Official Protocol Title:	A Phase 2b, Randomized, Active-Controlled, Double-Blind, Dose-Ranging Clinical Study to Evaluate a Switch to Islatravir (ISL) and MK-8507 Once-Weekly in Adults with HIV-1 Virologically Suppressed on Bictegravir/ Emtricitabine/Tenofovir Alafenamide (BIC/FTC/TAF) Once-Daily
NCT Number:	NCT04564547
Document Date:	24-FEB-2025

Supplemental Statistical Analysis Plan (sSAP)

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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

This sSAP was created based on the latest protocol amendment after dosing of participants was stopped based on recommendations from eDMC and agreement by EOC and prior to the final database lock.

sSAP Version	Section	Description of Change	Rationale
Version 1	All applicable sections	Specific sections and changes are summarized below.	Primary updates due to protocol amendments 2 and 3 in which dosing of participants was stopped based on recommendations from eDMC and agreement by EOC.
	3.1	• Part 1 was stopped and Parts 2 and 3 are no longer applicable. Participants in Groups 1-3 were switched to other ARTs and entered the unblinded safety monitoring period. • Efficacy endpoints are no longer applicable and, treatment comparison, IA Weeks 24 & 48 analyses, and eDMC are on longer needed. Available efficacy and safety data will only be summarized.	Dosing stopped.
	3.2	• Weeks 24 and 48 analyses in Part 1 and Parts 2 & 3 are no longer applicable.	Dosing stopped.

sSAP Version	Section	Description of Change	Rationale
	3.4-3.4.2	• Treatment comparisons will not be performed for efficacy and safety endpoints except urine fluoride at Week 4. Available efficacy data and all safety data will be summarized by treatment group and period, where applicable.	Dosing stopped and only limited safety parameters are monitored.
	3.4.3, 3.4.4, 3.6.3, 3.7, 3.10	• No longer applicable.	Dosing stopped and no available data.
	3.5-3.5.1.2, 3.5.3	• Resistant analysis set and PRO related analysis populations are no longer applicable.	Dosing stopped and no available data.
	3.6-3.6.1.2	• Statistical methods specified previously are no longer applicable. Available data will be summarized based on data as observed for efficacy.	Dosing stopped and no available data.
Version 1	3.6.2	• Except the comparison of urine fluoride at Week 4, no other comparisons will be performed for safety. No p-value will be provided. All available safety data will be summarized when applicable.	Dosing stopped and only limited safety parameters' data are available.
	3.9-3.9.2	• No longer applicable except urine fluoride at Week 4.	Dosing stopped
	3.11, 3.12	• Compliance and exposure will be summarized using all available data collected in the double-blinded period.	Dosing stopped and only limited data available

3. ANALYTICAL AND METHODOLOGICAL DETAILS

3.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 3.2-3.12.

Study Design Overview	A Phase 2b, Randomized, Active-Controlled, Double-Blind, Dose-Ranging Clinical Study to Evaluate a Switch to ISL + MK-8507 QW in Adults with HIV-1 Virologically Suppressed on BIC/FTC/TAF QD
Treatment Assignment	Part 1 (Double-blind Dose Ranging Treatment Period): ~140 participants will be randomized in a 1:1:1:1 ratio to receive 1 of the 4 following study interventions: • Group 1: ISL 20 mg QW + MK-8507 100 mg QW (n=35) • Group 2: ISL 20 mg QW + MK-8507 200 mg QW (n=35) • Group 3: ISL 20 mg QW + MK-8507 400 mg QW (n=35) • Group 4: BIC/FTC/TAF QD (n=35)
Analysis Populations	[Unless otherwise specified, FAS will be used for efficacy summary while APaT will be used for safety summary/analysis.] Efficacy: Full Analysis Set (FAS) Safety: All Participants as Treated (APaT)
Primary Endpoint(s)	[Primary efficacy endpoint is no longer applicable as of Protocol Amendment 013-02.] Efficacy: None Safety: 1. Percentage of participants experiencing AEs 2. Percentage of participants experiencing AEs leading to discontinuation of study intervention
Statistical Methods for Efficacy and Safety Analyses	[Treatment comparison is no longer applicable for efficacy and safety except urine fluoride which will be specified in Section 3.6.2.]
Multiplicity	Since there are no formal hypothesis tests, no multiplicity adjustment is needed in this study.
Interim Analysis	[Weeks 24 and 48 analyses will not be conducted. Periodic eDMC reviews after dosing stopped are no longer needed. However, periodic safety reviews by Sponsor will continue and the recovery of lymphocyte and CD4+ T-cell counts will be monitored closely.]
Sample Size	[No between study treatment comparisons of HIV-1 RNA will be conducted and power calculations in this section are no longer applicable.]

