

This is ACTG A5355 SAP Version 4.0 with names of authors, names of publication writing team members and analysis timeline redacted.

A5355

Primary Statistical Analysis Plan

Version 4.0

September 24, 2024

Phase II, Double-Blind, Randomized, Placebo-Controlled Trial to Evaluate the Safety and Immunogenicity of a Modified Vaccinia Ankara (MVA)-based anti-Cytomegalovirus (CMV) Vaccine (Triplex®), in Adults Living with Both Human Immunodeficiency Virus (HIV)-1 and CMV who are on Potent Combination ART with Conserved Immune Function

ClinicalTrials.gov Identifier: NCT05099965

Protocol Version 2.0 LOA #1 and LOA #2

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Version History

Version	Changes Made	Date Finalized
1.0	Original Version	17 Sep 2021
2.0	Updated title page and header. Added ClinicalTrials.gov Identifier. Changed language throughout to match the latest protocol (e.g. changed "Entry/Day 0" to "Day 0", updated phrasing used to describe safety trigger, etc.).	10 Aug 2023
3.0	Updated title page and header. Updated Section 2.5 with new LOA language for safety events which trigger an ad-hoc SMC review.	13 Dec 2023
4.0	Moved primary and secondary hypotheses, objectives, and outcome measures related to cellular immunogenicity to exploratory based on LOA #2. Updated sample size language based on primary inflammation outcome. Removed cellular immunogenicity from primary estimand section. Reorganized analyses and report contents.	24 Sep 2024

1 Introduction

1.1 Purpose

This Primary Statistical Analysis Plan (SAP) describes the primary and key secondary estimands and other secondary outcome measures that will address specific study objectives and interim monitoring of the A5355 study. The Primary SAP includes general analytic approaches for all primary estimands, key secondary estimands, and other outcome measures in the primary manuscript(s) or submitted to ClinicalTrials.gov (regardless of the reporting timeline). The Primary SAP facilitates discussion of the statistical analysis components among the lead study investigators and statisticians, helping them agree on the statistical analyses to be performed and presented in the primary analysis report.

The Analysis Implementation Plan (AIP) provides detailed outlines of tables, figures, and coding descriptions.

Since most of the other outcome measures will follow a similar analysis approach as the primary or secondary outcome measures, all analyses will be outlined in this Primary SAP except for the exploratory outcome measures identified as “pending external funding”.

1.2 Version History

Major modifications made to align with A5355 protocol version 2.0 LOA #2 include moving primary and secondary hypotheses, objectives, and outcome measures related to cellular immunogenicity to exploratory. Revised list of primary estimands in Section 5, and reorganized contents of Sections 6 and 7.

2 Study Overview

2.1 Overview of Study Design

A5355 is a phase II, double-blind, randomized, placebo-controlled study to evaluate the safety, and immunogenicity of two injections of Modified Vaccinia Ankara (MVA) Vaccine Encoding Cytomegalovirus (CMV) antigens (Triplex®) in adults living with both HIV and CMV. Participants will be followed for 92 weeks after the last scheduled vaccination at Week 4, for a total study duration of 96 weeks. We plan to enroll 90 participants (of whom at least 25% are individuals assigned female sex at birth not on testosterone or individuals assigned male sex at birth on feminizing hormones). The target population for this study will be adults between the ages of 18 and 65 years with both HIV and CMV. Participants must be HIV virologically suppressed on antiretroviral therapy (ART) with current CD4+ cell count >250 cells/μL and nadir CD4+ cell count >100 cells/μL. Participants will be randomized in a 2:1 ratio to receive either two injections of CMV-MVA Triplex® (5×10^8 plaque-forming unit (pfu) $\pm 0.5 \times 10^8$ pfu of MVA vaccine encoding CMV antigens) by intramuscular (IM) deltoid injections or placebo (7.5% Lactose in phosphate-buffered saline [PBS]) that matches the volume of the active vaccine injection by IM deltoid injections; both administered at study Day 0 and Week 4.

2.2 Hypotheses

2.2.1 Primary

- Safety: Two injections of MVA vaccine encoding CMV antigens (Triplex®) administered according to a 4-week, two-injection schedule will be safe over the first 48 weeks.
- Inflammation: Blood plasma levels of soluble receptors for tumor necrosis factor type II (sTNFRII) will decrease over the first 48-week study period in participants receiving the active vaccine, compared to placebo.

