences (MK-8591 treatment groups minus MK-1439A) in the percentage of participants with these events; these analyses will be performed using the Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985], an unconditional, asymptotic method. No stratification factor will be included.

Adverse events (preferred terms and system organ class terms) and PDLCs in laboratory parameters will be classified as belonging to "Tier 2" or "Tier 3", based on the number of events observed. Membership in Tier 2 requires that at least 4 participants in at least 1 treatment group exhibit the event; all other AEs and PDLCs will belong to Tier 3.

The threshold of at least 4 events prior to dose selection was chosen because the 95% CI for the between-group difference in percent incidence will include zero when treatment groups of equal size each have less than 4 events and thus, would add little to the interpretation of potentially meaningful differences. Because many 95% CIs may be provided without adjustment for multiplicity, the CIs should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in adverse events and predefined limits of change.

Continuous measures such as changes from baseline in laboratory and vital signs parameters will be considered Tier 3 safety parameters. Summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group.

Table 10 Analysis Strategy for Safety Parameters

| Safety Tier | Safety Endpoint | 95% CI for Treatment Comparison | Descriptive Statistics |
|---|---|---|---|
| Tier 2 | Proportion of participants:<br>(1) With at least one AE<br>(2) With a drug-related AE<br>(3) With a serious AE<br>(4) With serious and drug-related AE<br>(5) Who discontinued due to an AE<br>Specific AEs (preferred terms), System Organ Classes, or PDLCs (incidence of ≥4 participants in one of the treatment groups) | X | X |
| Tier 3 | Specific AEs (preferred terms), System Organ Classes, or PDLCs (incidence of <4 participants in all of the treatment groups)<br>Change from baseline in laboratory measurements and vital signs | | X |
| AE = adverse event; CI = confidence interval; PDLC = pre-defined limit of change | | | |

The key periods of interest for safety analyses are Day 1 through Week 24 and Day 1 through Week 48.

### 10.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

#### 10.6.3.1 Demographic and Baseline Characteristics

The comparability of the treatment groups for each relevant characteristic will be assessed by the use of descriptive statistics. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants screened, randomized, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables (age, gender, race, region, etc.), baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment group using descriptive statistics for continuous or categorical variables, as appropriate. Summary statistics for baseline disease characteristics to be used as efficacy measures such as HIV-1 RNA and CD4+ T-cell count will also be provided by treatment.

#### 10.6.3.2 Population PK and PK/PD Analyses

PK samples will be used to develop a population PK model and to explore the exposure-response relationship of MK-8591 in the trial population. Association between efficacy responses and PK parameters predicted from the population PK model will be graphically explored.

## 10.7 Interim Analyses

The analyses described in Sections 10.7.4 and 10.7.5 will be performed by an external unblinded statistician and reviewed by the eDMC. Details regarding the eDMC will be described in a DMC Charter. Analyses described in Sections 10.7.1, 10.7.2, and 10.7.3 will be performed by the Sponsor.

### 10.7.1 Interim Analysis at Week 24

When all participants have reached Week 24 or have discontinued prior to Week 24, the Sponsor will be unblinded to treatment assignment to assess the safety and efficacy objectives for the 3-drug regimen. Details of these analyses will be shared with the eDMC.

### 10.7.2 Interim Analysis at Week 48

When all participants have reached Week 48 or have discontinued prior to Week 48, the Sponsor will conduct analyses for selecting a dose of MK-8591. Safety and efficacy results will be assessed, and details will be shared with the eDMC.

### 10.7.3 Interim Analysis at Week 96

Analysis will be conducted when all participants have reached Week 96 or have discontinued prior to Week 96. Safety and efficacy results will be assessed, and details will be shared with the eDMC.

### 10.7.4 Periodic Safety Assessments

To supplement the routine safety monitoring outlined in this protocol, the eDMC will monitor ongoing safety data and provide recommendations to ensure the safety of study participants and the integrity of the trial to the EOC (Appendix 3). HIV-1 RNA data may be included as part of the reviews. The eDMC will monitor the trial with suggested periodic reviews to occur every ~ 4 to 6 months or as specified in the DMC charter.

### 10.7.5 Virologic Failure Assessments

Participants who meet the protocol-defined virologic failure criteria in Part 1 (Section 5.4.1.1.1) will be communicated to the unblinded statistician. If 3 or more participants (10% or more out of 30 expected participants) in any treatment group are observed to have virologic failure by the unblinded statistician, this will be reported to the eDMC. The eDMC may recommend dropping a treatment group on the basis of this criterion.

## 10.8 Multiplicity

No multiplicity adjustment will be made as this is a Phase 2 dose-selection trial and there are no hypotheses for this trial.

## 10.9 Sample Size and Power Calculations

### 10.9.1 Sample Size and Power for Efficacy Analyses

This trial will include ~120 participants randomized to receive 1 of 3 MK-8591 treatment groups or MK-1439A. Table 11 displays the differences in proportions (MK-8591 treatment group minus MK-1439A group) that can be ruled out with 80% power and 30 participants per group. The power calculation is based on an asymptotic method proposed by Farrington and Manning [Farrington, C. P. and Manning, G. 1990].

Table 11 Difference in Efficacy Proportions (MK-8591 Treatment Group minus MK-1439A Group) That Can Be Ruled Out With 80% Power and 95% Confidence with 30 Participants Per Group

| Response Rate (%) in the Comparator Group (MK-1439A) | True Difference in Response Rates[a] (Experimental [MK-8591 Treatment Group] – Comparator [MK-1439A] Group) | | | | |
|---|---|---|---|---|---|
| | -10 Percentage Points | -5 Percentage Points | 0 Percentage Points | 5 Percentage Points | 10 Percentage Points |
| 60 | 25.7 | 30.4 | 35.0 | 42.6 | 43.8 |
| 65 | 25.7 | 30.6 | 35.4 | 40.1 | 44.5 |
| 70 | 25.3 | 30.5 | 35.5 | 40.2 | 44.9 |
| 75 | 24.6 | 30.0 | 35.1 | 40.0 | 44.9 |
| 80 | 23.5 | 29.0 | 34.3 | 39.4 | 44.4 |
| 85 | 21.7 | 27.4 | **33.0** | 38.3 | 43.5 |
| 90 | 19.2 | 25.2 | 30.9 | 36.5 | 41.9 |

[a] Calculated using SAS v9.4.

It is anticipated that ~85% of participants will achieve <50 copies/mL at Weeks 24 and 48. With 30 participants per group, the trial has 80% power to declare with 95% confidence that the difference in the proportions of participants achieving HIV-1 RNA <50 copies/mL at Week 24 and at Week 48 between a MK-8591 treatment group and MK-1439A group will be no more than 33.0%, when the true proportions are in fact equal to 85% in each treatment group (Table 11).