3.2 Responsibility for Analyses/In-House Blinding

[Weeks 24 and 48 analyses in Part 1 are no longer applicable. Parts 2 and 3 are on longer applicable.]

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

Part 1 is double-blinded with in-house blinding through Week 48 (eg, the participant, the investigator, and Sponsor personnel are unaware of the intervention assignments). Clinical site personnel and participants will remain blinded in Part 1 (through at least Week 48).

The Clinical Biostatistics department will generate the randomized allocation schedule(s) for study intervention assignment. Randomization will be implemented via an IRT.

3.3 Hypotheses/Estimation

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

3.4 Analysis Endpoints

[Note As of Amendment 013-02, this section is no longer applicable except CD4+ T-cell counts will continue to be monitored through the Unblinded Safety Monitoring period, according to Sections 1.3.3 and 1.3.4 of the protocol. Treatment comparisons are no longer applicable for efficacy and safety endpoints except urine fluoride at Week 4. Unless otherwise specified, available efficacy data and all safety data will be summarized by Part 1 treatment group based on DAO approach.]

3.4.1 Efficacy Endpoints

[Comparisons of efficacy endpoints are no longer applicable. HIV-1 RNA and CD4+ T-cell endpoints will only be summarized based on data as observed by Part 1 treatment group if post-baseline data is available.]

Percentage of Participants with Predefined HIV-1 RNA Levels

[Comparisons of HIV-1 RNA endpoints are no longer applicable. HIV-1 RNA ≥50 copies/mL, HIV-1 RNA <50 copies/mL, and HIV-1 RNA <40 copies/mL at available post-treatment time points will only be summarized based on data as observed by Part 1 treatment group.]

The Abbott Real Time PCR assay with a reliable LLOQ of 40 copies/mL will be used to measure the HIV-1 RNA level in blood samples obtained at each visit. The efficacy endpoints associated with HIV-1 RNA will be derived based on HIV-1 RNA test results and reconfirmed results, if applicable.

Change from Baseline in CD4+ T-cell Count

[Comparisons of CD4+ T-cell endpoints are no longer applicable. Change from baseline in CD4+ T-cell counts at post-baseline available time points will only be summarized based on data as observed by Part 1 treatment group.]

Results of CD4+ T-cell counts from the central laboratory will be used to evaluate the immunologic effect. Changes in CD4+ T-cell count will be estimated at each applicable timepoint.

Clinically-significant Confirmed Viremia

[There is no clinically-significant confirmed viremia reported. No analysis or summary will be performed.]

Viral Resistance-associated Substitutions

[There are no post-baseline resistance data, so no analysis or summary will be performed.]

3.4.2 Safety Endpoints

[Note: As of Protocol Amendment 013-02, this section is no longer applicable except AEs, DILI laboratory criteria, PDLC, and selected laboratory parameters will continue to be monitored through the unblinded Safety Monitoring period, according to Sections 1.3.3 and 1.3.4 of the Protocol. The safety endpoints will only be evaluated for available periods including the double-blind period and unblinded safety monitoring period. Events that are described in Table 7 will be summarized descriptively by Part 1 treatment group and period, where applicable.]

Unless otherwise specified, the safety endpoints will be evaluated for the following periods:

- Double-blind period through 42 days follow-up
- Safety monitoring period

Unless otherwise indicated in Section 3.6.2, safety summaries will be presented by Part 1 treatment group, and by combining Groups 1-3 where appropriate.

Adverse Events

The percentage of participants falling into the following clinical AE categories will be summarized: 1) at least 1 AE; 2) at least 1 drug-related AE; 3) at least 1 SAE; 4) at least 1 serious and drug-related AE; 5) AEs leading to discontinuation of study intervention; and 6) AE(s) leading to death.

Events of Clinical Interest (ECI)

Specific ECIs, including events meeting DILI lab criteria and AEs of periostitis, fracture, and bone pain (predefined in Section 8.4.7 of the protocol), will be summarized.

Predefined Limits of Change in Laboratory Parameters

For the summaries of laboratory tests, participants must have both a baseline and postrandomization 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 intervention) will be classified as to whether they fall outside of the PDLC and are worse in grade (ie, 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, July 2017, Version 2.1 [National Institute of Allergy and Infectious Diseases 2017] (Appendix 3 of the protocol). A listing of the participants who meet the criteria will also be provided.