2.2.2 Secondary

- Inflammation: The blood plasma levels of selected soluble inflammatory biomarkers (including but not limited to IL-6, sCD163, IP-10, sTNFRII, D-Dimers) at study Weeks 12, 24, 48, and 72 will decrease in participants receiving the active vaccine, compared to placebo. Inflammation might temporarily increase early after vaccine administration.
- CMV DNA shedding: Vaccination will reduce the frequency and levels of CMV DNA in peripheral blood mononuclear cells (PBMC), urine, genital secretion, and oral secretion at study Weeks 12, 48, and 72 in participants receiving the active vaccine compared to participants receiving placebo.
- Prolonged safety: Two injections of MVA vaccine encoding CMV antigens (Triplex®) administered according to a 4-week, two-injection schedule will be safe over the 96-week study period.

2.2.3 Exploratory

- Cellular immunogenicity: Anti-CMV CD8+ T-cell responses (measured as pp65-specific CD137+ CD8+ T-cells) between Day 0 and study Week 12 will increase in participants receiving the active vaccine, compared to placebo.
- Cellular immunogenicity (IE1 and IE2): Anti-CMV CD8+ T-cell responses (measured as IE1 and IE 2 -specific CD137+ CD8+ T-cells) between Day 0 and study Week 12 will increase in participants receiving the active vaccine, compared to placebo.
- Prolonged cellular immunogenicity: The increase in anti-CMV CD8+ T-cell responses (pp65, IE1 and IE2) will be higher in participants receiving the active vaccine, compared to placebo, over the 48-week study period (area under the curve).
- Detection of persistence of MVA DNA after immunizations: Viral DNA derived from the recombinant MVA vaccine will decay in blood and will be undetectable by study Week 12.
- Inflammation: The blood plasma levels of soluble inflammatory biomarkers other than those listed as secondary hypothesis (including but not limited to IL-18, IL-7, sCD14) at study Weeks 12, 24, 48, and 72 will decrease in participants receiving the active vaccine, compared to placebo. Inflammation might temporarily increase early after vaccine administration.
- T-cell dysfunction: Participants completing the vaccination series will have less evidence for T-cell dysfunction (including, but not limited to, less activation, proliferation, and exhaustion of T-cells) in their blood at study Weeks 12 and 48, and 72 when compared to those receiving placebo.

- Quality of cellular responses (pending external funding): Broad and maintained anti-CMV T-cell receptor (TCR) diversity in response to the immunogen will be observed post-vaccination at 12 and 48 weeks, as opposed to lower quality responses resulting from narrowing of the TCR repertoire due to expansion of limited anti-CMV TCRs present at Day 0.
- HIV Reservoir (pending external funding): Vaccination will reduce the size and transcriptional activity of the HIV DNA reservoir at study Weeks 12, 24, 48, and 72 in participants receiving the active vaccine compared to participants receiving placebo.
- Microbiome (pending external funding): The rectal microbiome composition will predict the magnitude of the vaccine immune response.
- Substance use: Use of non-prescribed stimulatory drugs (e.g., cocaine, methamphetamine) will be associated with increased immune activation in both arms.

2.3 Study Objectives

This Primary SAP addresses the following primary, secondary, and exploratory objectives listed in the study protocol.

Analysis of the study objectives below will be analyzed under a superiority framework. These analyses will be finalized once the last participant has completed the Week 72 study visit, all queries have been resolved, and the study database closure/data lock has been completed.

2.3.1 Primary Objectives

- Safety: To determine whether a 2-injection regimen of MVA vaccine encoding CMV antigens is safe (over 48 weeks).
- Inflammation: To determine whether the active vaccine decreases inflammation, as measured by sTNFRII, compared to placebo (Week 48).

2.3.2 Secondary Objectives

- Inflammation: To determine if anti-CMV vaccination reduces plasma levels of selected soluble inflammatory biomarkers (e.g. IL-6, sCD163, IP-10, TNFRII, D-Dimers).
- CMV DNA shedding: To determine if vaccination influences the shedding of CMV DNA in PBMC, oral secretion, genital secretion, and urine.
- Prolonged safety: To determine whether a 2-injection regimen of MVA vaccine encoding CMV antigens is safe over 96 weeks of follow-up.

2.3.3 Exploratory Objectives

- Cellular immunogenicity: To determine the anti-CMV CD8+ T-cell responses (pp65) in participants receiving the active vaccine versus placebo (Week 12).
- Cellular immunogenicity (IE1 and IE2): To determine the anti-CMV CD8+ T-cell responses (IE1 and IE2) in participants receiving the active vaccine versus placebo (Week 12).

