Official Protocol Title:	A Phase 2a, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Oral MK-8591 Once-Monthly in Participants at Low-Risk for HIV-1 Infection
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Supplemental Statistical Analysis Plan (sSAP)

1. INTRODUCTION

This supplemental SAP (sSAP) is a companion document to the protocol. In addition to the information presented in the protocol SAP which provides the principal features of confirmatory analyses for this trial, this supplemental SAP provides additional statistical analysis details/data derivations and documents modifications or additions to the analysis plan that are not "principal" in nature and result from information that was not available at the time of protocol finalization.

2. SUMMARY OF CHANGES

The following changes to the protocol SAP are detailed in this document:

- Section 3.10 Analysis of implant/depot DDI subgroup added
- Section 3.11 Alternative compliance calculation added

3. ANALYTICAL AND METHODOLOGICAL DETAILS

3.1 Statistical Analysis Plan Summary

Study Design Overview	A Phase 2a, double-blind, placebo-controlled study to evaluate the safety, tolerability, and PK of oral MK-8591 QM in participants at low-risk for HIV-1 infection
Treatment Assignment	A total of 250 participants will be randomized to Group 1 (60 mg MK-8591), Group 2 (120 mg MK-8591), or Group 3 (placebo) in a 2:2:1 ratio.
Analysis Populations	Safety: APaT
Primary Endpoint(s)	AEs AEs leading to discontinuation of study intervention
Key Secondary Endpoints	Plasma MK-8591 $AUC_{0\text{-}672hr}$, C_{max}, C_{trough} and $t_{1/2}$ Intracellular MK-8591-TP $AUC_{0\text{-}672hr}$, C_{max}, C_{trough} and $t_{1/2}$
Statistical Methods for Key Pharmacokinetic Analyses	Geometric means and 95% CIs will be provided for Plasma MK-8591 and PBMC MK-8591-TP $AUC_{0\text{-}672hr}$, C_{max} and C_{trough} by dose level.
Statistical Methods for Key Safety Analyses	95% CIs (Tier 2 endpoints) will be provided for between-group differences in the percentage of participants with events; these analyses will be performed using the Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985].
Interim Analyses	There are no planned interim analyses for this study.
Multiplicity	No multiplicity adjustment is necessary as there are no hypothesis tests for this protocol.
Sample Size and Power	There are no hypotheses in this study. The primary objective will compare the 95% CI for between-group differences. Given the planned sample size of 250 participants (2:2:1), the study has 80% probability at an overall 2-sided 5% α-level to rule out an 18.4% risk difference in AEs from the placebo group assuming an underlying incidence of 10% in the placebo group. The study has an 80% probability to rule out a 15% risk difference in AE between MK-8591 120 mg and 60 mg groups assuming an underlying incidence of 10% in the MK-8591 60 mg group. Assuming plasma MK-8591 C_{max} has a true between-participant standard deviation (log-scale) of 0.25, given 100 participants receiving MK-8591 at one of the dose levels, it is 80% likely that the half-width of the 95% CI for the true arithmetic mean C_{max} on the log scale will be at most 0.0525.

3.2 Responsibility for Analyses/In-House Blinding

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

For clinical site personnel, participants, and the Sponsor's clinical team this study will be a double-blind study under in-house blinding procedures through Week 24. The Sponsor will be unblinded at Week 24 for the primary safety assessment. For the PBMC/PK Bridging Subset only, investigators/clinical site personnel and participants will be unblinded to MK-8591/placebo between Weeks 36 and 44 while remaining blinded to MK-8591 dose. For those participants not in the PBMC/PK Bridging Subset, participants and investigators/clinical site personnel will remain blinded for the duration of the study.

To allow timely completion of population PK modeling, Sponsor PK personnel will be unblinded for the duration of the study. No personnel directly associated with study conduct will be unblinded. Before granting select personnel access to unblinded PK data, an official memo detailing unblinding procedures will be generated per Sponsor SOP. This memo will list the names of the personnel who will have access to unblinded PK data. 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.