Selected Laboratory Parameters

The mean change from baseline to available time points in select laboratory parameters will be summarized.

3.4.3 Pharmacokinetic Endpoints

[Analysis and summary will not be performed for PK endpoints.]

3.4.4 Patient-reported Outcome (PRO) Endpoints

[Analysis and summary will not be performed for PRO endpoints.]

3.5 Analysis Populations

[Note: As of Amendment 013-02, this section is no longer applicable except FAS and APaT populations for summaries associated with available data of Part 1. The Unblinded Non-study ART Treated population is defined as participants who were in Groups 1, 2, and 3 and were to switch to non-study ART treatment.]

3.5.1 Efficacy Analysis Populations

3.5.1.1 Full Analysis Set (FAS)

The FAS population will serve as the primary population for the analysis of efficacy data in this study. The FAS population consists of all randomized participants who:

- Received at least 1 dose of study treatment, and
- 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.

3.5.1.2 Resistance Analysis Subset

[This analysis population is no longer applicable.]

3.5.2 Safety Analysis (APaT) Population

The APaT population will be used for the analysis of safety data in this study. The APaT population consists of all randomized participants who received at least 1 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. For most participants, this will be the treatment group to which they are randomized. Participants who take incorrect study intervention for the entire treatment period will be included in the treatment group corresponding to the study intervention actually received. Participants in Group 4 who receive at least 1 dose of weekly study intervention (ISL + MK-8507) in Part 3 will be included in summaries and analyses from Week 96 through Week 144.

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

3.5.3 Patient-reported Outcome (PRO) Analysis Population

[This analysis population is no longer applicable.]

3.6 Statistical Methods

[Note: As of Protocol Amendment 013-02, this section is no longer applicable. Efficacy data will be summarized separately for available data observed from Part 1 and the Unblinded Safety Monitoring period.]

3.6.1 Statistical Methods for Efficacy Analyses

All available efficacy data will be summarized over time by Part 1 treatment group based on DAO approach. Applicable analysis visits up to Week 36 for the double-blind period defined in Section 3.6.1.2 will be used for summaries according to period where applicable.

3.6.1.1 Missing Data Approaches

[These missing data approaches will not be applied.]

3.6.1.2 Definition of Time Points (or Analysis Visit)

[Note: As of Protocol Amendment 013-02, the definition of time points after Week 24 associated with Parts 1, 2, and 3 in this section is no longer applicable. The definition of time windows for Unblinded Safety Monitoring period in Sections 1.3.3 and 1.3.4 of the Protocol is presented in Table 10. Available data will be summarized or analyzed by analysis visits when applicable.]

Table 1 lists the definition of timepoint by time windows (day-ranges) that will be used for the purposes of the statistical analyses and the target relative day for the scheduled visits in the study which will be used for all analyses by timepoint. The last available on-treatment

measurement within a window will be used for analyses at a specific timepoint, unless otherwise specified.

Table 1 Definition of Time Points (or Analysis Visit)

Treatment Phase	**Treatment Period**	**Analysis Visit**	**Day-Range Rules**	**Target Day[a]**
Pretreatment	Baseline	Day 1	≤1	1
Treatment	Double-blind Dose-ranging Treatment Period (Part 1)	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 24	≥127 and ≤210	169
		Week 36	≥211 and ≤294	253
	Follow-up	Follow-up Through Day 42	42 days after the last dose of study treatment	NA
Non-study ART Treatment	Unblinded Safety Monitoring and Long-term Unblinded Safety Monitoring Periods	Follow-up Week x	Every 4 weeks (or 28 days) after the last dose of study treatment + 42 days	NA

ISL=islatravir.
[a] Relative days and target days are computed from the first day of study intervention.

3.6.2 Statistical Methods for Safety Analyses

[Note: As of Protocol Amendment 013-02, only descriptive statistics based on available data for Part 1 and Unblinded Safety Monitoring period is applicable for this section. Events that are described below as either Tier 1, 2, or 3 events will be summarized descriptively.]

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory tests, and vital signs. Specific safety endpoints that will be summarized are listed in Table 2. No comparisons will be conducted except the comparison of urine fluoride at Week 4. Change from baseline in urine fluoride will be assessed by ANCOVA models, adjusted by the baseline value. No p-value will be provided. All available safety data will be summarized based on data as observed except laboratory data for the post-treatment period which will be summarized based on last observation carried forward approach, i.e., the last post-treatment measurement prior to a missing visit is used for that missing value, when applicable. Applicable analysis visits for on-treatment/double-blind period and all available follow-up visits for post-treatment/safety monitoring period defined in Section 3.6.1.2 will be used where applicable. Participants with quantifiable plasma fluoride values detected will be listed.