### 10.9.2 Sample Size and Power for Safety Analyses

The probability of observing at least 1 of a particular type of AE in this trial depends on the number of participants treated and the underlying percentage of participants with that AE in the study population.

If the underlying incidence of a particular AE is 1% (1 of every 100 participants receiving study treatment), there is a 26.0% chance of observing at least 1 AE among 30 participants in any treatment group. If no AE of that type is observed among the 30 participants in any

treatment group, this trial will provide 95% confidence that the underlying percentage of participants with that particular AE is <11.6% for that treatment group.

The estimate of, and the upper bound of the 95% CI for, the underlying percentage of participants with an AE given various hypothetical observed number of participants with the AE within each treatment group are provided in Table 12. These calculations are based on the exact binomial method proposed by Clopper and Pearson [Clopper, C. J. and Pearson, E. S. 1934].

Table 12 Estimate of Incidence of AEs and 95% Upper Confidence Bound Based on Hypothetical Number of Participants with AEs Among 30 Participants in Each Treatment Group

| Hypothetical Number of Participants With Adverse Event | Estimate of Incidence | 95% Upper Confidence Bound[a] |
|---|---|---|
| 0 | 0.0% | 11.6% |
| 1 | 3.3% | 17.2% |
| 2 | 6.7% | 22.1% |
| 5 | 16.7% | 34.7% |
| 7 | 23.3% | 42.3% |
| 10 | 33.3% | 52.8% |

AE=adverse event

[a] Based on the 2-tailed exact confidence interval of a binomial proportion [Clopper, C. J. and Pearson, E. S. 1934].

Table 13 gives the difference in the incidence of AEs (MK-8591 treatment group minus MK-1439A group) that can be ruled out with different power levels and 95% confidence when there are 30 participants in each treatment group. The underlying incidence of AEs is assumed to be the same for the treatment groups. For an AE that occurs in 10% of participants in 1 of the MK-8591 treatment groups or the control group, the trial has 80% power to declare with 95% confidence that the true difference between the treatment groups is no more than 21.7 percentage points. The calculations are based on an asymptotic method proposed by Farrington and Manning [Farrington, C. P. and Manning, G. 1990].

Table 13 Difference in Incidence of AEs (MK-8591 treatment group minus MK-1439A) That Can Be Ruled Out With 30 Participants in Each Treatment Group

| | **Difference[a] in Percentage Points That Can Be Ruled Out with Target Power Assuming the Underlying Incidence of the AE is:** | | | | |
|---|---|---|---|---|---|
| **Target Power** | **10%** | **20%** | **30%** | **40%** | **50%** |
| 80 | **21.7** | 28.9 | 33.1 | 35.4 | 36.2 |
| 85 | 23.2 | 30.9 | 35.5 | 37.9 | 38.7 |
| 90 | 25.1 | 33.5 | 38.4 | 41.0 | 41.8 |
| 95 | 27.9 | 37.2 | 42.7 | 45.6 | 46.5 |

AE = adverse event

[a] The upper bound of the 2-sided 95% confidence interval [Farrington, C. P. and Manning, G. 1990] for the difference in AE incidences (MK-8591 treatment group minus MK-1439A) assuming the incidences are the same.

## 10.10 Subgroup Analyses

To assess the consistency of the treatment effect across various subgroups, the estimate of the between-group treatment effect for the primary endpoint will be assessed and plotted within each category of the following classification variables:

- Age category (≤median, >median)
- Sex (female, male)
- Region
- Race (White, Black, Asian, Other)
- Ethnicity (Hispanic/Latino, not Hispanic/Latino)
- Screening HIV-1 RNA categories (HIV-1 RNA ≤100,000 copies/mL, HIV-1 RNA >100,000 copies/mL)
- Baseline HIV-1 RNA categories (HIV-1 RNA ≤100,000 copies/mL, HIV-1 RNA >100,000 copies/mL)

The OF approach will be used to handle missing values in these subgroup analyses. Nominal 2-sided 95% CIs will be calculated for variables with a sufficient number of participants in each treatment group. No stratification will be used in these analyses.

## 10.11 Compliance (Medication Adherence)

Study Medication Diary Cards will be used to ensure and document drug compliance. Participants are to take 1 pill QD from each container of study medication. A day within the trial will be considered an "On-Therapy" day if the participant takes the required number of tablets from all containers provided for this trial (as noted in Section 7.5.1).

For a participant who is followed for the entire trial period, the "Number of Days Should be on Therapy" is the total number of days from Day 1 to the last scheduled day for treatment

administration for that participant. For a participant who discontinued from the trial permanently, the "Number of Days Should be on Therapy" is the total number of days from Day 1 to the date of the last dose of study medication.

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

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

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

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

### 10.12 Extent of Exposure

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

## 11. References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# 12. Appendices

## 12.1 Appendix 1: Abbreviations and Trademarks

| Abbreviation | Definition |
|---|---|
| 3TC | lamivudine |
| AE | adverse event |
| AIDS | acquired immune deficiency syndrome |
| ALT | alanine aminotransferase |
| APaT | All Participants as Treated |
| ART | anti-retroviral therapy |
| AST | aspartate aminotransferase |
| BMD | bone mineral density |
| $C_{24}$ | concentration after 24 hours |
| CD4+ | CD4-positive |
| CI | confidence interval |
| $Cl_{cr}$ | creatinine clearance |
| CONSORT | Consolidated Standards of Reporting Trials |
| CRF | case report form |
| CSR | clinical study report |
| $C_{trough}$ | lowest concentration reached by a drug before the next dose is administered |
| CYP | cytochrome P450 |
| DAIDS | Division of Acquired Immunodeficiency Syndrome |
| DDI | drug-drug interaction |
| DEXA | dual-energy x-ray absorptiometry |
| DMC | Data Monitoring Committee |
| DOR | doravirine (MK-1439) |
| DRV | darunavir |
| ECG | electrocardiogram |
| ECI | event of clinical interest |
| eCRF | electronic case report form |
| eDMC | external Data Monitoring Committee |
| EFV | Efavirenz |
| eGFR | estimated glomerular filtration rate |
| EOC | Executive Oversight Committee |
| FAS | Full Analysis Set |
| FBR | Future Biomedical Research |
| FDC | fixed-dose combination |
| FSH | follicle-stimulating hormone |