3.3 Hypotheses/Estimation

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

3.4 Analysis Endpoints

3.4.1 Safety Endpoints

Section 4 of the protocol provides an initial description of safety measures.

The primary safety assessment will include all accumulated safety data during the intervention period with follow-up of 4 weeks after the last dose (Week 24 visit). AEs leading to discontinuation from study intervention are assessed until Week 20 (last dose received). In the extended, unblinded PK follow-up period (after FW 12 visit through FW 44 visit), only SAEs and nonserious AEs related to study procedures will be collected. Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs and laboratory values.

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 Grade 3 to 5 AE; 5) participants with at least 1 AE which is both serious and drug-related; 6) participants with at least 1 AE which is both Grade 3 to 5 and drug-related; 7) participants who discontinued study therapy due to an AE; and 8) participants with an AE which results in death. The percentage of participants with specific AEs by system organ class will also be summarized.

Predefined Limits of Change in Laboratory Parameters

Participants must have both a baseline and post-randomization on-treatment measurement to be included in the summaries of laboratory tests. Participants' laboratory values (based on their most abnormal laboratory test values, in the direction of interest, while on study therapy) will be classified as to whether or not they fall outside of the PDLC and are worse in grade (ie, more abnormal in the direction of interest) than at baseline. The PDLC grading criteria are adapted from DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, July 2017, Version 2.1. A listing of the participants who meet the PDLC grading criteria will be provided.

3.4.2 Pharmacokinetics Endpoints

There are no primary PK endpoints.

The secondary PK endpoints in the study are: plasma MK-8591 $AUC_{0\text{-}672hr}$, C_{max}, C_{trough}, and $t_{1/2}$ and PBMC MK-8591-TP $AUC_{0\text{-}672hr}$, C_{max}, C_{trough}, and $t_{1/2}$.

Exploratory endpoints include tissue concentrations of MK-8591, MK-8591-TP and MK-8591-DP, as well as plasma concentrations of ENG, MPA, and NET (in a subset of participants).

3.5 Analysis Populations

Safety analyses will be conducted in the APaT population, which consists of all randomized participants who received at least 1 dose of study intervention. Participants will be included in the group corresponding to the study intervention they actually received for the analysis of safety data using the APaT population. This will be the 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 group corresponding to the study intervention actually received.

PK analyses will be conducted in 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. Compliance covers such considerations as exposure to treatment, availability of measurements, and absence of important protocol deviations. Important protocol deviations will be identified to the extent possible prior to unblinding by individuals responsible for data collection/compliance, and its analysis and interpretation. Any participants or data values excluded from analysis will be identified, along with their reason for exclusion, in the CSR. At the end of the study, all participants who are compliant with the study procedure as aforementioned and have available data from at least one dose will be included in the PK analysis dataset. This population will be used for the PK analyses.

3.6 Statistical Methods

3.6.1 Statistical Methods for Safety Analyses

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

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

- MK-8591 (60 mg) vs placebo
- MK-8591 (120 mg) vs placebo
- MK-8591 (60 mg) vs MK-8591 (120 mg)

The analysis of safety results will follow a tiered approach (Table 1). The tiers differ with respect to the analyses that will be performed. AEs (specific terms as well as system organ class terms) and events that meet PDLCs in laboratory parameters are either pre-specified as "Tier 1" endpoints, or will be classified as belonging to "Tier 2" or "Tier 3" based on the number of events observed.

Safety parameters or AEs of special interest that are identified a priori constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance. There are no a priori clinical events of concern that have been identified; therefore, there are no Tier 1 events for this protocol

Tier 2 Events

Tier 2 parameters will be assessed via point estimates with 95% CI provided for differences in the proportion of participants with events (also via the Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985]).