Table 2 summarizes the key safety analyses of the study.

Table 2 Analysis Strategy for Key Safety Endpoints

Safety Endpoint[a]	95% CI for Treatment Difference	Descriptive Statistics
• Change from baseline in urine fluoride	X	X
• The percentage of participants with any AE potentially related to skeletal fluorosis[b] • The percentage of participants with an AE in each of the following categories: 1 or more AE(s); drug-related AE(s), serious AE(s), AE(s) which are both drug-related and serious, AE(s) [drug-related and nondrug-related] leading to discontinuation of study intervention, and AE(s) leading to death • Specific AEs (preferred terms), SOCs, or PDLCs • Change from baseline in select laboratory parameters and vital signs • ECIs		X

AE=adverse event; CI=confidence interval; ECIs=events of clinical interest; PDLC=predefined limit of change; SOC=System Organ Class.
[a] Adverse Experience references refer to both Clinical and Laboratory AEs.
[b] Includes AEs predefined in Section 3.4.2.

3.6.3 Statistical Methods for PRO Analyses

[Analysis and summary will not be performed for PRO endpoints.]

3.7 Interim Analyses

[Note: As of Protocol Amendment 013-02, interim analyses at Weeks 24 and 48 will no longer be conducted and eDMC are longer needed.]

3.8 Multiplicity

Since there are no formal hypothesis tests, no multiplicity adjustment is planned in this study.

3.9 Sample Size and Power Calculations

[Note: As of Protocol Amendment 013-02, no between group comparisons will be conducted and power calculations are no longer applicable except for urine fluoride at Week 4.]

3.9.1 Sample Size and Power for Efficacy Analyses

[This section is no longer applicable.]

3.9.2 Sample Size and Power for Safety Analyses

Adverse Events

[This section is no longer applicable.]

Changes in Urine Fluoride

There is interest to estimate the change in 4-hour urine fluoride excretion associated with the doses of MK-8507 in this study. Although there are no formal hypotheses associated with changes in urine fluoride, there is interest in ensuring the study is sufficiently large to detect clinically meaningful changes in urine fluoride excretion, assuming a nominal alpha level of 0.05.

MK-8507 Protocol 005 evaluated changes in urine fluoride associated with 200 mg and 800 mg weekly doses of MK-8507; a weekly placebo was also evaluated. Results from this study serve as the basis for expected treatment differences and variance estimates used in the power calculations presented here. BIC/FTC/TAF is not anticipated to excrete fluoride in urine and as such the MK-8507 Protocol 005 placebo responses are assumed to be representative. Estimating/interpolating results from the 200 mg and 800 mg doses included in MK-8507 Protocol 005 to the MK-8507 100 mg, 200 mg, and 400 mg doses in this study, the treatment differences in change from baseline (MK-8507 minus control) in 4-hour urine collected at Week 4 are assumed to be ~3 µmol, ~5 µmol, and ~9 µmol for the 100 mg, 200 mg, and 400 mg dose groups, respectively. Furthermore, an SD of 9.66 µmol is assumed; this is comprised of an SD of 3.5 µmol arising from treatment with MK-8507 and an SD of 9 µmol associated with an unrestricted diet. (The MK-8507 treatment effects in Protocol 005

were measured on a background of a fluoride restricted diet; however, an estimate of the variability associated with diet and drinking water was obtained during the study run-in phase. The impact of diet and drinking water on variability was assumed to be additive.)

Power calculations were computed in 2 ways, both presented in Table 3. The first approach evaluated power using a 2-sample t-test with an assumed SD=9.66 µmol. The second approach used an ANCOVA model, which is the approach planned for the analysis of this endpoint in this study: a model with change from baseline as the dependent variable and baseline and treatment as independent variables. For the ANCOVA approach, data were simulated (1000 replicates) under 3 different correlation structures. (Note, the correlation observed in MK-8507 Protocol 005 between baseline and treatment response varied between 0.7 and >0.9.)

Table 3 Power Calculations for Differences in 4-hour Urine Fluoride using a T-Test and ANCOVA

MK-8507 Dose	Assumed Difference from BIC/FTC/TAF Control	T-Test[a]	ANCOVA via Simulation[b]		
		SD=9.66	Corr=0	Corr=0.5	Corr=0.8
100 mg	3 µmol	24.9%	25.5%	27.1%	49.0%
200 mg	5 µmol	56.9%	58.2%	67.3%	90.4%
400 mg	9 µmol	97.0%	97.8%	99.2%	>99.9%

ANCOVA=analysis of covariance; BIC=bictegravir; CI=confidence interval; FTC=emtricabine; SD=standard deviation; TAF=tenofovir alafenamide.

