Official Protocol Title:	A Phase 2a, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Oral MK-8527 Once-Monthly in Participants at Low-Risk for HIV-1 Infection
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TITLE PAGE

STATISTICAL ANALYSIS PLAN

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Protocol Title:
A Phase 2a, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Oral MK-8527 Once-Monthly in Participants at Low-Risk for HIV-1 Infection

Protocol Number: 007-02

Compound Number: MK-8527

Sponsor Name:
Merck Sharp & Dohme LLC (hereafter called the Sponsor or MSD)

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TABLE OF CONTENTS

LIST OF TABLES

1 INTRODUCTION

The SAP is a companion document to the protocol. While Section 9 of the protocol provides the principal features of the confirmatory analyses for this study, this SAP provides additional statistical analysis details/data derivations and may document modifications or additions to the protocol-specified analysis plan that are not principal in nature and/or result from information that was not available at the time of protocol finalization.

2 SUMMARY OF CHANGES

SAP Version #	SAP Section # and Name	Description of Change	Brief Rationale
Amendment 01	3.5.1 Statistical Methods for Safety Analyses	Added details about handling of missing data in safety analyses	To add clarity on how missing data points are treated in the analysis.
Amendment 02	3.1 Responsibility for Analyses/In-house Blinding	Updated the timing of Sponsor being unblinded.	To enable strategic decision making by the Sponsor.

3 ANALYTICAL AND METHODOLOGICAL DETAILS

This section outlines the principal statistical analysis strategy and procedures for the study. Changes to analyses made after the protocol has been finalized, but prior to unblinding, will be documented in an amendment of the SAP and referenced in the CSR for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

3.1 Responsibility for Analyses/In-house Blinding

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

This study will be conducted as a double-blind study under in-house blinding procedures. To allow programmatic decisions, there will be an unblinded Sponsor team to review data on an ongoing basis for the duration of the study. The official, final database will not be locked until medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete. The detailed list of unblinded Sponsor team is presented in section 6.3.3 of the protocol. All Sponsor personnel except for a blinded medical monitoring team will be unblinded after the last expected Follow-up Week 4 visit.

The Clinical Biostatistics department of the Sponsor will generate the randomized allocation schedule for study treatment assignment.

3.2 Hypotheses/Estimation

There are no hypotheses to be tested in this study. Objectives of the study are stated in Section 3 of the protocol.

3.3 Analysis Endpoints

Safety and PK endpoints that will be evaluated for within- and between-treatment differences are listed below.

3.3.1 Safety Endpoints

The primary safety assessment will include all accumulated safety data through the last follow-up visit. AEs leading to discontinuation from study intervention are assessed until Week 20 (last dose received). Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs and laboratory test results.

3.3.2 Pharmacokinetics Endpoints

The secondary PK endpoints for the study are MK-8527 $AUC_{0\text{-last}}$ and C_{max}.

Exploratory PK endpoints are:

- PBMC MK-8527-MP, MK-8527-DP, and MK-8527-TP: AUC0-last, Cmax, Ctrough, concentrations at common time points
- MK-8527-TP AUC0-last, Ctrough, Cmax, and t1/2

3.4 Analysis Populations

3.4.1 Safety Analysis Population

Safety Analyses will be conducted in the APaT population, which consists of all randomized participants who received at least one dose of study intervention. Participants will be included in the treatment group corresponding to the study intervention they actually received for the analysis of safety data using the APaT population. This will generally be the treatment group to which they are randomized except for participants who take incorrect study intervention for the entire treatment period; such participants will be included in the treatment group corresponding to the study intervention actually received.

Analyses of laboratory test results will include only participants with at least one measurement obtained after at least one dose of study intervention. If the analysis will assess change from baseline, a baseline measurement is also required.

3.4.2 PK Analysis Population

The PK analysis population consists of the subset of participants who comply with the protocol sufficiently to ensure that generated data will be likely to exhibit the effects of treatment, according to the underlying scientific model. Any participants or data values excluded from analysis will be identified, along with their reason for exclusion, in the CSR.