Membership in Tier 2 requires that at least 4 participants in any intervention group exhibit the event; all other AEs and predefined limits of change will belong to Tier 3.

The threshold of at least 4 events was chosen because the 95% CI for the between-group difference in percent incidence will always include zero when intervention 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 for Tier 2 events 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 AEs and safety parameters that meet predefined limits of change.

In addition to individual events that occur in 4 or more participants in any intervention group, the broad AE categories consisting of the proportion of participants with any AE, a drug-related AE, a SAE, a Grade 3 to 5 AE, an AE which results in death, an AE which is both drug-related and serious, an AE which is both drug-related and Grade 3 to 5, and discontinuation due to an AE will be considered Tier 2 endpoints.

Tier 3 Events

Safety endpoints that are not Tier 1 or 2 events are considered Tier 3 events. Only point estimates by intervention group are provided for Tier 3 safety parameters.

Table 1 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	95% CI for Treatment Comparison[a]	Descriptive Statistics
Tier 2	Any AE[b]	X	X
	Any Serious AE	X	X
	Any Drug-Related AE	X	X
	Any Grade 3 to 5 AE	X	X
	Any Serious and Drug-Related AE	X	X
	Any Grade 3 to 5 and Drug-Related AE	X	X
	Discontinuation due to AE	X	X
	AE which Results in Death	X	X
	Specific AEs, SOCs, or PDLCs (incidence ≥4 participants in one of the intervention groups)	X	X
Tier 3	Specific AEs, SOCs or PDLCs (incidence <4 participants in all of the intervention groups)		X

AE=adverse event; CI =confidence interval; SOC=System Organ Class; PDLC=Predefined Limit of Change; X=results will be provided.
% CIs will be based on the method of Miettinen and Nurminen [Miettinen, O. and Nurminen, M. 1985].
dicates broad AE category of the number of participants reporting any AE.

3.6.2 Pharmacokinetics Analyses

Plasma MK-8591 AUC0-672hr, Cmax, Ctrough, and t1/2 will be summarized separately by dose level as appropriate, with geometric means and 95% CIs based on natural log-transformed endpoints and t-distribution.

PBMC MK-8591-TP AUC0-672hr, Cmax, Ctrough and t1/2 will be assessed with a similar method as above.

3.7 Interim Analyses

There are no planned interim analyses for this study.

3.8 Multiplicity

No multiplicity adjustment is planned for this study.

3.9 Sample Size and Power Calculations

3.9.1 Sample Size and Probability Calculations for Safety Analysis

The sample size of this study was chosen to allow for the accumulation of approximately 100 person-years of safety data (200 participants × 0.5 years).

While not the basis of the sample size for this study, information on the probability of observing a difference between intervention groups is provided. If the underlying incidence of a particular AE is 1%, there is a 63.4% chance of observing at least 1 AE among 100 participants in either MK-8591 group. If no AE of that type is observed among the 100 participants in the MK-8591 group, this study provides 97.5% confidence that the underlying percentage of participants with that particular AE is <3.62% (1 out of every 27 participants).

The estimate of and the upper bound of the 95% CI for the underlying percentage of participants with a particular AE given various hypothetical observed number of participants with a particular AE within either MK-8591 group are provided in Table 2. These calculations are based on the exact binomial method proposed by Clopper and Pearson (1934) [Clopper, C. J. and Pearson, E. S. 1934].

Table 3 summarizes differences in the incidence of AEs between the 2 MK-8591 groups and for either MK-8591 group compared with placebo that can be ruled out with different probabilities and 95% confidence for a variety of hypothetical underlying incidences of an AE. These calculations assume 100 participants in each MK-8591 group and 50 participants in the placebo group and that the underlying incidence of AEs is the same for both groups. The calculations are based on an asymptotic method proposed by Farrington and Manning (1990) [Farrington, C. P. and Manning, G. 1990]; no multiplicity adjustments were made.