- Prolonged cellular immunogenicity: To determine the anti-CMV CD4+/CD8+ T-cell immune responses (pp65, IE1 and IE2) to vaccine in participants over 48 weeks of follow-up.
- Detection of persistence of MVA DNA after immunizations: To determine the persistence of viral DNA derived from MVA vaccine in blood specimens.
- Inflammation: To determine if anti-CMV vaccination reduces plasma levels of soluble inflammatory biomarkers (other than those listed in Section 2.3.2).
- T-cell dysfunction: To determine if anti-CMV vaccination reduces markers of T-cell dysfunction.
- Quality of cellular responses (pending external funding): To determine the quality of the anti-CMV T-cell response (i.e., the breadth and persistence of the anti-CMV TCR repertoire) induced by vaccination at Weeks 12 and 48 as compared to Day 0.
- HIV Reservoir (pending external funding): To determine if vaccination influences the size and transcriptional activity of the HIV reservoir.
- Microbiome (pending external funding): To determine if the composition of the rectal microbiome predicts the magnitude of the vaccine immune response.
- Substance use: To determine if stimulatory drugs influence immune activation in both arms.

2.4 Overview of Sample Size Considerations

The sample size for A5355 is calculated to be 90 participants with a 2:1 randomization to CMV-MVA Triplex®: placebo injection ratio, 60 participants will receive vaccine and 30 will receive placebo. Note that this resulting sample size of 90 has been inflated to account for the 20% of participants not being included in the primary analysis due to missing samples, laboratory error, LTFU, not meeting per-protocol definition, etc.

Prior to inflation, 72 participants (48 vaccine, 24 placebo) would provide 80% power to detect a 0.142 log₁₀ pg/mL difference in sTNFRII (the co-primary outcome) between the treatment arms (between), using a two-sample t-test, the change SD of 0.20 log₁₀ pg/mL, and a two-sided 5% alpha. A reduction of 0.142 log₁₀ pg/mL corresponds to a 27% reduction in the geometric mean fold change compared to placebo.

2.5 Overview of Formal Interim Monitoring

An ACTG-appointed Study Monitoring Committee (SMC) will review accrual, baseline characteristics, conduct of the study (including premature study discontinuations and premature study treatment discontinuations), adverse events (AEs) by study treatment arm (including protocol team assessment of relationship to study treatment), CD4+ T-cell counts and HIV-1 RNA levels/suppression over time by study treatment arm, and possibly data/sample availability. The first SMC review will occur 6 months after the first participant is enrolled and then every 12 months as long as participants remain in follow-up. The SMC may elect to deviate from this timeline. An interim review may also be convened if a concern is identified by the DAIDS clinical representative, the study chairs, or study statistician in consultation with the team.

As stated in Section 10.5 of the protocol, the protocol team will monitor AEs and virologic failures (confirmed VL >200 copies/mL) monthly. If there are two or more participants with new unexpected (in terms of duration) study drug-related Grade ≥ 3 AEs, or three or more new virologic failures prior to the Week 48 visit pooled across the treatment arms since the last study pause, enrollment and study drug administration will be paused and an ad-hoc SMC review will be conducted.

The following expected study drug-related Grade 3 AEs will not trigger an ad-hoc SMC review if they improve to Grade 2 or lower within 3 days of onset:

1. Injection-site pain/tenderness
2. Fatigue
3. Generalized myalgia
4. Generalized arthralgia
5. Chills
6. Headache
7. Gastroenteritis including nausea, vomiting and/or diarrhea (unless IV hydration/rehydration required)
8. Malaise
9. Fever

3 Outcome Measures

3.1 Primary Outcome Measures

- Safety: Occurrence of Grade ≥ 3 AEs over 48 weeks.
- Inflammation: Absolute change in sTNFRII from Day 0 to Week 48.

3.2 Secondary Outcome Measures

- Inflammation: Absolute change from Day 0 to Weeks 12, 24, 48, and 72 in levels of inflammatory biomarkers (including but not limited to IL-6, sCD163, IP-10, sTNFRII, D-Dimers).
- CMV DNA shedding: CMV DNA in PBMC, urine, and genital secretion, oral secretions at Weeks 12, 48, and 72.