3.5 Statistical Methods

3.5.1 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of AEs and other relevant parameters, including laboratory test results.

Safety analyses will be performed for the following between-group comparisons:

- MK-8527 (3 mg) vs placebo
- MK-8527 (6 mg) vs placebo
- MK-8527 (12 mg) vs placebo

3.5.1.1 Overall Safety Assessment

The analysis strategy of safety results is summarized in Table 1. The overall safety evaluation will include a summary by intervention group of the number and percentage of participants with at least one AE, SAE, drug-related AE, drug-related SAE, Grade 3 to 4 AE, drug-related Grade 3 to 4 AE, discontinuation from study intervention due to an AE; and AE resulting in death. Point estimates and 95% CIs for the differences between each MK-8527 group and placebo in the percentages of participants with the event will be provided using the M&N method [Miettinen, O. and Nurminen, M. 1985].

For continuous safety measures, such as change from baseline in laboratory values, summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group.

The number and percentage of participants with specific AEs will also be provided.

3.5.1.2 Statistical Methods for Safety Analyses

There are no safety topics of special interest in this study.

Table 1 Analysis Strategy for Safety Parameters

Analysis Part	Safety Endpoint	Descriptive Statistics	95% Between-group CI
Overall Safety Assessment	Any AE	X	X
	Any serious AE	X	X
	Any drug-related AE	X	X
	Any Grade 3 to 4 AE	X	X
	Any serious and drug-related AE	X	X
	Any Grade 3 to 4 and drug-related AE	X	X
	Discontinued study intervention due to AE	X	X
	AE that resulted in death	X	X
	Specific AEs, SOCs, or PDLCs	X	
	Change from baseline results for laboratory values	X	

AE=adverse event; CI=Confidence Interval; PDLC=Pre-Defined Limit of Change; SOC=System Organ Class.

Handling of Missing Data in Safety Analyses

Missing safety parameters, unless otherwise specified, will not be imputed; as such, any participant with a missing value will be excluded from the analysis. Change from baseline summaries require a baseline value. 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 prior to Day 1 will be used as baseline, when available. If no baseline result is available for a given analysis, that participant will not be included in the analysis.

3.5.2 Statistical Methods for Pharmacokinetic Analyses

Plasma MK-8527 endpoints will be summarized separately by dose level as appropriate, with geometric means and %GCV.

3.5.3 Demographic and Baseline Characteristics

The comparability of the treatment groups for each relevant demographic and baseline characteristic will be assessed using tables. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants screened and randomized and the primary reasons for screening failure and discontinuation will be displayed. Demographic variables (eg, age), baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment group either by descriptive statistics or categorical tables.

3.5.4 Population PK Analyses

Based on PK data obtained within this study, a separate population PK analysis will be performed. The prospective details of this analysis will be specified in a separate population PK analysis plan.

3.6 Interim Analyses

The siDMC will be responsible for an interim safety review. An interim safety analysis will be performed once 50% of the planned enrollment has reached Week 12 or discontinued from study intervention.

Treatment-level results and/or participant-level data from the IA will be provided by the unblinded statistician to the siDMC which consists of Sponsor personnel. Limited additional Sponsor personnel may be unblinded to the treatment-level results of the IAs, if required, to act on the recommendations of the siDMC. The list of individuals who are unblinded with respect to results of IAs will be documented by the unblinded statistician.

The processes by which recommendations and decisions are reached and communicated are documented in the siDMC charter. Individuals who have been unblinded at any level will not be involved in any discussions regarding modifications to the protocol, statistical methods, identification of protocol deviations, or data validation efforts after the IA.

An intervention group may be recommended for early termination due to safety concerns based on the following criteria along with an evaluation of the totality of safety data.

- At least 10% of participants meet discontinuation criteria as detailed in Table 3 of Section 7.1 of the protocol.

- The upper bound of the 95% CI of the difference between the treatment group and the placebo group for the percent change from baseline in lymphocyte count is less than 0.

If at least 10% of participants in a study intervention group meet discontinuation criteria as detailed in Table 3 of Section 7.1 of the protocol, study enrollment will be paused until the siDMC review has been completed.