| Abbreviation | Definition |
|---|---|
| FTC | emtricitabine |
| HBsAg | hepatitis B surface antigen |
| HBV | hepatitis B virus |
| HCV | hepatitis C virus |
| HIV-1 | human immunodeficiency virus type 1 |
| HRT | hormonal replacement therapy |
| IB | Investigator's Brochure |
| $IC_{50}$ | half-maximal inhibitory concentration |
| ICF | informed consent form |
| IEC | Independent Ethics Committee |
| IL-6 | interleukin-6 |
| InSTI | integrase strand transfer inhibitor |
| IQ | inhibitory quotient |
| IRB | Institutional Review Board |
| IVRS/IWRS | Interactive Voice/Web Response System |
| MK-1439 | doravirine |
| MK-1439A | doravirine + lamivudine + tenofovir disoproxil fumarate |
| NC=F | Non Completer=Failure |
| NNRTI | non-nucleoside reverse transcriptase inhibitor |
| NRTI | nucleoside reverse transcriptase inhibitors |
| NRTTI | nucleoside reverse transcriptase translocation inhibitor |
| OF | observed failure |
| PBMC | peripheral blood mononuclear cell |
| PCR | polymerase chain reaction |
| PDLC | pre-defined limit of change |
| PDVF | protocol-defined virologic failure |
| PI | protease inhibitor |
| PK | pharmacokinetic |
| QD | once daily |
| r | ritonavir |
| RNA | ribonucleic acid |
| RT | reverse transcriptase |
| SAE | serious adverse event |
| SoA | Schedule of Activities |
| sSAP | supplemental statistical analysis plan |
| TAF | tenofovir alafenamide |
| TDF | tenofovir disoproxil fumarate |

| Abbreviation | Definition |
|---|---|
| TLOVR | time to loss of virologic response |
| TP | triphosphate |
| ULN | upper limit of normal |
| WOCBP | woman of childbearing potential |

## 12.2 Appendix 2: Clinical Laboratory Tests

- Clinical laboratory tests detailed in Table 14 will be performed by a central laboratory.
- Local laboratory results are only required when central laboratory results are not available in time for either study treatment administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if local laboratory results are used to make either a study treatment decision or response evaluation, the results must be entered into the case report form (CRF).
- The investigator must document his/her review of each laboratory safety report.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Clinical laboratory test results will be graded according to criteria adapted from the DAIDS Laboratory Tables for Grading the Severity of Adult and Pediatric Adverse Events, Publish Date: November 2014 Version 2 (Appendix 2A).

Table 14 Protocol-Required Laboratory Assessments and Approximate Blood Draw Volumes

| Laboratory Assessments | Parameters | Approximate Blood Volume (mL) |
|---|---|---|
| Pregnancy | Serum β-human chorionic gonadotropin (hCG) test | 2 |
| | Urine β-human chorionic gonadotropin (hCG) test | Not applicable |
| Hematology | Hematocrit | 4 |
| | Hemoglobin | |
| | Platelet count | |
| | Red blood cell count | |
| | Mean corpuscular volume | |
| | Mean corpuscular hemoglobin | |
| | Mean corpuscular hemoglobin concentration | |
| | Red cell distribution width | |
| | White blood cell count (total and differential)<br>Neutrophils<br>Lymphocytes<br>Monocytes<br>Eosinophils<br>Basophils | |
| | CD4% and absolute CD4/lymphocytes | 2 |
| | CD8% and absolute CD8/lymphocytes | |
| | CD4/CD8 ratio | |

| Laboratory Assessments | Parameters | Approximate Blood Volume (mL) |
|---|---|---|
| Chemistry (non-fasting) | Aspartate aminotransferase (AST) | 8.5 |
| | Alanine aminotransferase (ALT) | |
| | Alkaline phosphatase | |
| | Creatine kinase | |
| | Total bilirubin | |
| | Direct bilirubin | |
| | Indirect bilirubin | |
| | Amylase | |
| | Lipase | |
| | Blood urea nitrogen | |
| | Creatinine | |
| | Calcium | |
| | Phosphorus | |
| | Magnesium | |
| | Protein | |
| | Albumin | |
| | Sodium | |
| | Potassium | |
| | Chloride | |
| | Bicarbonate | |
| | Glucose, non-fasting | |
| Chemistry (fasting for at least 8 h) | Glucose, fasting | 8.5 |
| | High-density lipoprotein cholesterol (HDL) | |
| | Low-density lipoprotein cholesterol (LDL-C) | |
| | Triglycerides | |
| | Total cholesterol | |
| Urinalysis | Specific gravity | Not Applicable |
| | pH | |
| | Glucose | |
| | Protein | |
| | Blood | |
| | Ketones | |
| | Bilirubin | |
| | Urobilinogen | |
| | Nitrite | |
| | Leukocytes | |
| | Erythrocytes | |
| Urinary analytes | Albumin<br>Protein<br>Beta-2-microglobulin/creatinine ratio (B-2M/Cr) | Not Applicable |
| | Retinol binding protein/creatinine ratio (RBP/Cr) | |
| Renal function | Estimated glomerular filtration rate (eGFR) by MDRD equation | Not Applicable |
| Hemostatic function | Prothrombin test (PT) | 4.5 |
| | Activated partial thromboplastin time (APTT) | |
| | International normalized ratio (INR) | |

| Laboratory Assessments | Parameters | Approximate Blood Volume (mL) |
|---|---|---|
| Hepatitis screen (Screening) | Hepatitis B virus surface antigen<br>Hepatitis B virus surface antibody<br>Hepatitis C antibody (if positive perform plasma hepatitis C virus PCR quantitative test) | 5 |
| Hepatitis screen (Post randomization) | Hepatitis B virus surface antigen<br>Hepatitis C antibody (if positive perform plasma hepatitis C virus PCR quantitative test) | 5 |
| HIV-1 Screen | Enzyme immunoassay HIV-1 antibody | 5 |
| Virology | HIV-1 viral RNA quantification (real time PCR) | 5 |
| | HIV-1 viral resistance | 15 |
| | HIV-1 RNA single-copy assay | 20 |
| PK and inflammatory markers | MK-8591 PK | 4 |
| | D-dimer | 2 |
| | IL-6 | 2 |
| | Soluble CD163 | 2 |
| Blood for Genetic Analysis | | 8.5 |
| Blood (plasma) for repeat HIV-1 viral resistance or PK | | 4 |
| CD=cluster of differentiation; HIV-1=human immunodeficiency virus type 1; IL-6=interleukin-6; MDRD=Modification of Diet in Renal Disease; PCR=polymerase chain reaction; PK=pharmacokinetics; RNA=ribonucleic acid; U=unscheduled. | | |