3.3 Other Outcome Measures

- Cellular immunogenicity: Absolute change in pp65-specific CD137+ CD8+ T-cells from Day 0 to Week 12.
- Cellular immunogenicity: Absolute change in IE1 and IE2-specific CD137+ CD8+ T-cells from Day 0 to Week 12.
- Prolonged cellular immunogenicity: Absolute change in the percent of pp65-, IE1- and IE2-specific CD137+ CD8+ T-cells over 48 weeks.
- Detection of persistence of MVA DNA after immunizations: Viral DNA from recombinant MVA vaccine at Week 12.

- Inflammation: Absolute change from Day 0 to Weeks 12, 24, 48, and 72 in levels of inflammatory biomarkers (including but not limited to IL-18, IL-7, sCD14).
- T-cell dysfunction: Absolute change from Day 0 to Weeks 12, 48, and 72 in levels of T-cell immune activation, proliferation, and exhaustion as well as CD4+/CD8+ T-cell ratio.
- Prolonged safety: Occurrence of Grade ≥ 3 AEs over 96 weeks.
- Quality of cellular responses (pending external funding): Frequency of unique anti-CMV T-cell receptors at Day 0 and at Weeks 12 and 48.
- HIV Reservoir (pending external funding): Change from Day 0 to Weeks 12, 24, 48, and 72 in the size and transcriptional activity of the HIV DNA reservoir.
- Microbiome (pending external funding): Change from Day 0 to Weeks 12 and 48 in the composition of the microbiome and possible effect of the microbiome to the magnitude of the immune response.

4 General Considerations

- All statistical tests will be two-sided with a nominal alpha level of 0.05 (unless otherwise noted) and no adjustment for multiple testing.
- Outcome measures will be transformed for analyses and summaries on the \log_{10} scale, as appropriate, if determined to not be approximately normally distributed.
- All enrolled participants make up the randomized population.
- All enrolled, eligible participants make up the intent-to-treat (ITT) population.
- Safety analyses will use a modified ITT (mITT) population consisting of all participants who initiated study treatment.
- Because this is a phase II study and biologic activities of the intervention are of interest, efficacy analyses will use a per-protocol (PP) population limited to participants who 1) received the Day 0 CMV-MVA Triplex®/placebo injection, 2) have not used prohibited medications and 3) do not have a confirmed virologic failure, defined as the occurrence of two sequential plasma HIV-1 RNA values ≥ 200 copies/mL, unless otherwise noted.
- Absolute change refers to the value at the follow-up time point minus the value at baseline.
- Baseline refers to the study evaluation closest to Entry prior to initiation of study treatment.
- The following analysis visit windows will be used:
 - Entry: randomization date to date of first vaccination
 - Week 4: weeks (2, 6]
 - Week 8: weeks (6, 10]
 - Week 12: weeks (10, 18]
 - Week 24: weeks (18, 36]
 - Week 48: weeks (36, 60]
 - Week 72: weeks (60, 84]
 - Week 96: > week 84 to off study date

In the event of multiple results within a study window, the result closest to the scheduled evaluation week will be used.

5 Estimand and Estimation

5.1 First Primary Estimand

Primary Objective 1: To determine whether a 2-injection regimen of MVA vaccine encoding CMV antigens is safe (over 48 weeks).	
Estimand description	The effect of Triplex on the probability of Grade ≥ 3 adverse events within 48 weeks of initiating therapy among HIV-infected adults with CMV.
Treatment	CMV-MVA Triplex®
Target population	Analysis set
Adults between the ages of 18 and 65 years with both HIV and CMV, with HIV RNA suppression on ART with current CD4+ cell count >250 cells/ μ L and nadir CD4+ cell count ≥ 100 cells/ μ L.	Safety set (Participants who receive at least one injection of study treatment)
Variable(s)	Outcome measure(s)
Occurrence of Grade ≥ 3 AEs within 48 weeks of the first vaccination.	Outcome measure as defined by the Variable. Only events occurring within 48 weeks of the first injection of study treatment are included.
Handling of intercurrent events	Handling of missing data
<p>The following intercurrent events are relevant to the estimand:</p> <ol style="list-style-type: none"> 1. Change in background ART regimen: ignored (treatment policy) 2. Use of prohibited medications: ignored (treatment policy) 3. Failure to receive second vaccination: ignored (treatment policy) 4. Confirmed HIV virologic failures: ignored (treatment policy) 5. Pregnancy: ignored (treatment policy) 	<p>Participants who discontinue follow-up before Week 48 will have their outcome determined based on data available until the time of discontinuation (i.e., a participant who discontinued follow-up without a prior AE is assumed not to have an AE had they been observed for the intended duration [48 weeks]).</p> <p>A sensitivity analysis will use the Kaplan-Meier estimator of time to first Grade ≥ 3 AEs with participants censored at the time of study discontinuation.</p>