In addition to the planned IA review, an ad hoc siDMC review will be triggered if ≥10% of all enrolled participants meet the criteria as detailed in Table 3 of Section 7.1 of the protocol at any point during the course of the study. During this time, enrollment in the study will be paused until the siDMC review has been completed.

3.7 Multiplicity

No multiplicity adjustment is planned for this study.

3.8 Sample Size and Power Calculations

The sample size of this study will allow for the accumulation of approximately 150 person-years of safety data on MK-8527.

3.8.1 Sample Size and Power for Safety Analyses

Table 2 summarizes the power under various assumptions of the underlying standard deviation to detect the difference in the mean percent change from baseline in lymphocytes. The power is based on the two-sample t-test assuming 100 participants in the MK-8527 group and 50 in the placebo group. For example, if the standard deviation of percent change from baseline in both groups is 20, this study has 81.8% power to detect a difference at least as large as 10%.

Table 2 Power (%) to Rule Out Difference in Mean Percent Change from Baseline (With 100 Participants Randomized to MK-8527 and 50 Randomized to Placebo)

Underlying Standard Deviation of Percent Change from Baseline[a]	Underlying Difference of Mean Percent Change from Baseline in Lymphocytes (MK-8527 - Placebo)					
	-5%	-10%	-15%	-20%	-25%	-30%
10	81.8	>99.9	>99.9	>99.9	>99.9	>99.9
15	48.1	96.9	>99.9	>99.9	>99.9	>99.9
20	29.9	81.8	99.0	>99.9	>99.9	>99.9
25	20.8	63.1	93.1	99.6	>99.9	>99.9
30	15.8	48.1	81.8	96.9	99.8	>99.9

Table 3 summarizes the differences in the incidence of AEs (MK-8527 minus placebo) that can be ruled out with different power levels and 95% confidence when there are 100 participants in the MK-8527 group and 50 participants in the placebo group. The underlying incidence of AE is assumed to be the same in the MK-8527 group as that in the placebo group. The calculations are based on an asymptotic method proposed by M&N method [Miettinen, O. and Nurminen, M. 1985]. No multiplicity adjustments were made.

Table 3 Difference in Incidence of AEs (MK-8527 Group Minus Placebo) That Can Be Ruled Out With 100 Participants in the MK-8527 Group and 50 Participants in the Placebo Group

Target Power	Difference[a] in Percentage Points That Can Be Ruled Out with Target Power Assuming the Underlying Incidence of the AE is				
	10%	20%	30%	40%	50%
80	20	23	24	24	23
85	21	24	25	26	25
90	23	26	27	28	27

[a]The upper bound of the two-sided 95% confidence interval M&N method [Miettinen, O. and Nurminen, M. 1985] for the difference in AE incidences assuming the incidences are the same.

3.9 Subgroup Analyses

No subgroup analyses are prespecified in the protocol.

3.10 Compliance (Medication Adherence)

Study intervention data for MK-8527 and placebo will be collected during the study. A day within the study will be considered an "On-Therapy" day if the participant takes the required number of pills from all containers provided for this study. A participant will have to take all 4 capsules per dose to be considered compliant.

For a participant who is followed for the entire study period, the "Planned Number of Days on Therapy" is the total number of days from randomization to the last scheduled day for treatment administration for that participant. For a participant who discontinued from the study permanently, the "Planned Number of Days on Therapy" is the total number of days from randomization to the date of the last dose of study medication.

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

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

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

3.11 Extent of Exposure

Each study participant is planned to be exposed to 6 doses of either 3 mg, 6 mg, or 12 mg of MK-8527 or placebo over a 6-month period. The amount of intervention received by the participants during the study will be summarized.

4 LIST OF REFERENCES

[Miettinen, O. and Nurminen, M. 1985]	Miettinen O and Nurminen M. Comparative Analysis of Two Rates. Stat Med 1985;4:213-26.	[03QCDT]

5 SUPPORTING DOCUMENTATION

5.1 Appendix 1: Technical Details

Not Applicable.

5.2 Appendix 2: Approval Information

CCI

[redacted]