## 12.2 Appendix 2A: Division of AIDS (DAIDS) Tables for Grading the Severity of Adult and Pediatric Adverse Events

*Laboratory Values**
Chemistries

| PARAMETER | GRADE 1 MILD | GRADE 2 MODERATE | GRADE 3 SEVERE | GRADE 4 POTENTIALLY LIFE-THREATENING |
|---|---|---|---|---|
| **Acidosis** | NA | pH ≥ 7.3 to < LLN | pH < 7.3 without life-threatening consequences | pH < 7.3 with life-threatening consequences |
| **Albumin, Low** (g/dL; *g/L*) | 3.0 to < LLN<br>*30 to < LLN* | ≥ 2.0 to < 3.0<br>*≥ 20 to < 30* | < 2.0<br>*< 20* | NA |
| **Alkaline Phosphatase, High** | 1.25 to < 2.5 x ULN | 2.5 to < 5.0 x ULN | 5.0 to < 10.0 x ULN | ≥ 10.0 x ULN |
| **Alkalosis** | NA | pH > ULN to ≤ 7.5 | pH > 7.5 without life-threatening consequences | pH > 7.5 with life-threatening consequences |
| **ALT or SGPT, High** *Report only one* | 1.25 to < 2.5 x ULN | 2.5 to < 5.0 x ULN | 5.0 to < 10.0 x ULN | ≥ 10.0 x ULN |
| **Amylase (Pancreatic) or Amylase (Total), High** *Report only one* | 1.1 to < 1.5 x ULN | 1.5 to < 3.0 x ULN | 3.0 to < 5.0 x ULN | ≥ 5.0 x ULN |
| **AST or SGOT, High** *Report only one* | 1.25 to < 2.5 x ULN | 2.5 to < 5.0 x ULN | 5.0 to < 10.0 x ULN | ≥ 10.0 x ULN |
| **Bicarbonate, Low** (mEq/L; *mmol/L*) | 16.0 to < LLN<br>*16.0 to < LLN* | 11.0 to < 16.0<br>*11.0 to < 16.0* | 8.0 to < 11.0<br>*8.0 to < 11.0* | < 8.0<br>*< 8.0* |
| **Bilirubin** ***Direct Bilirubin[13], High*** *> 28 days of age* | NA | NA | > ULN with other signs and symptoms of hepatotoxicity. | > ULN with life-threatening consequences (e.g., signs and symptoms of liver failure) |
| *≤ 28 days of age* | ULN to ≤ 1 mg/dL | > 1 to ≤ 1.5 mg/dL | > 1.5 to ≤ 2 mg/dL | > 2 mg/dL |
| ***Total Bilirubin, High*** *> 28 days of age* | 1.1 to < 1.6 x ULN | 1.6 to < 2.6 x ULN | 2.6 to < 5.0 x ULN | ≥ 5.0 x ULN |
| *≤ 28 days of age* | See Appendix A. Total Bilirubin for Term and Preterm Neonates | See Appendix A. Total Bilirubin for Term and Preterm Neonates | See Appendix A. Total Bilirubin for Term and Preterm Neonates | See Appendix A. Total Bilirubin for Term and Preterm Neonates |

*Reminder: An asymptomatic abnormal laboratory finding without an accompanying AE should not be reported to DAIDS in an expedited time frame unless it meets protocol-specific reporting requirements.

[13] Direct bilirubin > 1.5 mg/dL in a participant < 28 days of age should be graded as grade 2, if < 10% of the total bilirubin.

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## Chemistries

| PARAMETER | GRADE 1 MILD | GRADE 2 MODERATE | GRADE 3 SEVERE | GRADE 4 POTENTIALLY LIFE-THREATENING |
|---|---|---|---|---|
| **Calcium, High** (mg/dL; *mmol/L*) | | | | |
| *≥ 7 days of age* | 10.6 to < 11.5<br>*2.65 to < 2.88* | 11.5 to < 12.5<br>*2.88 to < 3.13* | 12.5 to < 13.5<br>*3.13 to < 3.38* | ≥ 13.5<br>*≥ 3.38* |
| *< 7 days of age* | 11.5 to < 12.4<br>*2.88 to < 3.10* | 12.4 to < 12.9<br>*3.10 to < 3.23* | 12.9 to < 13.5<br>*3.23 to < 3.38* | ≥ 13.5<br>*≥ 3.38* |
| **Calcium (Ionized), High** (mg/dL; *mmol/L*) | > ULN to < 6.0<br>*> ULN to < 1.5* | 6.0 to < 6.4<br>*1.5 to < 1.6* | 6.4 to < 7.2<br>*1.6 to < 1.8* | ≥ 7.2<br>*≥ 1.8* |
| **Calcium, Low** (mg/dL; *mmol/L*) | | | | |
| *≥ 7 days of age* | 7.8 to < 8.4<br>*1.95 to < 2.10* | 7.0 to < 7.8<br>*1.75 to < 1.95* | 6.1 to < 7.0<br>*1.53 to < 1.75* | < 6.1<br>*< 1.53* |
| *< 7 days of age* | 6.5 to < 7.5<br>*1.63 to < 1.88* | 6.0 to < 6.5<br>*1.50 to < 1.63* | 5.50 to < 6.0<br>*1.38 to < 1.50* | < 5.50<br>*< 1.38* |
| **Calcium (Ionized), Low** (mg/dL; *mmol/L*) | < LLN to 4.0<br>*< LLN to 1.0* | 3.6 to < 4.0<br>*0.9 to < 1.0* | 3.2 to < 3.6<br>*0.8 to < 0.9* | < 3.2<br>*< 0.8* |
| **Cardiac Troponin I, High** | NA | NA | NA | Levels consistent with myocardial infarction or unstable angina as defined by the local laboratory |
| **Creatine Kinase, High** | 3 to < 6 x ULN | 6 to < 10x ULN | 10 to < 20 x ULN | ≥ 20 x ULN |
| **Creatinine, High**<br>**Report only one* | 1.1 to 1.3 x ULN | > 1.3 to 1.8 x ULN OR Increase to 1.3 to < 1.5 x participant's baseline | > 1.8 to < 3.5 x ULN OR Increase to 1.5 to < 2.0 x participant's baseline | ≥ 3.5 x ULN OR Increase of ≥ 2.0 x participant's baseline |
| **Creatinine Clearance**[14] **or eGFR, Low**<br>**Report only one* | NA | < 90 to 60 ml/min or ml/min/1.73 m$^2$ OR 10 to < 30% decrease from participant's baseline | < 60 to 30 ml/min or ml/min/1.73 m$^2$ OR 30 to < 50% decrease from participant's baseline | < 30 ml/min or ml/min/1.73 m$^2$ OR ≥ 50% decrease from participant's baseline or dialysis needed |
| **Glucose** (mg/dL; *mmol/L*) | | | | |
| ***Fasting, High*** | 110 to 125<br>*6.11 to < 6.95* | > 125 to 250<br>*6.95 to < 13.89* | > 250 to 500<br>*13.89 to < 27.75* | ≥ 500<br>*≥ 27.75* |
| ***Nonfasting, High*** | 116 to 160<br>*6.44 to < 8.89* | > 160 to 250<br>*8.89 to < 13.89* | > 250 to 500<br>*13.89 to < 27.75* | ≥ 500<br>*≥ 27.75* |

[14] Use the applicable formula (i.e., Cockcroft-Gault in mL/min or Schwartz, MDRD, CKD-Epi in mL/min/1.73m2). Sites should choose the method defined in their study and when not specified, use the method most relevant to the study population.