Population-level summary measure	Analysis approach
The probability of a Grade ≥ 3 adverse event within 48 weeks of the first Triplex vaccination compared to the probability of an event had no vaccination been given.	<p>Absolute difference (Triplex arm relative to placebo arm) in the proportion of participants with any Grade ≥ 3 adverse event (yes/no) within 48 weeks of the first injection of study treatment.</p> <p>An exact 95% confidence interval around the observed difference in proportions (and the associated p-value) will be constructed based on the standardized statistic and inverting two 1-sided tests.</p>

5.2 Second Primary Estimand

Primary Objective 2: To determine whether the active vaccine decreases inflammation, as measured by sTNFRII, compared to placebo (Week 48).	
Estimand description	The effect of Triplex on sTNFRII 48 weeks after initiating therapy, among HIV-infected adults with CMV without virologic failure or use of prohibited medications.
Treatment	CMV-MVA Triplex.®
Target population	Analysis set
Adults between the ages of 18 and 65 years with both HIV and CMV, with HIV RNA suppression on ART with current CD4+ cell count >250 cells/ μ L and nadir CD4+ cell count ≥ 100 cells/ μ L.	Efficacy set (Participants who initiated study treatment and do not have confirmed virologic failure or receive prohibited medications over 48 weeks).
Variable(s)	Outcome measure(s)
Change in sTNFRII 48 weeks after the first vaccination.	Outcome measure as defined by the Variable.
Handling of intercurrent events	Handling of missing data

<p>The following intercurrent events are relevant to the estimand:</p> <ol style="list-style-type: none"> 1. Death: Excluded (principal stratum) 2. Change in background ART regimen: ignored (treatment policy) 3. Use of prohibited medications: excluded (principal stratum) 4. Failure to receive second vaccination: ignored (treatment policy) 5. Confirmed HIV virologic failures: excluded (principal stratum) 6. Pregnancy: excluded (principal stratum) 	<p>The analysis will be performed on the efficacy set and subset to intercurrent events (principal stratum). Missing data in this population will be assumed to be missing completely at random and thus ignored.</p>
Population-level summary measure	Analysis approach
<p>The average change in sTNFRII 48 weeks after initiating Triplex compared to the average change had no vaccination been given.</p>	<p>Linear regression of sTNFRII change (log₁₀-transformed prior to calculating absolute change) on treatment arm adjusted for the stratification factor.</p>

5.3 First Secondary Estimand

Secondary Objective 1: Inflammation: To determine if anti-CMV vaccination reduces plasma levels of selected soluble inflammatory biomarkers (e.g. IL-6, sCD163, IP-10, , D-Dimers).	
Estimand description	The effect of Triplex on changes in IL-6, sCD163, IP-10 and D-Dimers 48 weeks after initiating therapy, among HIV-infected adults with CMV without virologic failure or use of prohibited medications,
Treatment	CMV-MVA Triplex.®
Target population	Analysis set
<p>Adults between the ages of 18 and 65 years with both HIV and CMV, with HIV RNA suppression on ART with current CD4+ cell count >250 cells/μL and nadir CD4+ cell count ≥100 cells/μL.</p>	<p>Efficacy set (Participants who initiated study treatment and do not have confirmed virologic failure or receive prohibited medications over 48 weeks).</p>

Variable(s)	Outcome measure(s)
Changes in IL-6, sCD163, IP-10 and D-Dimers 48 weeks after the first vaccination.	Outcome measure as defined by the Variable.
Handling of intercurrent events	Handling of missing data
<p>The following intercurrent events are relevant to the estimand:</p> <ol style="list-style-type: none"> 1. Death: Excluded (principal stratum) 2. Change in background ART regimen: ignored (treatment policy) 3. Use of prohibited medications: excluded (principal stratum) 4. Failure to receive second vaccination: ignored (treatment policy) 5. Confirmed HIV virologic failures: excluded (principal stratum) 6. Pregnancy: excluded (principal stratum) 	<p>The analysis will be performed on the efficacy set and subset to intercurrent events (principal stratum). Missing data in this population will be assumed to be missing completely at random and thus ignored.</p>
Population-level summary measure	Analysis approach
<p>The average changes in IL-6, sCD163, IP-10 and D-Dimers 48 weeks after initiating Triplex compared to the average change had no vaccination been given.</p>	<p>Linear regression of IL-6, sCD163, IP-10 and D-Dimers changes (\log_{10}-transformed prior to calculating absolute change, if necessary) on treatment arm adjusted for the stratification factor.</p>