3.9.2 Sample size and Probability Calculations for PK Analysis

No estimates of variability for AUC_{672hr} or C_{trough} following monthly oral dosing are available. The precision of the estimates of plasma MK-8591 C_{max} can be assessed by calculating the half-width of the 95% CIs expected for the given sample size and assumed variability. The calculations for C_{max} are based on assumed true between-participant standard deviations (log-scale) of 0.25 as observed in MK-8591 Protocol 001 and take into account the sampling distribution of the observed sample variance as described in [Wang, Y., et al 2012]. For the given sample size (100 participants receiving MK-8591 at one of the dose levels) and assumed between-participant variability, it is 80% likely that the half-width of the 95% CI for the true arithmetic mean C_{max} on the log scale will be at most 0.0525 (the lower and upper 95% confidence limits for the true geometric mean C_{max} will be OBS/1.05 and OBS × 1.05, where OBS is the observed geometric mean).

Table 2 Estimate of Incidence of AEs and 95% Upper Confidence Bound Based on Hypothetical Number of Participants With a Particular AE Among 100 Participants in Either MK-8591 Intervention Group

Hypothetical Number of Participants with a Particular AE	Estimate of Incidence	95% Upper Confidence Bound[a]
0	0%	3.6
3	3%	6.3
5	5%	11.3
10	10%	17.6
15	15%	25.5
20	20%	29.2

AE=adverse event.

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

Table 3 Difference in Incidence of AEs (MK-8591 Intervention Group Minus Placebo) That Can Be Ruled Out

	Difference[a] in Percentage Points That Can Be Ruled Out with Target Probability Assuming the Underlying Incidence of the AE is:				
Target Probability	**10%**	**20%**	**30%**	**40%**	**50%**
Compare MK-8591 to placebo					
80	18.4	21.9	23.5	24.0	23.5
85	20.1	23.6	25.2	25.6	24.9
90	22.2	25.7	27.3	27.5	26.7
95	25.3	28.9	30.3	30.3	29.2
Compare MK-8591 intervention groups					
80	15.0	17.9	19.3	19.7	19.3
85	16.2	19.2	20.6	21.0	20.6
90	17.8	20.9	22.3	22.7	22.1
95	20.1	23.4	24.8	25.1	24.4

AE=adverse event.

[a] The upper bound of the two-sided 95% confidence interval [Farrington, C. P. and Manning, G. 1990] for the difference in AE incidences assuming the incidences are the same. Assuming 100 participants in the MK-8591 intervention groups and 50 participants in the placebo group.

3.10 Subgroup Analyses and Effect of Baseline Factors

To evaluate potential differential pharmacokinetics between groups, plasma MK-8591 will be assessed with a similar method as described in Section 9.6 within each category of the following classification variables:

- Sex (female, male)
- Race (white, non-white)
- Region (Africa, non-Africa)
- Age (≤45 years; >45 years)

Safety will be assessed by treatment group within the implant/depot DDI subset. This subset consists of those female participants who are using an ENG-releasing implant (ie, Nexplanon® or Implanon NXT®) or injectable-MPA or injectable-NET-EN (eg, Noristerat, Syngestal).

3.11 Compliance (Medication Adherence)

Study intervention data for MK-8591 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 "Number of Days Should be 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 "Number of Days Should be on Therapy" is the total number of days from randomization to the last dose of study intervention.

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

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

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

If there are participants who only take partial doses at any visit, an alternative compliance measure will be calculated using the number of capsules taken using the following formula:

$$\text{Alternative Percent Compliance} = \frac{\text{Number of Capsules Taken}}{\text{Number of Capsules Should Have Taken}} x\ 100$$

Summary statistics will be provided for this alternative percent compliance by intervention group for the APaT population.

3.12 Extent of Exposure

Each study participant is planned to be exposed to 6 doses of either 60 mg or 120 mg of MK8591 or placebo over a 6-month period. The amount of intervention received by the participants during the study will be summarized.