*Reminder: Choose the method that selects for the higher grade.

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## Chemistries

| PARAMETER | GRADE 1 MILD | GRADE 2 MODERATE | GRADE 3 SEVERE | GRADE 4 POTENTIALLY LIFE-THREATENING |
|---|---|---|---|---|
| **Glucose, Low** (mg/dL; *mmol/L*) | | | | |
| *≥ 1 month of age* | 55 to 64<br>*3.05 to <3.55* | 40 to < 55<br>*2.22 to < 3.05* | 30 to < 40<br>*1.67 to < 2.22* | < 30<br>*< 1.67* |
| *< 1 month of age* | 50 to 54<br>*2.78 to < 3.00* | 40 to < 50<br>*2.22 to < 2.78* | 30 to < 40<br>*1.67 to < 2.22* | < 30<br>*< 1.67* |
| **Lactate, High** | ULN to < 2.0 x ULN without acidosis | ≥ 2.0 x ULN without acidosis | Increased lactate with pH < 7.3 without life-threatening consequences | Increased lactate with pH < 7.3 with life-threatening consequences |
| **Lipase, High** | 1.1 to < 1.5 x ULN | 1.5 to < 3.0 x ULN | 3.0 to < 5.0 x ULN | ≥ 5.0 x ULN |
| **Lipid Disorders** (mg/dL; *mmol/L*) | | | | |
| ***Cholesterol, Fasting, High*** *≥ 18 years of age* | 200 to < 240<br>*5.18 to < 6.19* | 240 to < 300<br>*6.19 to < 7.77* | ≥ 300<br>*≥ 7.77* | NA |
| *< 18 years of age* | 170 to < 200<br>*4.40 to < 5.15* | 200 to < 300<br>*5.15 to < 7.77* | ≥ 300<br>*≥ 7.77* | NA |
| ***LDL, Fasting, High*** *≥ 18 years of age* | 130 to < 160<br>*3.37 to < 4.12* | 160 to < 190<br>*4.12 to < 4.90* | ≥ 190<br>*≥ 4.90* | NA |
| *> 2 to < 18 years of age* | 110 to < 130<br>*2.85 to < 3.34* | 130 to < 190<br>*3.34 to < 4.90* | ≥ 190<br>*≥ 4.90* | NA |
| ***Triglycerides, Fasting, High*** | 150 to 300<br>*1.71 to 3.42* | >300 to 500<br>*>3.42 to 5.7* | >500 to < 1,000<br>*>5.7 to 11.4* | > 1,000<br>*> 11.4* |
| **Magnesium[15], Low** (mEq/L; *mmol/L*) | 1.2 to < 1.4<br>*0.60 to < 0.70* | 0.9 to < 1.2<br>*0.45 to < 0.60* | 0.6 to < 0.9<br>*0.30 to < 0.45* | < 0.6<br>*< 0.30* |
| **Phosphate, Low** (mg/dL; *mmol/L*) | | | | |
| *> 14 years of age* | 2.0 to < LLN<br>*0.65 to < LLN* | 1.4 to < 2.0<br>*0.45 to < 0.65* | 1.0 to < 1.4<br>*0.32 to < 0.45* | < 1.0<br>*< 0.32* |
| *1 to 14 years of age* | 3.0 to < 3.5<br>*0.97 to < 1.13* | 2.5 to < 3.0<br>*0.81 to < 0.97* | 1.5 to < 2.5<br>*0.48 to < 0.81* | < 1.5<br>*< 0.48* |
| *< 1 year of age* | 3.5 to < 4.5<br>*1.13 to < 1.45* | 2.5 to < 3.5<br>*0.81 to < 1.13* | 1.5 to < 2.5<br>*0.48 to < 0.81* | < 1.5<br>*< 0.48* |
| **Potassium, High** (mEq/L; *mmol/L*) | 5.6 to < 6.0<br>*5.6 to < 6.0* | 6.0 to < 6.5<br>*6.0 to < 6.5* | 6.5 to < 7.0<br>*6.5 to < 7.0* | ≥ 7.0<br>*≥ 7.0* |
| **Potassium, Low** (mEq/L; *mmol/L*) | 3.0 to < 3.4<br>*3.0 to < 3.4* | 2.5 to < 3.0<br>*2.5 to < 3.0* | 2.0 to < 2.5<br>*2.0 to < 2.5* | < 2.0<br>*< 2.0* |

[15] To convert a magnesium value from mg/dL to mmol/L, laboratories should multiply by 0.4114.

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## Chemistries

| PARAMETER | GRADE 1 MILD | GRADE 2 MODERATE | GRADE 3 SEVERE | GRADE 4 POTENTIALLY LIFE-THREATENING |
|---|---|---|---|---|
| **Sodium, High** (mEq/L; *mmol/L*) | 146 to < 150<br>*146 to < 150* | 150 to < 154<br>*150 to < 154* | 154 to < 160<br>*154 to < 160* | ≥ 160<br>*≥ 160* |
| **Sodium, Low** (mEq/L; *mmol/L*) | 130 to < 135<br>*130 to < 135* | 125 to < 130<br>*125 to < 130* | 121 to < 125<br>*121 to < 125* | ≤ 120<br>*≤ 120* |
| **Uric Acid, High** (mg/dL; *mmol/L*) | 7.5 to < 10.0<br>*0.45 to < 0.59* | 10.0 to < 12.0<br>*0.59 to < 0.71* | 12.0 to < 15.0<br>*0.71 to < 0.89* | ≥ 15.0<br>*≥ 0.89* |