6 Analysis of Objectives

6.1 Primary Analyses

1. For primary safety analysis:
 - a. Using the mITT population, Grade 3 or greater AEs through Week 48 will be summarized by treatment arm.
 - b. Using the mITT population, Kaplan-Meier curves of time from first vaccination to first Grade 3+ AE (participants will be censored at time of study discontinuation) will be provided along with the corresponding log-rank test p-value.
2. For primary inflammation analysis:
 - a. Using the PP population, absolute changes in sTNFRII from Day 0 to Week 48 will be compared between the CMV-MVA Triplex® arm and the placebo arm by linear regression. For this model each participant will have a single outcome

- measure of sTNFRII change from Day 0 to Week 48. The predictor variables will be study arm and sex/use of gender-affirming hormones (the stratification factor).
- b. Three supplemental linear regression analyses will be performed with the treatment effect summarized. The first will additionally adjust for Day 0 sTNFRII values (continuous). The second will assess differential CMV-MVA Triplex® effects by Day 0 sTNFRII tertile by additionally adjusting for the sTNFRII tertile main effect and the study arm by sTNFRII tertile interaction. The third will perform the primary analysis using the mITT population.
 - c. An exploratory subgroup analysis will assess the differential treatment effects between cisgender men and cisgender women using the PP population. The linear regression model will additionally adjust for the cisgender main effect and the study arm by cisgender interaction.
 - d. If subgroups have sufficient sample sizes (at least five participants), an additional subgroup analysis will assess differential treatment effects by gender identity (cisgender men, transmen, cisgender women, transwomen, and gender non-binary).

6.2 Secondary and Other Analysis

1. For secondary inflammation analysis:
 - a. Using the PP population, 48-week absolute changes in IL-6, sCD163, IP-10 and D-Dimer will be analyzed in the same manner as the primary inflammation analysis (including the supplemental and exploratory subgroup analyses).
 - b. Using the PP population, absolute changes from baseline to Weeks 12, 24, 48 and 72 in IL-6, sCD163, IP-10, sTNFRII, and D-Dimer will use generalized estimating equation (GEE) models with an identity link and the appropriate correlation structure and splines, if necessary.
2. For secondary CMV DNA shedding analysis:
 - a. Using the PP population, CMV DNA shedding (binary outcome for shedding in any compartment) at weeks 12, 48 and 72 will be analyzed using GEE models with a log link and the appropriate correlation structure to estimate the shedding risk ratio, 95% CI and associated p-value.
3. For secondary prolonged safety analysis:
 - a. Using the mITT population, Grade 3 or greater AEs through Week 96 will be analyzed in the same manner as the primary safety analysis.
 - b. Using the mITT population, Kaplan-Meier curves of time from first vaccination to first Grade 3+ AE (participants will be censored at time of study discontinuation) will be provided along with the corresponding log-rank test p-value.
4. For exploratory cellular immunogenicity analysis:
 - a. Using the PP population, absolute changes in pp65-, IE1- and IE2-specific CD137+ CD8+ T-cells from Day 0 to Week 12 will analyzed in the same manner as the primary inflammation analysis (including the supplemental and exploratory subgroup analyses).
5. For exploratory prolonged cellular immunogenicity analysis:

- a. Using the PP population, 48-week absolute change in pp65-, IE1- and IE2-specific CD137+ CD8+ T-cells will be analyzed in the same manner as the exploratory cellular immunogenicity analysis above.
6. For exploratory detection of persistence of MVA DNA after immunizations analysis:
 - a. Using the PP population and the Triplex® arm, the proportion of participants with viral DNA from recombinant MVA vaccine will be summarized.
7. For exploratory inflammation analyses:
 - a. IL-18, IL-7 and sCD14 data will be analyzed in the same manner as the secondary inflammation analysis.
8. For exploratory T-cell dysfunction analysis:
 - a. T-cell immune activation (CD38+DR+), proliferation (Ki67+), and exhaustion (PD-1) and CD4+/CD8+ T-cell ratio will be analyzed in the same manner as the secondary inflammation analysis.
9. For exploratory substance use analysis:
 - a. Using the ITT population and prior to treatment initiation, all participants will be pooled and the distributions of sTNFRII, sCD163, sCD14, IP-10, CD4+CD38+HLA-DR+ T cells and CD8+CD38+HLA-DR+ T cells will be compared between current stimulant users (use of cocaine or amphetamines in the past month) and non-users using the Wilcoxon rank-sum test.