[a]Power calculations using a t-test assume a common SD of 9.66 µmol.

[b]Power calculations using simulation assume a common SD associated with diet and drinking water of 9 µmol, a treatment effect SD of 3.5 µmol, and the stated correlation (Corr). Simulated study data were analyzed using an ANCOVA model with terms for baseline and treatment, and a result was considered statistically significant if the lower bound of the 95% CI for the indicated treatment comparison was >0.

As can be seen from the simulated ANCOVA results, under an assumed correlation of 0.8 (consistent with the correlations observed in MK-8507 Protocol 005), there is >90% power to detect between-group differences in change in urine fluoride as small as 5 µmol.

3.10 Subgroup Analyses and Effect of Baseline Factors

[Note: As of Protocol Amendment 013-02, subgroup analyses will no longer be conducted.]

3.11 Compliance (Medication Adherence)

[Note: As of Protocol Amendment 013-02, the summary associated with Part 1 is applicable and summaries for Parts 2 and 3 are no longer applicable for this section.]

Compliance will be summarized for Part 1 (double-blind period). In addition, compliance will be presented separately for weekly treatments (ISL and its placebo, MK-8507 and its placebo, ISL, and MK-8507) from daily treatments (BIC/FTC/TAF and its placebo).

Daily Compliance:

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

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

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

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

Weekly Compliance:

For a participant who is followed for the entire period, the "Number of Weeks Should be on Therapy" is the total number of complete weeks from the first dose day to the last scheduled day for treatment administration for that participant per period. For a participant who discontinued from the study permanently, the "Number of Weeks Should be on Therapy" is the total number of complete weeks from the first dose day to the date of the last dose of study medication. A participant must take all required study intervention during a week to be counted in the numerator for a given week.

$$\text{Percent Compliance} = \frac{\text{Number of Complete Weeks on Therapy}}{\text{Number of Complete Weeks Should be on Therapy}} \text{ X } 100$$

A completed week is defined as a complete weekly dose being taken (i.e., all capsules/tablets from a blister pack) during each expected week (with a -1/+6 days window). For example, the 1st dose is Day 1 and the next dose is expected on Day 8; if the 2nd weekly dose is taken on Day 7, the 2nd week is considered complete as Day 7 occurs within -1/+6 days of Day 8 (between Day 7 and Day 14). If two consecutive complete weekly doses occur within the same window, the earliest complete weekly dose that is not counted in the previous expected week will be selected as the complete weekly dose for that expected week. This approach will be used as the primary for listings and compliance summary.

Summary statistics will be provided on percent compliance for weekly treatments by treatment group according to the study part for the FAS population.

Another supportive approach will calculate weekly compliance as:

$$\text{Percent Compliance} = \frac{\text{Number of Complete Weekly Dose Taken}}{\text{Number of Complete Weeks Should be on Therapy}} \text{ x } 100$$

A complete weekly dose is defined as all capsules/tablets being taken from a blister pack, regardless of timing. This approach will be used as secondary to support compliance summary using the FAS population.

Because this assessment does not account for when these weekly treatments are taken relative to the target/scheduled day, additional summaries (including graphical presentations) may be made looking at when doses were taken over time and how dosing deviates from scheduled dosing days.

3.12 Extent of Exposure

[Note: As of Protocol Amendment 013-02, the summary associated with Part 1 is applicable and summaries for Parts 2 and 3 are no longer applicable for this section.]

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.

4. REFERENCES

[National Institute of Allergy and Infectious Diseases 2017]	National Institute of Allergy and Infectious Diseases. Division of AIDS (DAIDS) table for grading the severity of adult and pediatric adverse events, corrected version 2.1 [Internet]. Bethesda, MD: NIAID; 2017. Available from: https://rsc.tech-res.com/docs/default-source/safety/division-of-aids-(daids)-table-for-grading-the-severity-of-adult-and-pediatric-adverse-events-corrected-v-2-1.pdf?sfvrsn=2.	[04R7PK]

5. SUPPORTING DOCUMENTATION

5.1 APPENDIX 1: APPROVAL INFORMATION

The sSAP of Protocol MK-8591-013-04 was approved by the BARDS TA head on 24FEB2025.

Name: PPD Date: 24-Feb-2025