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## Hematology

| PARAMETER | GRADE 1 MILD | GRADE 2 MODERATE | GRADE 3 SEVERE | GRADE 4 POTENTIALLY LIFE-THREATENING |
|---|---|---|---|---|
| **Absolute CD4+ Count, Low** (cell/mm$^3$; *cells/L*) | | | | |
| *> 5 years of age (not HIV infected)* | 300 to < 400<br>*300 to < 400* | 200 to < 300<br>*200 to < 300* | 100 to < 200<br>*100 to < 200* | < 100<br>*< 100* |
| **Absolute Lymphocyte Count, Low** (cell/mm$^3$; *cells/L*) | | | | |
| *> 5 years of age (not HIV infected)* | 600 to < 650<br>*0.600 x $10^9$ to < 0.650 x $10^9$* | 500 to < 600<br>*0.500 x $10^9$ to < 0.600 x $10^9$* | 350 to < 500<br>*0.350 x $10^9$ to < 0.500 x $10^9$* | < 350<br>*< 0.350 x $10^9$* |
| **Absolute Neutrophil Count (ANC), Low** (cells/mm$^3$; *cells/L*) | | | | |
| *> 7 days of age* | 800 to 1,000<br>*0.800 x $10^9$ to 1.000 x $10^9$* | 600 to 799<br>*0.600 x $10^9$ to 0.799 x $10^9$* | 400 to 599<br>*0.400 x $10^9$ to 0.599 x $10^9$* | < 400<br>*< 0.400 x $10^9$* |
| *2 to 7 days of age* | 1,250 to 1,500<br>*1.250 x $10^9$ to 1.500 x $10^9$* | 1,000 to 1,249<br>*1.000 x $10^9$ to 1.249 x $10^9$* | 750 to 999<br>*0.750 x $10^9$ to 0.999 x $10^9$* | < 750<br>*< 0.750 x $10^9$* |
| *≤ 1 day of age* | 4,000 to 5,000<br>*4.000 x $10^9$ to 5.000 x $10^9$* | 3,000 to 3,999<br>*3.000 x $10^9$ to 3.999 x $10^9$* | 1,500 to 2,999<br>*1.500 x $10^9$ to 2.999 x $10^9$* | < 1,500<br>*< 1.500 x $10^9$* |
| **Fibrinogen, Decreased** (mg/dL; *g/L*) | 100 to < 200<br>*1.00 to < 2.00*<br>OR<br>0.75 to < 1.00<br>x LLN | 75 to < 100<br>*0.75 to < 1.00*<br>OR<br>≥ 0.50 to < 0.75<br>x LLN | 50 to < 75<br>*0.50 to < 0.75*<br>OR<br>0.25 to < 0.50<br>x LLN | < 50<br>*< 0.50*<br>OR<br>< 0.25 x LLN<br>OR Associated with gross bleeding |
| **Hemoglobin[16], Low** (g/dL; *mmol/L*)[17] | | | | |
| *≥ 13 years of age (male only)* | 10.0 to 10.9<br>*6.19 to 6.76* | 9.0 to < 10.0<br>*5.57 to < 6.19* | 7.0 to < 9.0<br>*4.34 to < 5.57* | < 7.0<br>*< 4.34* |
| *≥ 13 years of age (female only)* | 9.5 to 10.4<br>*5.88 to 6.48* | 8.5 to < 9.5<br>*5.25 to < 5.88* | 6.5 to < 8.5<br>*4.03 to < 5.25* | < 6.5<br>*< 4.03* |

[16] Male and female sex are defined as sex at birth. For transgender participants ≥13 years of age who have been on hormone therapy for more than 6 consecutive months, grade hemoglobin based on the gender with which they identify (i.e., a transgender female should be graded using the female sex at birth hemoglobin laboratory values).

[17] The most commonly used conversion factor to convert g/dL to mmol/L is 0.6206. For grading hemoglobin results obtained by an analytic method with a conversion factor other than 0.6206, the result must be converted to g/dL using appropriate conversion factor for the particular laboratory.

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## Hematology

| PARAMETER | GRADE 1 MILD | GRADE 2 MODERATE | GRADE 3 SEVERE | GRADE 4 POTENTIALLY LIFE-THREATENING |
|---|---|---|---|---|
| *57 days of age to < 13 years of age (male and female)* | 9.5 to 10.4<br>*5.88 to 6.48* | 8.5 to < 9.5<br>*5.25 to < 5.88* | 6.5 to < 8.5<br>*4.03 to < 5.25* | < 6.5<br>*< 4.03* |
| *36 to 56 days of age (male and female)* | 8.5 to 9.6<br>*5.26 to 5.99* | 7.0 to < 8.5<br>*4.32 to < 5.26* | 6.0 to < 7.0<br>*3.72 to < 4.32* | < 6.0<br>*< 3.72* |
| *22 to 35 days of age (male and female)* | 9.5 to 11.0<br>*5.88 to 6.86* | 8.0 to < 9.5<br>*4.94 to < 5.88* | 6.7 to < 8.0<br>*4.15 to < 4.94* | < 6.7<br>*< 4.15* |
| *8 to ≤ 21 days of age (male and female)* | 11.0 to 13.0<br>*6.81 to 8.10* | 9.0 to < 11.0<br>*5.57 to < 6.81* | 8.0 to < 9.0<br>*4.96 to < 5.57* | < 8.0<br>*< 4.96* |
| *≤ 7 days of age (male and female)* | 13.0 to 14.0<br>*8.05 to 8.72* | 10.0 to < 13.0<br>*6.19 to < 8.05* | 9.0 to < 10.0<br>*5.59 to < 6.19* | < 9.0<br>*< 5.59* |
| **INR, High** (not on anticoagulation therapy) | 1.1 to < 1.5 x ULN | 1.5 to < 2.0 x ULN | 2.0 to < 3.0 x ULN | ≥ 3.0 x ULN |
| **Methemoglobin** (% hemoglobin) | 5.0 to < 10.0% | 10.0 to < 15.0% | 15.0 to < 20.0% | ≥ 20.0% |
| **PTT, High** (not on anticoagulation therapy) | 1.1 to < 1.66 x ULN | 1.66 to < 2.33 x ULN | 2.33 to < 3.00 x ULN | ≥ 3.00 x ULN |
| **Platelets, Decreased** (cells/mm$^3$; *cells/L*) | 100,000 to < 125,000<br>*100.000 x $10^9$ to < 125.000 x $10^9$* | 50,000 to < 100,000<br>*50.000 x $10^9$ to < 100.000 x $10^9$* | 25,000 to < 50,000<br>*25.000 x $10^9$ to < 50.000 x $10^9$* | < 25,000<br>*< 25.000 x $10^9$* |
| **PT, High** (not on anticoagulation therapy | 1.1 to < 1.25 x ULN | 1.25 to < 1.50 x ULN | 1.50 to < 3.00 x ULN | ≥ 3.00 x ULN |
| **WBC, Decreased** (cells/mm$^3$; *cells/L*) | | | | |
| *> 7 days of age* | 2,000 to 2,499<br>*2.000 x $10^9$ to 2.499 x $10^9$* | 1,500 to 1,999<br>*1.500 x $10^9$ to 1.999 x $10^9$* | 1,000 to 1,499<br>*1.000 x $10^9$ to 1.499 x $10^9$* | < 1,000<br>*< 1.000 x $10^9$* |
| *≤ 7 days of age* | 5,500 to 6,999<br>*5.500 x $10^9$ to 6.999 x $10^9$* | 4,000 to 5,499<br>*4.000 x $10^9$ to 5.499 x $10^9$* | 2,500 to 3,999<br>*2.500 x $10^9$ to 3.999 x $10^9$* | < 2,500<br>*< 2.500 x $10^9$* |