7 Report Contents

Note that specific statistics used to describe “summary” will be more explicitly defined in the corresponding AIP. All sections below pertain to both the interim and final report analyses, unless noted otherwise. For the SMC Open Interim Report, all summaries will be pooled over treatment arms. For the SMC Closed Interim Report as well as for final analysis, all summaries will be presented both pooled (overall) and by unblinded treatment arms. All eligible ITT participants with available data will be used for the following summaries and analyses, unless specified otherwise.

1. Study history
 - a. A summary of changes to and clarifications of the protocol.
 - b. A brief summary of the SMC reviews.
2. Study entry
 - a. Accrual: Tables of accrual by month and by site.
3. Baseline characteristics (for ITT, mITT and PP populations)
 - a. Demographics: age, sex, gender, sex and use of gender-affirming hormones, race, ethnicity
 - b. Weight and BMI
 - c. HIV status: Antiretroviral (ARV) regimen, nadir CD4 count, CD4 count, HIV RNA
 - d. Laboratory results: Hemoglobin, platelet count, AST/SGOT, ALT/SGPT, alkaline phosphatase, and hemoglobin A1c
4. Study status
 - a. Number of participants off study with off study reasons.
 - b. Number of weeks from study entry to last clinic visit.
5. Treatment status
 - a. Number of participants who did not start study treatment.
 - b. Number of participants off treatment with off treatment reasons.
 - c. Number of days from study entry to first dose of study treatment.
 - d. Number of weeks from study entry to permanent discontinuation of study treatment.
 - e. Number of doses of study treatment administered.
6. Adverse events and deaths
 - a. Summary of all reportable AEs through Week 48 by MedDRA PT grouped by SOC and grade.
 - b. Summary of serious adverse events (SAEs) through Week 48 by MedDRA PT grouped by SOC and grade.
 - c. Summary of SAEs that are expedited adverse events (EAEs) through Week 48 by MedDRA PT grouped by SOC and grade.
 - d. Summary of all reportable AEs through Week 96 by MedDRA PT grouped by SOC and grade.
 - e. Summary of SAEs through Week 96 by MedDRA PT grouped by SOC and grade.
 - f. Summary of SAEs that are EAEs through Week 96 by MedDRA PT grouped by SOC and grade.
 - g. Listing of participants who died, including the primary cause of death, study week of death and death narrative.

7. Pregnancies
 - a. Listing and description of all available information related to pregnancy and outcome.
8. ART Adherence
 - a. Summary of self-reported ART adherence (<100% vs. 100%) by study visit.
 - b. Summary of overall ART adherence (<100% vs. 100%) while on study.
9. Virologic failures
 - a. Number of confirmed virologic failures.
 - b. Listing of all available HIV-1 RNA data and ART adherence for virologic failures.
10. CD4 cell counts
 - a. Summary of cross-sectional CD4 cell counts and changes from entry.
11. Concomitant medications (final report only)
 - a. Summary of concomitant medications continued at study entry and started on study.
12. Analysis of primary safety outcome described in Section 6.1 (final report only, mITT population)
 - a. Summary of the number of participants with a Grade 3 or greater AE through Week 48 by treatment arm, the proportion within each arm and the resulting difference in proportions, 95% CI and associated p-value.
 - b. Kaplan-Meier curves of time from treatment initiation to first Grade 3 or greater (participants will be censored at time of study discontinuation) will be provided along with the corresponding log-rank test p-value.
13. Analysis of primary inflammation outcome described in Section 6.1 (final report only, PP population)
 - a. Summary of sTNFRII at each time point as well as changes from baseline by treatment arm.
 - b. Summary of the linear regression model of 48-week absolute change in sTNFRII with treatment arm and stratification factor covariates. The estimated effects, 95% CIs, and associated p-values will be provided.
 - c. Similar summary for each of the three supplemental linear regression models.
 - d. Similar summary for the exploratory subgroup linear regression models.
14. Analysis of secondary inflammation outcomes described in Section 6.2 (final report only, PP population)
 - a. Summary of IL-6, sCD163, IP-10 and D-Dimer at each time point as well as changes from baseline by treatment arm.
 - b. Summary of the linear regression models of 48-week absolute change in IL-6, sCD163, IP-10 and D-Dimer with treatment arm and stratification factor covariates. The estimated effects, 95% CIs, and associated p-values will be provided.
 - c. Similar summary for each of the three supplemental linear regression models.
 - d. Similar summary for the exploratory subgroup linear regression models.
 - e. Summary of the GEE models of absolute change from baseline to Weeks 12, 24, 48 and 72 in IL-6, sCD163, IP-10, sTNFRII, and D-Dimer. The estimated slopes, 95% CIs, and associated p-values will be provided.