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## Urinalysis

| PARAMETER | GRADE 1 MILD | GRADE 2 MODERATE | GRADE 3 SEVERE | GRADE 4 POTENTIALLY LIFE-THREATENING |
|---|---|---|---|---|
| **Glycosuria** (random collection tested by dipstick) | Trace to 1+ or ≤ 250 mg | 2+ or > 250 to ≤ 500 mg | > 2+ or > 500 mg | NA |
| **Hematuria** (not to be reported based on dipstick findings or on blood believed to be of menstrual origin) | 6 to < 10 RBCs per high power field | ≥ 10 RBCs per high power field | Gross, with or without clots OR With RBC casts OR Intervention indicated | Life-threatening consequences |
| **Proteinuria** (random collection tested by dipstick) | 1+ | 2+ | 3+ or higher | NA |

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Source: [National Institute of Allergy and Infectious Diseases 2017]

## 12.3 Appendix 3: Study Governance Considerations

## 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 participant 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 (eg, 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 participant preferences, etc.

The design (ie, participant population, duration, statistical power) must be adequate to address the specific purpose of the trial. Research participants 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 participants, 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. Participant Protection**

**A. IRB/IEC review**

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

**B. Safety**

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

All participation in Merck clinical trials is voluntary. Participants are enrolled only after providing informed consent for participation. Participants 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 participant 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 participant 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 participants in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

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

**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/IEC 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 (eg, 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."

**Financial Disclosure**

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. 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.

**Data Protection**

Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

**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/IEC) 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.

**Confidentiality of Participant Records**

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, 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 participant agrees to this process. If trial documents will be photocopied during the process of verifying worksheet/case report form information, the participant 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 participant data used and disclosed in connection with this trial in accordance with all applicable privacy laws, rules and regulations.

**Confidentiality of IRB/IEC Information**

The Sponsor is required to record the name and address of each IRB/IEC 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.

**Committees Structure**

**Executive Oversight Committee**

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

**Data Monitoring Committee**

To supplement the routine trial monitoring outlined in this protocol, an external Data Monitoring Committee (DMC) will monitor the interim data from this trial. The voting members of the committee are external to the Sponsor. The members of the DMC must not be involved with the trial in any other way (eg, they cannot be trial investigators) and must have no competing interests that could affect their roles with respect to the trial.

The DMC will make recommendations to the EOC regarding steps to ensure both participant safety and the continued ethical integrity of the trial. Also, the DMC will review interim trial results, consider the overall risk and benefit to trial participants (see Section 10.7 - Interim Analyses) and recommend to the EOC if the trial should continue in accordance with the protocol.

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

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

**Publication Policy**

The results of this study may be published or presented at scientific meetings. The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

If publication activity is not directed by the sponsor, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

**Compliance with Trial Registration and Results Posting Requirements**

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

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

**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 (eg, 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 this appendix under the Merck Code of Conduct for Clinical Trials.

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

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

The Investigator agrees to provide the Sponsor with relevant information from inspection observations/findings to allow the Sponsor to assist in responding to any citations resulting from regulatory authority inspection, and will provide the Sponsor with a copy of the proposed response for consultation before submission to the regulatory authority.

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.

**Data Quality Assurance**

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

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

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

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 or regulatory authority as a result of an audit or inspection to cure deficiencies in the trial documentation and worksheets/case report forms.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

### Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

### Study and Site Closure

The sponsor or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

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

## 12.4 Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

**Definition of AE**

| **AE Definition** |
|---|
| • An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment.<br>• NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study treatment.<br>• NOTE: for purposes of AE definition, study treatment (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, device, diagnostic agent or protocol specified procedure whether investigational (including placebo or active comparator product) or marketed, manufactured by, licensed by, provided by or distributed by the sponsor for human use in this study. |

| **Events <u>Meeting</u> the AE Definition** |
|---|
| • Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.<br>• Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.<br>• New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.<br>• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.<br>• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication.<br>• For all reports of overdose (whether accidental or intentional) with an associated adverse event, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."<br>• Any new cancer or progression of existing cancer. |

| **Events NOT Meeting the AE Definition** |
|---|
| ● Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.<br>● Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).<br>● Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.<br>● Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened.<br>● Refer to section 9.3.5 for protocol specific exceptions |

**Definition of SAE**

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met

| **A SAE is defined as any untoward medical occurrence that, at any dose:** |
|---|
| **a. Results in death** |
| **b. Is life-threatening**<br>● The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe. |
| **c. Requires inpatient hospitalization or prolongation of existing hospitalization**<br>● 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. |
| **d. Results in persistent or significant disability/incapacity**<br>● The term disability means a substantial disruption of a person's ability to conduct normal life functions.<br>● This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption. |

**e. Is a congenital anomaly/birth defect**

- in offspring of participant taking the product regardless of time to diagnosis

**f. Other important medical events:**

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

**Additional Events reported**

**Additional Events which require reporting**

- In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor.
  - Is a cancer;
  - Is associated with an overdose.

**Recording AE and SAE**

**AE and SAE Recording**

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the Adverse Event case report forms/worksheets at each examination.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

**Assessment of Intensity**

- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.
- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) reported during the study and assign it to 1 of the following categories:
  - Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities. (for pediatric trials, awareness of symptoms, but easily tolerated)
  - Moderate: An event that causes sufficiently discomfort and interferes with normal everyday activities. (for pediatric trials, definitely acting like something is wrong)
  - Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe (for pediatric trials, extremely distressed or unable to do usual activities).

**Assessment of Causality**

- 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 product and the adverse event based upon the available information
  - **The following components are to be used to assess the relationship between the Sponsor's product and the AE;** the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the adverse event:
    - **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
    - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
    - **Likely Cause:** Is the AE not reasonably explained by another etiology such as

underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

- **Dechallenge:** Was the Sponsor's product discontinued or dose/exposure/frequency reduced?
  - If yes, did the AE resolve or improve?
    - If yes, this is a positive dechallenge.
  - If no, this is a negative dechallenge.