15. Analysis of secondary CMV DNA shedding outcome described in Section 6.2 (final report only, PP population)
 - a. Summary of CMV DNA shedding (yes/no) in PBMC, urine and genital secretion compartments as well as the composite of any CMV DNA shedding at each time point.
 - b. Summary of the GEE model of any CMV DNA shedding at Weeks 12, 48 and 72. The estimated risks and risk ratios, 95% CIs, and associated p-values will be provided.
16. Analysis of secondary prolonged safety outcome described in Section 6.2 (final report only, mITT population)
 - a. Summary of the number of participants with a Grade 3 or greater AE through Week 96 by treatment arm, the proportion within each arm and the resulting difference in proportions, 95% CI and associated p-value.
 - b. Kaplan-Meier curves of time from treatment initiation to first Grade 3 or greater (participants will be censored at time of study discontinuation) will be provided along with the corresponding log-rank test p-value.
17. Analysis of exploratory cellular immunogenicity outcome described in Section 6.2 (final report only, PP population)
 - a. Summary of pp65, IE1- and IE2-specific -specific CD137+ CD8+ T-cells at each time point as well as changes from baseline by treatment arm.
 - b. Summary of the linear regression model of 12-week absolute change with treatment arm and stratification factor covariates. The estimated effects, 95% CIs, and associated p-values will be provided.
 - c. Similar summary for each of the three supplemental linear regression models.
 - d. Similar summary for the exploratory subgroup linear regression models.
18. Analysis of secondary prolonged cellular immunogenicity outcome described in Section 6.2 (final report only, PP population)
 - a. Summary of the linear regression model of 48-week absolute change in pp65-, IE1- and IE2-specific CD137+ CD8+ T-cells with treatment arm and stratification factor covariates. The estimated effects, 95% CIs, and associated p-values will be provided.
 - b. Similar summary for each of the three supplemental linear regression models.
 - c. Similar summary for the exploratory subgroup linear regression models.
19. Analysis of exploratory detection of persistence of MVA DNA after immunizations outcome described in Section 6.2 (final report only, PP population, Triplex® arm)
 - a. Summary of MVA DNA at Week 12.
 - b. Estimated proportion (95% CI) of participants with detectable MVA DNA.
20. Analysis of exploratory inflammation outcomes described in Section 6.2 (final report only, PP population)
 - a. Summary of IL-18, IL-7 and sCD14 at each time point as well as changes from baseline by treatment arm.
 - b. Summary of the linear regression models of 48-week absolute change in IL-18, IL-7 and sCD14 with treatment arm and stratification factor covariates. The estimated effects, 95% CIs, and associated p-values will be provided.
 - c. Similar summary for each of the three supplemental linear regression models.

- d. Similar summary for the exploratory subgroup linear regression models.
 - e. Summary of the GEE models of absolute change from baseline to Weeks 12, 24, 48 and 72 in IL-18, IL-7 and sCD14. The estimated slopes, 95% CIs, and associated p-values will be provided.
21. Analysis of exploratory T-cell dysfunction outcomes described in Section 6.2 (final report only, PP population)
- a. Summary of T-cell immune activation (CD38+DR+), proliferation (Ki67+), and exhaustion (PD-1) and CD4+/CD8+ T-cell ratio at each time point as well as changes from baseline by treatment arm.
 - b. Summary of the linear regression models of 48-week absolute change in T-cell immune activation (CD38+DR+), proliferation (Ki67+), and exhaustion (PD-1) and CD4+/CD8+ T-cell ratio with treatment arm and stratification factor covariates. The estimated effects, 95% CIs, and associated p-values will be provided.
 - c. Similar summary for each of the three supplemental linear regression models.
 - d. Similar summary for the exploratory subgroup linear regression models.
 - e. Summary of the GEE models of absolute change from baseline to Weeks 12, 24, 48 and 72 in T-cell immune activation (CD38+DR+), proliferation (Ki67+), and exhaustion (PD-1) and CD4+/CD8+ T-cell ratio. The estimated slopes, 95% CIs, and associated p-values will be provided.