  (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
- **Rechallenge:** Was the participant re-exposed to the Sponsor's product in this trial?
  - If yes, did the AE recur or worsen?
    - If yes, this is a positive rechallenge.
  - If no, this is a negative rechallenge.

  (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR, AND IF REQUIRED, THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.

- **Consistency with Study 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.
- 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: Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)

- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements

**Follow-up of AE and SAE**

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the CRF.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

## Reporting of AE, SAE, and Other Reportable Safety Events to the Sponsor

**AE, SAE, and Other Reportable Safety Event Reporting to Sponsor via Electronic Data Collection Tool**

- The primary mechanism for reporting to the Sponsor will be the electronic data collection (EDC) tool.
  - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
  - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
    - Reference section 9.3.1 – Time Period and Frequency for Collecting AE and SAE and Other Reportable Safety Event Information for reporting time requirements

- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Trial File Binder (or equivalent).

**SAE Reporting to the Sponsor via Paper CRF**

- If the electronic data collection tool is not operational, facsimile transmission or secure e-mail of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

## 12.5 Appendix 5: Contraceptive Guidance and Pregnancy Testing

### Definitions

### Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below)

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

### Contraception Requirements

### Female Participants

Female participants of childbearing potential are eligible to participate if they agree to use one of the contraception methods described in Table 15 consistently and correctly during the protocol-defined time frame in Section 6.1.

Table 15 Contraceptive Methods

| |
|---|
| **Acceptable Contraceptive Methods**<br>*Failure rate of >1% per year when used consistently and correctly.* |
| • Male or female condom with or without spermicide<br>• Cervical cap, diaphragm or sponge with spermicide |
| **Highly Effective Contraceptive Methods That Are User Dependent[a]**<br>*Failure rate of <1% per year when used consistently and correctly.* |
| • Combined (estrogen- and progestogen-containing ) hormonal contraception[b,c]<br>○ Oral<br>○ Intravaginal<br>○ Transdermal<br>○ Injectable |
| • Progestogen-only hormonal contraception[b,c]<br>○ Oral<br>○ Injectable |
| **Highly Effective Methods That Have Low User Dependency**<br>*Failure rate of <1% per year when used consistently and correctly.* |
| • Progestogen-only contraceptive implant[b,c]<br>• Intrauterine hormone-releasing system (IUS)[b]<br>• Intrauterine device (IUD)<br>• Bilateral tubal occlusion |
| • Vasectomized partner<br>A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. |
| • Sexual abstinence<br>Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.) |
| Notes:<br>Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies.<br>[a] Typical use failure rates are higher than perfect-use failure rates (i.e., when used consistently and correctly).<br>[b] If hormonal contraception efficacy is potentially decreased due to interaction with study treatment, condoms must be used in addition to the hormonal contraception during the treatment period and for at least 6 weeks after the last dose of study treatment.<br>[c] If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation. |

### Pregnancy Testing

Women of childbearing potential should only be included after a negative highly sensitive urine or serum pregnancy test.

Pregnancy testing will be performed whenever an expected menstrual cycle is missed or when **pregnancy** is otherwise suspected.

## 12.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research

### 1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

### 2. Scope of Future Biomedical Research

The specimens consented and/or collected in this trial as outlined in Section 9.8 – Future Biomedical Research Samples will be used in various experiments to understand:

- The biology of how drugs/vaccines work
- Biomarkers responsible for how a drug/vaccine enters and is removed by the body
- Other pathways drugs/vaccines may interact with
- The biology 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 the Sponsor or those working for or with the Sponsor.

### 3. Summary of Procedures for Future Biomedical Research

a. Participants for Enrollment

All participants enrolled in the clinical trial will be considered for enrollment in Future Biomedical Research.

b. Informed Consent

Informed consent for specimens (i.e., DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all participants 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 participants on the visit designated in the trial flow chart. If delayed, present consent at next possible Participant Visit.

Consent forms signed by the participant will be kept at the clinical trial site under secure storage for regulatory reasons.

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

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of participant consent for Future Biomedical Research will be captured in the electronic Case Report Forms (eCRFs). Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen(s)

Collection of specimens for Future Biomedical Research will be performed as outlined in the trial flow chart. In general, if additional blood specimens are being collected for Future Biomedical Research, these will usually be obtained at a time when the participant is having blood drawn for other trial purposes.

**4. Confidential Participant 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 participant' 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 participant 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, the Sponsor has developed secure policies and procedures. All specimens will be single-coded per ICH E15 guidelines as described below.

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

**5. Biorepository Specimen Usage**

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses utilizing the Future Biomedical Research specimens may be performed by the Sponsor, or an additional third party (eg, a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third party analyses will conform to the specific scope of analysis outlined in future biomedical research protocol and consent. Future biomedical research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

**6. Withdrawal From Future Biomedical Research**

Participants may withdraw their consent for Future Biomedical Research and ask that their biospecimens not be used for Future Biomedical Research. Participants 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). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to main study use only. If specimens were collected from study participants specifically for Future Biomedical Research, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/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 (eg, 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 participant's personal information and their specimens. In this situation, the request for withdrawal of consent and/or destruction cannot 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 the end of the main study. 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 Sponsor-designated biorepository. If a central laboratory is not utilized in a particular trial, the trial site will ship directly to the Sponsor-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 Sponsor policies and procedures and this destruction will be documented in the biorepository database.

**8. Data Security**

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

**9. Reporting of Future Biomedical Research Data to Participants**

No information obtained from exploratory laboratory studies will be reported to the participant, family, or physicians. Principle reasons not to inform or return results to the participant include: Lack of relevance to participant health, limitations of predictive capability, and concerns regarding misinterpretation.

If important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to

rapidly report this information to doctors and participants. Participants will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

## 10. Future Biomedical Research Study Population

Every effort will be made to recruit all participants diagnosed and treated on Sponsor clinical trials for Future Biomedical Research.

## 11. Risks Versus Benefits of Future Biomedical Research

For Future Biomedical Research, risks to the participant have been minimized. No additional risks to the participant have been identified as no additional specimens are being collected for Future Biomedical Research (i.e., only leftover samples are being retained).'

The Sponsor has developed strict security, policies and procedures to address participant 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.

## 12. Questions

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

## 13. References

1. National Cancer Institute: http://www.cancer.gov/dictionary/?searchTxt=biomarker
2. International Conference on Harmonization: DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES - E15; http://www.ich.org/LOB/media/MEDIA3383.pdf
3. Industry Pharmacogenomics Working Group. Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/
4. Industry Pharmacogenomics Working Group. Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/